Parexel International

Alexion Pharmaceuticals, Inc.

ALXN1910-HV-101

A Phase 1, Randomized, Double-blind, Placebo-controlled, Single Ascending Dose Study of Subcutaneously and Intravenously Administered ALXN1910 in Healthy Adult Participants

Statistical Analysis Plan

Version: 3.0

Parexel Project Number: PXL268911

SPONSOR SIGNATURE PAGE

Approved by: _____ _____

PPD Date

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Signatures below confirm that the Statistical Analysis Plan was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
Final 1.0	07 Jun 2022	
Final 2.0	27 Jan 2023	Page 14, updated the sentence "nominal infusion time is within 5 seconds" Due to protocol amendment 3, and the major changes are the EOS visit for all participant is at Day 75, and ADA titer category analysis removed.
Final 3.0	27 Mar 2023	In Section 4.8.1, "Exposure to IMP data will be summarized using descriptive statistics for each treatment cohort" removed

LIST OF ABBREVIATIONS

Abbreviation/Acronym	Definition/Expansion
ADA	Antidrug antibody
ADAAS	Antidrug antibody analysis set
AE	Adverse event
AESI	Adverse events of special interest
ANOVA	Analysis of variance
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
AUC_{∞}	AUC from time zero extrapolated to infinity
AUC_{0-t}	AUC from time zero to the last quantifiable concentration
BA	Bioavailability
BDRM	Blinded data review meeting
BL	Biostatistician Lead
BLQ	Below the lower limit of quantification
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
CI	Confidence interval
CL	Clearance
CL/F	Apparent clearance following extravascular (non-intravenous) administration, e.g., clearance following oral, subcutaneous, topical, nasal, sublingual routes
C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration at steady state
CPMS	Clinical Pharmacology, Modeling, and Simulation
eCRF	Electronic Case Report Form
CS	Clinically significant
CSP	Clinical Study Protocol
CS	Clinically significant
CTCAE	Common Terminology Criteria for Adverse Events

Abbreviation/Acronym	Definition/Expansion
CV	Coefficient of variation
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DRM	Data Review Meeting
ECG	Electrocardiogram
ENR	Enrolled Analysis Set
EOS	End of study
ET	Early termination
Fe	Fraction of administered drug excreted unchanged in the urine
Fe%	Urinary cumulative excretion as % of unchanged drug
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
GMR	Geometric mean ratio
IB	Investigator's Brochure
ICF	Informed consent form
IMP	Investigational medicinal product
IV	Intravenous(ly)
L	Linearity index
LLOQ	Lower limit of quantification
LOQ	Limit of quantification
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger ribonucleic acid
MRT	Mean residence time
MTD	Maximum tolerated dose
NA	Not available
NCS	Not clinically significant

Abbreviation/Acronym	Definition/Expansion
NK	Not known
NR	Not reportable
NS	No sample
OTC	Over the counter
PCS	Potentially clinically significant
PD	Pharmacodynamic(s)
PDAS	Pharmacodynamic analysis set
PK	Pharmacokinetic(s)
PKAS	Pharmacokinetic analysis set
PTF	Peak trough fluctuation
PTT	Peak-to-trough ratio
QTc	corrected QT interval
QTcF	QT corrected using Fridericia's formula
RAS	Randomized Analysis Set
SAD	Single ascending dose
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
sc	Subcutaneous
SD	Standard deviation
SE	Standard error of the mean
SI	Standard international
SOC	System Organ Class
$t_{½}$	Apparent terminal elimination half-life
TEAE	Treatment-emergent adverse event
TEMA	Treatment-emergent markedly abnormal
t_{last}	Time to last quantifiable concentration
t_{max}	Time corresponding to occurrence of C_{max}

Abbreviation/Acronym	Definition/Expansion
V_z	Volume of distribution during terminal phase following intravenous dosing
V_z/F	Apparent volume of distribution during terminal phase following extravascular dosing
WHO-DD	World Health Organization - Drug Dictionary
λ_z	Terminal elimination rate constant

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes all planned analyses for the Clinical Study Report (CSR) of Study ALXN1910-HV-101, A Phase 1, Randomized, Double-blind, Placebo-controlled, Single Ascending Dose Study of Subcutaneously and Intravenously Administered ALXN1910 in Healthy Adult Participants. It describes the data to be analysed, including details of the statistical analyses to be performed.

The content of this SAP is based on the following study documents:

- Study ALXN1910-HV-101 protocol Amendment 3 dated 27 Jul 2022.
- Electronic Case Report Form (eCRF) Version 11. 06 May 2022.
- Data Management Plan (DMP) Final 1.0 dated 18 Mar 2022.

This SAP will be finalized prior to database lock. Should circumstances arise during the study rendering these analyses inappropriate, or if improved methods of analysis arise, updates to the analyses may be made. Any changes after the finalization of this SAP will be documented in Statistical Method Modification Form. Any deviations from the final SAP after database lock and all alternative or additional statistical analyses that may be performed will be discussed in the Clinical Study Report (CSR)(changes to planned analysis) and, if applicable, in an SAP addendum.

2 STUDY OBJECTIVES

The primary and secondary objectives of the study are as mentioned below:

2.1 Primary Objective

Objective	Endpoint
• To assess the safety and tolerability of ALXN1910	• Incidence of TEAEs and TESAEs

2.2 Secondary Objective

Objective	Endpoint
• To assess the PK of single ascending doses of ALXN1910	• Serum ALXN1910 PK (activity) and PK parameters
• To explore the PD effects of single ascending doses of ALXN1910	• Plasma concentrations of PPi, PLP, PL, and PA versus time profiles
• To assess the immunogenicity of ALXN1910	• Incidence and titers of treatment-emergent ADAs
• To assess the absolute bioavailability of ALXN1910 SC	• GMR of AUC values of SC versus IV from serum concentrations of ALXN1910
• To compare the safety, tolerability, PK, and PD of ALXN1910 SC between Japanese and non-Japanese healthy participants	• Quantitative assessment of safety/tolerability and PK/PD parameters between Japanese and non-Japanese participants

Abbreviations: ADA = antidrug antibody; AUC = area under the serum concentration-time curve; GMR = geometric mean ratio; IV = intravenous; PA = pyridoxic acid; PD = pharmacodynamics(s); PK = pharmacokinetic(s); PL = pyridoxal; PLP = pyridoxal-5′ -phosphate; PPi = inorganic pyrophosphate; SC = subcutaneous; TEAE = treatment emergent adverse event; TESAE = treatment emergent serious adverse event

2.3 Exploratory Objective(s)

Not Applicable.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a Phase 1, randomized, double-blind, placebo-controlled study designed to evaluate the safety, tolerability, PK, PD, and immunogenicity of SADs of ALXN1910 SC and a SAD of ALXN1910 IV in up to approximately 48 healthy adult participants across treatment cohorts (up to approximately 36 participants to receive ALXN1910 and up to approximately 12 participants to receive placebo) (Table 1). Of the 48 participants, 8 will be of Japanese descent, defined as those participants whose parents and grandparents are both Japanese and who have spent less than 10 years outside of Japan.

Table 1 Planned ALXN1910-HV-101 Dosing Cohorts

Cohort[a]	Number of Participants (ALXN1910:Placebo)	Route of Administration	Dose	Number of Doses/Dose Interval
1	8 (3:1)	IV[b]	5 mg	Single dose
2	8 (3:1)	SC	15 mg	Single dose
3	8 (3:1)	IV[b]	15 mg	Single dose
4	8 (3:1) (Japanese participants)	SC	15 mg	Single dose
5	8 (3:1)	SC	45 mg	Single dose
6	8 (3:1)	SC	135 mg	Single dose

[a] Cohort 3, Cohort 4, and Cohort 5 can be initiated in parallel after dose escalation decision following SRC review of Cohort 2 safety and PK data.

[b] Slow IV infusions (rate of infusion = 6 mL/h) using a controllable infusion pump. The pharmacy manual will include details regarding infusion rate and duration.

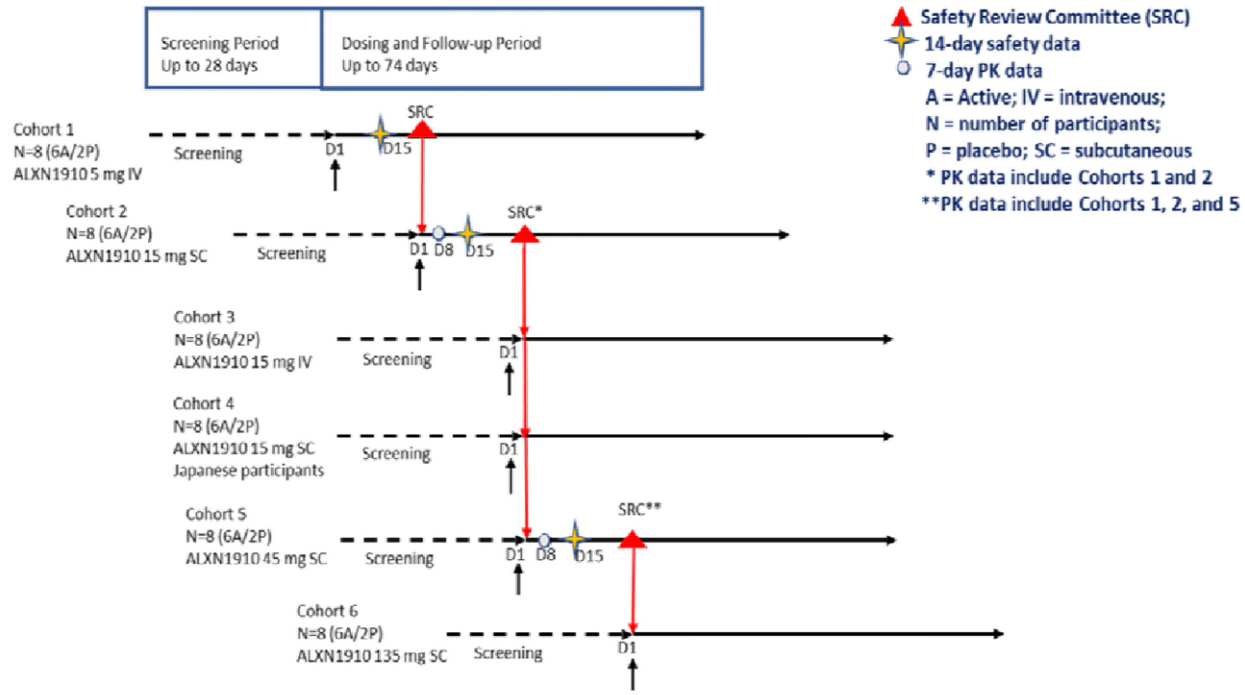
Abbreviations: IV = intravenous; PK =pharmacokinetic; SC = subcutaneous; SRC = Safety Review Committee

For this FIH study, 8 participants will be randomly assigned in a 3:1 ratio to treatment and placebo in each of the 6 cohorts with escalating doses of 5 mg IV (Cohort 1), 15 mg SC (Cohort 2), 15 mg IV (Cohort 3) in parallel with 15 mg SC in Japanese participants (Cohort 4) and 45 mg SC (Cohort 5), followed by 135 mg SC (Cohort 6). The first 2 participants randomized to each cohort will be dosed as a sentinel pair, with 1 participant on active treatment and 1 participant on placebo. This dosing strategy is justified given the large exposure margins (approximately 15-fold at the highest planned single dose of 135 mg SC).

Participants who meet the qualifications for the study based on screening will be admitted to the CRU the day prior to dosing (Day -1) to undergo Check-in assessments per the applicable SoA (Section 6.1).

Final determination of eligibility will be determined based on Check-in and predose procedures, and eligible participants will be randomized to ALXN1910 or placebo on Day 1 prior to dosing. There will be extensive PK/PD sampling during the first 24 hours after dosing. Safety assessments will be performed per the SoA. The study schematic is presented in Figure 1.

Figure 1 Study Design Schematic



3.2 Determination of Sample Size

No formal testing of hypotheses has been planned for this study. Therefore, no formal sample size calculations were performed. Approximately 48 participants are considered to be adequate to support and analyze the initial characterization of safety, tolerability, PK, PD, and immunogenicity for ALXN1910. The following table provides the probability of observing AEs under various underlying event incidence.

Incidence of AE in the Population	Probability to Observe at least 1 AE Occurrence in 6 Participants from Each Cohort
10%	46.9%
15%	62.3%
20%	73.8%
25%	82.2%
30%	88.2%
35%	92.5%
40%	95.3%

3.3 Endpoints and Associated Variables

The following endpoints will be used to investigate single ascending doses of ALXN1910 in participants.

3.3.1 Safety Variables

- Physical examinations
- Vital signs (Oral body temperature, pulse rate, respiratory rate, and supine blood pressure [BP])
- 12-lead electrocardiogram (ECG): Heart rate, PR interval, QRS interval, QT interval, QTC interval and QT interval using Fridericia's correction [QTcF]
- Clinical laboratory tests (hematology, clinical chemistry, coagulation, and urinalysis parameters)
- Treatment Emergent Adverse Event (TEAE) assessments
- Concomitant medication assessments

3.3.2 Pharmacokinetic Variables

Pharmacokinetic concentration data will be obtained at time point(s) described in the protocol, as detailed in Table 2 and Table 3 of study protocol and as follows:

Serum PK samples will be collected at the following nominal times: 0 (pre-dose sample), 30 min and, 2, 4, 8, 12, 24, 48, 72, 96 hours and on D6, D7, D8, D15, D22, D29, D36, D43 and D75 (after injection (for sc administration) or after start of infusion (for IV administration). The IV dose cohorts will also have an end-of-infusion PK time point (nominal infusion time is within 5 seconds and 0.5 hours for Cohort 1 and Cohort 3, respectively).

Unless otherwise stated, derivation of PK parameters will be the responsibility of Clinical Pharmacology, Modeling and Simulation (CPMS) group, Parexel.

If calculable, the following PK parameters listed in Table 2 will be determined for ALXN1910 in Serum following single SC or IV dose administration.

Table 2 Serum Pharmacokinetic Parameters After Single Dose Administration

Parameter	WNL Name	CDISC Name	Definition
C_{max}	Cmax	CMAX	Maximum observed concentration
DNC_{max}	Cmax_D	CMAXD	Dose-normalized C_{max}
t_{max}	Tmax	TMAX	Time corresponding to occurrence of C_{max}
$t_{½}$	HL_Lambda_z	LAMZHL	Apparent terminal elimination half-life
λ_z	Lambda_z	LAMZ	Terminal elimination rate constant
AUC_t	AUClast	AUCLST	AUC from time zero to the last quantifiable concentration
$DNAUC_t$	AUClast_D	AUCLSTD	Dose-normalized AUC_t
AUC_{0-168}	AUC_{0-168}	AUCINT	AUC from time zero to time 168 h

Parameter	WNL Name	CDISC Name	Definition
AUC_{∞}	AUCINF_obs	AUCIFO	AUC from time zero extrapolated to infinity
$DNAUC_{\infty}$	AUCINF_D_obs	AUCIFOD	Dose-normalized AUC_{∞}
$\%AUC_{ex}$	AUC_%Extrap_obs	AUCPEO	Percentage of AUC_{∞} obtained by extrapolation beyond t_{last}
CL or CL/F	Cl_F_obs	CLFO	Total body clearance (IV route)or apparent clearance (SC route)
V_d or V_d/F	Vd_F_obs	VZFO	Volume of distribution (IV route) or apparent volume of distribution (SC route)

Source: NCI EVS Terminology Resources website:
http://www.cancer.gov/cancertopics/cancerlibrary/terminologyresources/cdisc.

Additional PK parameters may be calculated if deemed appropriate.

3.3.3 Pharmacodynamic Variables

To assess the effect of ALXN1910 on pharmacodynamic (PD) variables PPi, PLP, PL, and PA versus time profiles, whole blood samples will be collected at the times specified in the Schedule of Assessments.

3.3.4 Immunogenicity Variables

ADA positive: Include participant with a positive response in the ADA assay at any time point will be categorized as follows:

- Pre-existing Immunoreactivity: Defined as ADA positive result in the assay at baseline with all post first dose ADA results negative or a positive result at baseline with all post first dose ADA results less than 4 folds over the baseline titer levels.
- Treatment-emergent ADA Responses: Defined as a positive result in the ADA assay post first dose, when baseline results are negative or missing.
- Treatment-boosted ADA responses: Defined as a positive result in the ADA assay post first dose, that is greater than or equal to 4-fold over baseline titer levels, when baseline results are positive.

ADA negative: ADA negative response in the ADA assay at all time points.

3.3.5 Exploratory Variables

Biomarker assays may be conducted as exploratory analyses on collected whole blood samples.

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures, and data listings to be included in the report will be independently checked for consistency, integrity, and in accordance with standard Parexel procedures.

4.2 General Presentation Considerations

This section is not applicable to PK data.

4.2.1 Treatment

During this study up to approximately 48 participants will be randomized in a 3:1 ratio to receive either of ALXN1910 or placebo as mentioned in Table 1.

4.2.2 Study Day

Study days will be numbered relative to the first day of study drug administration.

- If the date of event is before the study drug administration, then:

  Study day = (Date of measurement – Date of study drug administration [i.e. Day 1] in each cohort)

- If the date of event is on or after the study drug administration, then:

  Study day = (Date of measurement – Date of study drug administration [i.e. Day 1] in each cohort) + 1

4.2.3 End of Study

The end of the study is defined as the date the last participant completes the last safety follow up.

End of study visit is planned on Day 75.
A participant is considered to have completed the study if they complete all visits of the study including the last scheduled visit specified in the SoA.

4.2.4 Baseline

Baseline is defined as the last non-missing measurement recorded before first dose of study drug administration.

Measurements taken in triplicates:

For safety parameters (e.g. ECGs), where the study requires multiple replicates (e.g. triplicates) per time point, the average of these measurements would be calculated (if not already available in the database) before determining baseline.

Baseline is defined as average of non-missing triplicate measurement collected prior to study drug administration.

No imputation will be done for missing baseline value for derivation of change from baseline or summary tables and shift tables.

4.2.5 Controlled, Repeat, Retest, Scheduled and Unscheduled Assessment

Repeat, retest, and unscheduled assessment will not be considered for the calculation of summary statistics and figures, unless assessment qualifies as baseline.

Average of controlled and planned (scheduled) assessments will be considered for the calculation of summary statistics and figures, if more than one controlled/planned assessment will be performed at a specific time point.

4.2.6 Summary and Representation of Data

Continuous data will be summarized in terms of mean, standard deviation (SD), median, minimum, maximum, and number of observations, unless otherwise stated.

Categorical data will be summarized in terms of the number of participants providing data at the relevant time point (n), frequency counts, and percentages.

The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean and median will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistics.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using N as the denominator. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only. Percentage will be presented as whole number if value is 100.

If for any summary table, n is less than three then only n, mean, minimum, and maximum should be presented, and other summary statistics will be left blank.

4.3 Software

All report outputs will be produced using SAS® version 9.4 or later in a secure and validated environment.

The PK analyses will be conducted using Phoenix® WinNonlin (WNL) version 8.0 or later in a secure and validated environment.

All report outputs will be provided to the Sponsor in RTF and PDF format.

4.4 Study Participants

4.4.1 Analysis Sets

Randomized Analysis Set (RAS):

All eligible participants who have signed informed consent and assigned a randomization number, regardless of whether they actually received IMP.

Safety Analysis Set (SAF):

All participants who receive any amount of study intervention will be included in the Safety Set. Participants will be analyzed according to the study intervention received.

Pharmacokinetic Analysis Set (PKAS):

All treated participants for whom the PK profile of ALXN1910 can be adequately characterized will be included in the PK Set. PK analyses will be based upon the study intervention received.

Pharmacodynamic Analysis Set (PDAS):

All treated participants for whom the PD profile of ALXN1910 can be adequately characterized will be included in the PD Set.

ADA Analysis Set (ADAAS):

All randomized/enrolled participants who receive at least 1 dose of the study intervention and who after the dose have at least 1 reportable ADA result. Participants will be analyzed according to the study intervention they actually received.

A summary table with the number of participants in each of the analysis set will be provided and this table will be displayed by dose cohort, including pooled placebo, pooled active treatment across cohorts, pooled IV cohorts, pooled SC cohorts and overall. A listing of participants excluded from analysis sets will also be provided including reason of exclusion for RAS.

4.4.2 Disposition of Participants

A clear accounting of the disposition of all participants who enter the study will be provided, from screening to study completion.

A summary of participant study completion status and reason for study withdrawal will be provided for the RAS. This display will show the number and percentage of participants who withdrew from the study, including primary reasons for study withdrawal.

A summary of study treatment status will be provided for the RAS by dose cohort, including pooled placebo, pooled active treatment across cohorts, pooled IV cohorts, pooled SC cohorts and overall. This display will show the number and percentage of participants who have completed the study.

A by-participant listing of study discontinuation will be presented for the RAS. The listing will include dose date and reasons for study discontinuation, when applicable.

4.4.3 Protocol Deviations

All protocol deviations are predefined in the separate document, Protocol Deviation Specification.

4.4.3.1 Protocol Deviations with Non-PK Implications

The defined protocol deviations will be collected during the study period by site monitor/clinical team and programming team. All deviations related to study inclusion or exclusion criteria, conduct of the study, participant management or participant assessment, and handling of the participant's rights will be described.

4.4.3.2 Protocol Deviations with PK Implications

Protocol deviations that may potentially impact PK parameter derivations include, but are not limited to:

- IV administration deviations – interruption of administration, etc.
- Missed PK samples that impact estimation of PK parameter(s)
- Concomitant medications not authorized by protocol

- PK samples obtained out of allowance window that may impact the estimation of PK parameter(s)

Protocol deviations (mentioned in Sections 4.4.3.1 and 4.4.3.2) and analysis sets will be reviewed in the (blinded) data review meeting to decide inclusion or exclusion of participant(s) from analyses sets. Decisions regarding the exclusion of participants and/or participant data from analyses will be made prior to database lock and will be documented and approved.

A by-participant listing of major and minor protocol deviations will be provided including participant identifier, protocol deviation classification, and protocol deviation description and exclusion from specific analysis sets.

4.5 Demographics and Baseline Characteristics

The demographic characteristics (e.g., age, race, ethnicity, sex, height, body weight, body mass index [BMI]) will be summarized by dose cohort, including pooled placebo, pooled active treatment across cohorts, pooled IV cohorts, pooled SC cohorts and overall and listed by participant for the SAF.

Age, height, BMI, and weight will be summarized using the mean, SD, minimum, median, and maximum. The count and percentage will be computed for sex, race, and ethnicity. The summary table will be displayed by cohort and overall, for the SAF.

4.6 Medical and Surgical History

Medical and surgical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA®), Version 24.1(or higher) and assigned to a System Organ Class (SOC) and Preferred Term (PT).

A by-participant listing for medical and surgical history will be provided for the SAF.

A by-participant listing for substance use (drugs, alcohol, tobacco and caffeine) will be provided for the SAF.

4.7 Prior and Concomitant Medications

Medications will be considered as prior if the start date of the medication is before the date of administration of the first dose study drug.

Medications will be considered as concomitant if they are taken at least once in the treatment period starting from the first dose of study administration and up to the end of the study.

Medications starting prior to first administration of study drug and continuing during the study visit will be considered both prior and concomitant medication.

Prior and concomitant medication will be coded using the World Health Organization Drug Dictionary (WHO-DD Version Sept 2022) and will be classified by Anatomical Therapeutic Chemical (ATC) categories.

The number (percentage) of participants who take prior and concomitant medications will be summarized by dose cohort, including pooled placebo, pooled active treatment across cohorts, pooled IV cohorts, pooled SC cohorts and overall for the SAF by treatment, Anatomical Therapeutic Chemical (ATC) Classification, and WHO-DD PT.

By-participant listings of prior and concomitant medications will be provided for the SAF.

4.8 Treatment Exposure and Compliance

4.8.1 Treatment Exposure

A by-participant listing of participant exposure to study drug will be generated. The listing will include dose, volume, date and time, unit, formulation, and route.

4.9 Analysis Supporting Primary Objective(s)

Analysis for supporting primary objectives provided in Section 4.13.

4.10 Analysis Supporting Secondary Objective(s)

Analysis for supporting primary objectives provided in Section 4.12 and Section 4.14.

4.11 Efficacy Evaluation

Not applicable.

4.12 Pharmacokinetic Analysis, Concentration, and Parameter TFLs, and Statistical Analysis of Pharmacokinetic Parameters for Final Analysis

4.12.1 Pharmacokinetic Concentrations

Concentration Listings:

Pharmacokinetic concentration data for ALXN1910, will be listed by cohort, dose, day, route of administration (SC/IV), ethnicity category (Japanese/Non-Japanese), sex, age, weight, and participant for the SAF. Concentration listings will include nominal PK sampling time relative to dose administration or to start of infusion, actual sampling times relative to dose administration or actual sampling time relative to start of infusion, infusion duration, deviation from nominal time, and percent deviation from nominal time, and concentrations. Serum concentrations below the lower limit of quantification (LLOQ) will be presented as below the limit of quantification (BLQ) in the listings and the LLOQ value presented as a footnote. Missing PK samples will be reported as no sample (NS) or not reportable (NR) as appropriate and considered excluded from PK analysis.

Concentration Summary Tables:

Source data as reported from the laboratory will be used for calculation of concentration summary statistics. Tabular summaries for concentration-time data will report N (The number of Participants included in the pharmacokinetic analysis set for each treatment), n (number of participants with non-missing values), and n(BLQ) (the number of participants with BLQ samples).

Concentration for ALXN1910 will be summarized by cohort, dose and route of administration (SC/IV), and nominal timepoint for the PK set. The following descriptive statistics will be presented for Serum concentrations obtained at each nominal time point: N, n, n(BLQ), arithmetic mean, SD, coefficient of variation (CV%), geometric mean, geometric CV% (calculated as: gCV% =SQRT(e^{s^2}-1)*100; where s is the SD of the log-transformed values), median, minimum, and maximum values.

For summary tables, all BLQs will be considered zero, and the number of BLQs at each scheduled time point will be reported. Summary statistics will not be calculated if non-BLQ concentrations at a scheduled time point is <3 and will be reported as NC (not calculated).

The rules followed for calculation and presentation of concentration data with regards to the number of decimal places/significant digits for the listings of participant level concentrations and summary tables of concentration are as follows:

Concentration Listings and Tables	Rounding
Individual concentrations	*n* s f. as supplied by bioanalytical laboratory
Minimum and Maximum	*n* s.f. capped at 4
Mean/SD/Median/Geomean	*n+1* s.f. capped at 4
CV%/gCV%	*1* d.p.
N/n	Whole number

s.f = significant figures, d.p. = decimal place

Concentration Figures:

For arithmetic mean linear/linear graphs, all BLQ values will be substituted with zero for calculation of arithmetic mean and for log/linear graphs the log transformed arithmetic mean will be displayed (this should not include zero).

For individual linear/linear and log/linear graphs all BLQ values will be substituted as follows:

- BLQs at the beginning of a participant profile (i.e., before the first incidence of a measurable concentration) will be assigned to zero (except for intravenous administration when these BLQs should not be displayed). When using log/linear scale, these timepoints will be considered missing.
- BLQs at the end of a participant profile (i.e., after the last incidence of a measurable concentration) will be set to missing.
- Single BLQs which fall between two measurable concentrations will be set to missing.
- Consecutive BLQs which fall between measurable concentrations will be set to missing. Measurable concentrations after consecutive BLQs will be set to missing.

To visualize participant-level concentrations and the comparison between dose cohorts, Japanese/Non-Japanese or routes of administration (SC/IV) groups for each treatment, the descriptive PK graphs listed below will be generated. Include LLOQ line in individual and summary plots.

- Figure x.x.x: Individual participant profiles for ALXN1910 Serum Concentration versus Actual Time – (Linear Scale and Semi-Logarithmic Scale) (SAF) (show dose cohort, route of administration (SC or IV), Japanese/Non- Japanese and ADA response categories i.e. ADA negative, ADA positive- Pre-existing Immunoreactivity, ADA positive- Treatment-emergent, ADA responses and ADA positive- Treatment-boosted ADA responses for each profile)

- Figure x.x.x : Overlaid individual participant profiles for ALXN1910 Serum Concentration versus Actual Time – (Linear Scale and Semi-Logarithmic Scale) (SAF) by cohort (show cohort, dose, route of administration (SC or IV) or Japanese/Non- Japanese for each plot
- Figure x.x.x : Overlaid individual participant profiles for ALXN1910 Serum Concentration Actual Time Data by cohort with lines color coded by ADA response category i.e. ADA negative, ADA positive- Pre-existing Immunoreactivity, ADA positive- Treatment-emergent/Treatment-boosted ADA responses (show cohort, dose, route of administration (SC or IV) or Japanese/Non-Japanese for each plot)– (Linear Scale and Semi-Logarithmic Scale) (SAF)
- Figure x.x.x: Mean (± SD) ALXN1910 Serum Concentration versus Nominal Time grouped by dose cohort -Linear Scale and Semi-Logarithmic Scale) (PK set) (Different doses and formulations (i.v. and s.c.) will be plotted on the same graph, Non- Japanese only, but with differing colors/lines to distinguish the different treatment regimens).
- Figure x.x.x: Mean (± SD) ALXN1910 Serum Concentration Time Data grouped by Japanese /non-Japanese for the common SC dose (cohort 2 and cohort 4) -Linear Scale and Semi-Logarithmic Scale) (PK set) (show Japanese/Non-Japanese dose cohorts at the matching SC dose on the same plot but in different colors)

When presenting the mean semi-logarithmic plot, ± SD will be omitted.

Figures will be generated in color using unique line style and marker for each plot in the graph. For all PK concentration-time plots, linear scale will be used for x-axis (e.g., do not use an ordinal scale).

4.12.2 Pharmacokinetic Parameters

PK parameters will be provided by CPMS group. PK parameters will be calculated by NCA methods from the concentration-time data using Phoenix® WinNonlin® Version 8.0 or higher following these guidelines:

- Actual time from dose (SC administration) or from start of infusion (for IV administration) will be used in the calculation of all derived pharmacokinetic parameters, except when parameters are calculated for safety/dose escalation meetings when nominal times may be used to calculate PK parameters.
- There will be no imputation of missing data.
- Handling of BLQ samples for derivation of serum PK parameters after single dose administration
    - BLQs at the beginning of a participant profile (i.e., before the first incidence of a measurable concentration) will be assigned to zero.
    - BLQs at the end of a participant profile (i.e., after the last incidence of a measurable concentration) will be set to missing.
    - Single BLQs which fall between two measurable concentrations will be set to missing.
    - Consecutive BLQs which fall between measurable concentrations will be set to missing. Measurable concentrations after consecutive BLQs will also be set to missing.

Pharmacokinetic parameters will be estimated according to the guidelines presented in Table 3.

Table 3 Pharmacokinetic Parameter and Estimation

Parameter	Guideline for Derivation
C_{max}, t_{max},	Obtained directly from the observed concentration-time data
AUC_t	The AUC from zero time (pre-dose) to the time of last quantifiable concentration will be calculated by a combination of linear and logarithmic trapezoidal methods. Unless specifically requested and justified, the linear up/log down trapezoidal method will be employed. The AUC_t is the sum of areas up to the time of the last quantifiable sample: $AUC_t = \int_0^t C_{last} * dt$
$AUC_{0\text{-}168}$	The AUC from zero time to the specific time x is the sum of areas up to the specific time x sample: $AUC_{0\text{-}168} = AUC_{0-x} = \int_0^x Cx * dx$
AUC_∞	The area from zero time extrapolated to infinite time will be calculated as follows: $AUC_\infty = AUC_t + \frac{C_{last}}{\lambda_z}$ where C_{last} is the last observed quantifiable concentration.
$\%AUC_{ex}$	The percentage of $AUC_{0\text{-}inf}$ obtained by extrapolation will be calculated as follows: $\%AUC_{ex} = \frac{AUC_\infty - AUC_{0\text{-}t}}{AUC_\infty}$ x100 . Unless otherwise determined by PK Scientist's best knowledge and judgment, if the $\%AUC_{ex}$ is greater than 30%, the value, $\%AUC_{ex}$, will be flagged and all dependent parameters (ie, AUC_∞, V_d/F and CL/F (SC) or V_d and CL (IV) will be flagged in listings and excluded from summary tables and statistical analysis of PK parameters, unless instructed otherwise by the Sponsor. In the case that $20\% \leq \%AUC_{ex}, \leq 30\%$, the parameter together with all derived parameters will be flagged in listings. The reason for flagging/exclusion will be listed/footnoted in parameter listings.
λz and t½	1. The apparent terminal phase rate-constant (λz) will be estimated by linear regression of concentration versus time data presented in a log-linear scale. 2. Data are primarily monotonically decreasing in magnitude and are representative of the actual decline in the log concentration-time curve. 3. Only those data points that are judged to describe the terminal log-linear decline will be used in the regression. 4. A minimum number of three data points in the terminal phase will be used in calculating λz with the line of regression starting at any post-C_{max} data point (C_{max} should not be part of the regression slope). Unless otherwise determined by PK Scientist's best knowledge and judgment or if instructed by the Sponsor, if the adjusted correlation coefficient (R^2 adjusted) is <0.8, then λz and all the λz dependent parameters (i.e. t½, AUC_∞, CL/F and V_d/F (SC admin.) or CL and V_d (IV admin) will be flagged in listings and excluded accordingly from summary tables and statistical analysis of PK parameters. $\%AUC_{ex}$ will be flagged, but not excluded. In the case of $0.8 \leq R^2 < 0.9$, λz and all the λz dependent parameters will be flagged. The reason for flagging/exclusion will be listed/footnoted in parameter listings. 5. Unless otherwise determined by PK Scientist's best knowledge and judgment, the interval used to determine λz should be equal or greater than 1.5-fold the estimated t½, and if less than 1.5-fold, λz will be flagged in listings and might be excluded (based

Parameter	Guideline for Derivation
	on sponsor specific requirements) from summary tables and statistical analysis of PK parameters. All the derived parameters (i.e. $t_{½}$, AUC_{∞}, CL/F and Vd/F (SC) or CL and V_d (IV)) may also be flagged in listings and excluded from statistical analysis of PK parameters. $\%AUC_{ex}$ may also be flagged in listings, but not excluded. The reason for flagging/exclusion will be listed/footnoted in parameter listings. 6. The $t_{½}$ will be calculated as follows: $t_{½} = \ln 2/\lambda z = 0.693/\lambda z$ 7. Data points may be dropped from the linear regression if the PK Scientist considers the reported values to be anomalous. Any data points so designated should remain in the listings with a footnote and be identified in the study report with a rationale for exclusion.
CL or CL/F	Following IV or SC administration, systemic clearance of parent drug will be calculated from: $CL \text{ or } CL/F = \frac{Dose}{AUC_{\infty}}$ CL for IV cohorts and *CL/F for SC cohorts*
V_d or V_d/F	Volume of distribution at terminal phase following either intravascular or subcutaneous dosing may be calculated from: $V_d \text{ or } V_d/F = \frac{Dose}{\lambda_z \times AUC_{\infty}} = CL / \lambda_z \text{ or } (CL/F)/\lambda_z$ Vd for IV cohorts and Vd*/F for SC cohorts*
DNC_{max}, $DNAUC_t$ and $DNAUC_{\infty}$	Parameter value divided by dose

PK Parameters Listings:

PK parameters will be listed by participant, cohort, dose, administration route and Japanese/non-Japanese for the SAF. PK parameters that will be flagged and/or excluded from summary tables and statistical analyses of PK parameters will be flagged and footnoted with the reason for flagging/exclusion.

PK Parameter Summary Tables:

Biostatistics group will consider the derived PK parameters as source data and will use this data without rounding for calculation of PK parameters summary statistics tables.

PK parameters will be summarized by cohort, dose and route of administration (SC /IV), as appropriate for the PK set. Tabular summaries for PK parameters will report N (The number of Participants included in the pharmacokinetic analysis set for each treatment) and n (number of subjects with a specific parameter).

Descriptive statistics for calculated PK parameters will include N, n, arithmetic mean, SD, CV%, geometric mean, gCV%, median, minimum, and maximum values. For t_{max}, only N, n, median,

minimum, and maximum values will be presented. No descriptive statistics will be determined when fewer than three individual PK parameters are available.

The rules followed for presentation of PK parameters data with regards to the number of decimal places/significant digits for the listings of participant level PK parameters and summary tables of PK parameters are as follows:

PK Parameter Listings and Tables	Rounding
Derived Individual parameters	3 s f.
Directly Derived Individual parameters (C_{max}, C_{12}, C_{24})	*n* s.f. as supplied by the analytical laboratory but not more than 3 s f.
Minimum and Maximum	3 s f.
Mean/SD/Median/Geomean	4 s f.
CV%/gCV%	1 d.p.
Comparative estimates (e.g. ratios)	3 d.p.
CI and other percentages	2 d.p.
p-values	4 d.p.
N/n	Whole number
Exceptions for PK Tables	
t_{max} individuals and min/max	2 d.p
t_{max} median only	2 d.p

s.f = significant figures, d.p. = decimal place

PK Parameter Figures:

Scatter plots of individual PK parameters (C_{max}, AUC_{∞}, AUC_t) versus treatment cohort (x axis) with symbols for mean and median and box plots of dose-adjusted C_{max}, AUC_{∞}, AUC_t versus treatment cohort will be generated for :

- Different doses and formulations (i.v. and s.c.) plotted on the same graph, non-Japanese only, (cohorts 1, 2, 3, 5 and 6; show on the x axis cohort, dose, route of administration).
- Japanese and Non-Japanese SC cohorts at the matching dose (cohort 2 and Cohort 4; show on the x axis cohort, dose, route of administration and Japanese /Non-Japanese).

Scatter plots of C_{max}, AUC_{∞}, AUC_t versus ADA response categories (ADA- negative, ADA positive -Pre-existing Immunoreactivity, ADA positive- Treatment-emergent ADA responses and ADA positive- Treatment-boosted ADA responses) will be also generated by cohort, if there is sufficient number of participants in multiple ADA response categories (i.e. not all/almost all participants with the same ADA response category).

4.12.3 Interim Pharmacokinetic Analysis to Support SRC Dose Escalation Decisions

Cohort PK analysis is the responsibility of the CPMS group. The SRC will review blinded PK data (only for dose escalation from Cohort 2 to Cohort 5 and from Cohort 5 to Cohort 6) before dose escalation. Concentration data will be obtained directly from the bioanalytical laboratory Charles River Lab as per data transfer agreement in a unblinded manner. Phoenix® WinNonlin® version 8.0 or higher will be used to create an analysis ready dataset to conduct non-compartmental analysis (NCA) and to generate plots and tables for the blinded cohort PK analysis report to be discussed in the dose escalation/safety meeting. QCed (not QAed) concentration data from the bioanalytical laboratory, as agreed upon in data receipt agreement (DRA), will be used for PK analysis. All concentrations prior

to the first measurable concentration will be set to 0 and all concentrations within the individual profile, and after the last measurable concentration in a profile will be set to missing to create an analysis-dataset for non-compartmental analysis, as well as for creating tables and figures. Nominal time from dose or from start of infusion (not actual time) will be used to calculate PK parameters. PK parameters described in the SAP will be calculated as data permit. Linear-log trapezoidal rule will be used to calculate PK parameters. Individual linear and semi-log participant plots by dose group, and linear and semi-log arithmetic mean concentration (+/- SD) versus time plots will be created by dose group. Individual and summary concentration and parameters will be tabulated. Box plots of C_{max} and AUC or of dose normalized C_{max} and AUC may be plotted to visualize dose linearity and proportionality. No exclusions may be made to create descriptive summary tables. The blinded interim PK report will not reveal individual participant's treatment assignments. Anonymized individual and summary data will be reported in the interim PK report to maintain blinding. Alias numbers will be used in place of actual subject numbers to present individual PK data. Placebo data will not be included in the blinded interim PK report.

In the event of one or more missing samples (from the subjects on active treatment only), to keep the blind, these will be replaced with the mean value or mean and median values, respectively, of the available data at that sampling time point and summary statistics will be computed and reported in tables including these imputed samples. In case of one missing subject's profile (e.g. incomplete cohort of at least 7 subjects or in case of incomplete PK set of a subject (active or placebo) due to discontinuation), only data for a maximum of 5 subjects on active treatment will be provided to avoid unblinding. Parexel team will ensure the subject with the highest concentrations will not be removed.

4.12.4 Statistical Analysis of Pharmacokinetic Parameters

❖ **Assessment of Absolute Bioavailability**

The absolute bioavailability (F) for the ALXN1910 SC cohorts will be defined by the ratio of the geometric means for the area under the serum concentration-time curve from time 0 (dosing) to infinity parameter for the ALXN1910 SC cohort (cohort 2, 15 mg) over the ALXN1910 IV cohort (cohort 3, 15 mg).

A mixed effect model will be performed to the ln-transformed AUC_{∞} and the independent variables will include fixed effects for treatment and participant as a random effect. Geometric least-squares means for each treatment (SC or IV), point estimates and associated 95% CIs for the ratios for AUC_{∞} will be produced in tabular format. This will be anti-log transformed to obtain the point estimates and the 95% CI for the geometric mean ratio on the original scale. Estimates of between -participant variability (%CV) will also be provided.

SAS code for this analysis is mentioned in Section 6.5.

❖ **Assessment of Dose Proportionality**

Power model using linear regression method:

Dose proportionality will be assessed for sc cohorts, Non-Japanese only, for C_{max} and AUC (AUC_t, AUC_{∞}) using the PKAS who received single dose of ALXN1910 SC (Cohort 2, 5, and 6). PK parameters will be used to perform a LS linear regression analysis, using the formula ln_PK parameter =A× ln_dose + B, where 'ln PK Parameter' represents the natural log transformed C_{max} and AUC parameters and 'ln_dose' represents the natural log-transformed dose, A is the slope of the regression line and B is the intercept of the lines. The estimate obtained for A is a measure of dose proportionality.

An estimate of the slope and intercept of the regression line and corresponding 95% CI will be obtained for each PK parameter (C_{max}, AUC_t, and AUC_∞).

SAS code for this analysis is mentioned in Section 6.5.

Dose-proportionality based on the power model will be accepted ("not rejected", in terms of statistical inference) if the 95% CIs of the slope does not include 0 for each PK parameter.

Figure for Dose-Proportionality with 95% CI will be presented.

❖ **Assessment of Ethnicity Comparison**

The PK parameters for ALXN1910 will be evaluated for Japanese and non-Japanese participants (Cohort 2 versus Cohort 4) on active treatment, using an analysis of variance statistical model with cohort as the fixed effects on the natural logarithms of the data. In addition, the Japanese versus non-Japanese cohorts will be evaluated using descriptive statistics; for each cohort, the geometric means and the associated 95% CIs of difference of PK parameters will be reported.

PK parameters will be separately analyzed using a mixed effects model. The dependent variable will be the log-transformed PK parameters of interest (AUC_∞, AUC_t and C_{max}) and the independent variables will include a fixed effect for ethnicity (Japanese vs non-Japanese) and participant as a random effect.

The estimated difference and CI obtained on the log scale will be exponentiated to provide an estimate of the Japanese to non-Japanese ratio and its associated 95% CI. Estimates of between -participant variability (%CV) will also be provided.
Plots of adjusted GMR of Japanese to non-Japanese together with 95% CIs will be produced.

SAS code for this analysis is mentioned in Section 6.5.

4.12.5 Pharmacodynamic Analysis, Concentration, and Parameter TFLs, and Statistical Analysis of Pharmacodynamic Parameters

Individual participant PPi versus time profiles values, both observed and change from baseline, will be calculated by Charles River Lab and Individual participant PLP, PL, PA versus time profiles values, both observed and change from baseline, will be calculated by PPD Laboratories respectively. Baseline observed, observed, change from baseline, and percent change from Baseline PPi, PLP, PL, PA versus time profiles values will be listed by treatment, sampling time and participant. Listings will include actual sampling times relative to dose administration, observed PPi, PLP, PL, PA versus time profiles value, change from baseline value, and percentage change from baseline. Baseline will be taken as the last measurement prior to dosing, see Section 6.1 Descriptive statistics (number, mean, SD, CV%, minimum, median, and maximum) will be presented by dose cohort, including pooled placebo, pooled active treatment across cohorts, pooled IV cohorts, pooled SC cohorts and overall for absolute, and percentage change from baseline PD assessment, time of minimum and time of maximum will only have minimum, maximum, and median time.

To visualize the comparison between participants and treatments the following descriptive PD graphs will be generated.

- Figure x.x.x: Overlaid Participant Profiles for PPi, PLP, PL, and PA Time Profile Data (Observed, Change from Baseline, and percent change from Baseline)
- Figure x.x.x: Mean (± SD) PPi, PLP, PL, and PA Time Profile Data (Observed, Change from Baseline, and percent change from Baseline)

For each figure, participants belonging to each category will be shown on the same plot with separate figures for each level of dose. Participant level figures will use actual time, while mean plots will use planned time, except for predose time point(s), where time 0 will be used rather than actual time.

4.12.5.1 Pharmacodynamics Analysis and Tables, Figures, and Listings

All PD analyses will be performed on the PD Analysis Set and will be reported by each cohort. Observed values and changes from baseline in plasma concentrations of PPi, PLP, PL, and PA versus time will be presented graphically by treatment over time compared with placebo-treated participants.

The PD parameters for ALXN1910 will be evaluated over time for Japanese and non-Japanese participants (Cohort 2 versus Cohort 4) on active treatment by using MMRM model with cohort, visit, and cohort by visit interaction as fixed effects, participant as a random effect, and baseline value as a covariate. The unstructured covariance structure will be employed; however, if the model fails to converge, Toeplitz, heterogeneous compound symmetry, and compound symmetry covariance structure will be applied in the order listed until the model converges.

In the case that all covariance structures fail to converge, the analysis of variance statistical model with baseline and cohort as the fixed effects will be used. In addition, the Japanese versus non-Japanese cohorts will be evaluated using descriptive statistics; for each cohort, the geometric means and the associated 95% CIs of difference of PD parameters in observed value and CFB value will be reported. Figures of absolute values and change from baseline over time may be produced if needed.

4.13 Safety Evaluation

All safety summaries and analyses will be based upon the SAF as defined in Section 4.4.1 unless otherwise specified in specific section.

All summaries will be provided by cohort and placebo across cohorts will be pooled.

In addition, the summary tables will be presented for by dose cohort, including pooled placebo, pooled active treatment across cohorts, pooled IV cohorts, pooled SC cohorts and overall.

4.13.1 Adverse Events

All outputs for AEs/treatment-emergent adverse events (TEAEs) will be based on the SAF unless specified separately in TLF shells. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), version 24.1 or latest.

All AE summaries should provide the number and percentages of participants reporting at least one AE and the total number of events reported.

Summaries of AEs will include the following:

- Incidence of TEAEs (by dose and by cohort and overall, SOC, and PT)
- Incidence of TEAEs by highest relationship (by cohort and overall, SOC, and PT)
- Incidence of TEAEs by worst severity (mild/moderate/severe/life threatening/fatal, by cohort and overall, SOC, and PT)

Summary tables will contain counts of participants, percentages of participants in parentheses, and the number of events where applicable. A participant who has multiple events in the same SOC and PT will be counted only once in the participant counts, but all events will be included.

All Adverse Events (AEs)

All AEs will be listed including pretreatment AEs.

Treatment-emergent Adverse Event (TEAE)

A TEAE will be defined as any AE that emerges during treatment (i.e., an AE that started after study drug administration or pre-existed that worsened in severity after study drug administration) and will be analyzed for the purpose of safety analysis.

TEAEs will be summarized by SOC and PT, including the number and percentage of participants experiencing events, separately.

A by-participant listing of all TEAEs leading to withdrawal from the study will be provided.

Severity

TEAEs will be summarized by SOC, PT, and severity, including the number and percentage of participants experiencing events. If a participant reports the same TEAE more than once within that SOC and PT, the TEAE with the highest severity will be used in the corresponding severity summaries.

In summaries including severity, the following intensity categories will be summarized as per CTCAE version 5.0 published 27 Nov 2017: 'Mild', 'Moderate', 'Severe' ,'Life-threatening', 'Fatal'. Participants who experience the same event multiple times will be included in the most severe category. Events with missing intensity will be considered as 'Severe' events for summary purposes but recorded as missing in the listings.

If severity is reported by Common Terminology Criteria for Adverse Events (CTCAE) grade, then summary of severity will be presented using CTCAE grade.

Relationship (Causality)

TEAEs will be summarized by SOC, PT, and causality, including the number and percentage of participants experiencing events. Relationship to study drug will be tabulated respectively. If a participant reports the same TEAE more than once within that SOC and PT, the TEAE with the strongest relationship to study drug will be counted. In summaries including relationship to study treatment, the following relationships will be summarized: 'Not related', 'Related'. Participants who experience the same event multiple times will be included in the most related category. Events with missing relationship will be considered as 'Related' to the last given study drug for summary purposes but recorded as missing in the listings.

Adverse Events of Special Interest (AESI)

Adverse events of special interest (AESI) will be summarized by SOC and PT, including the number and percentage of participants experiencing events. Listing of AESI will be provided.

4.13.2 Deaths, Serious Adverse Events, and Other Significant Adverse Events

A by-participant listing of all serious adverse events will be created. These may include the following listings:

- A by-participant listing of all TESAEs leading to withdrawal from the study

Listings should follow the format described for AEs in Section 4.13.1 if appropriate.

4.13.3 Clinical Laboratory Evaluation

Clinical laboratory test results of hematology, clinical chemistry, coagulation, urinalysis, urinary drug screening will be provided by participant. A list of laboratory assessments is included in Section 6.3. Individual data listings of all the laboratory results will be presented for each participant.

All TLFs will display only the standard international (SI) units after conversion by means of standard conversion factors.

Quantitative clinical laboratory variables, i.e., hematology, biochemistry, and urinalysis will be summarized using descriptive statistics (n, mean, SD, minimum, maximum and median) by dose cohort, including pooled placebo, pooled active treatment across cohorts, pooled IV cohorts, pooled SC cohorts and overall , by visit. Additionally, a within-participant change will be calculated as the post-baseline measurement minus the baseline measurement and summarized in the same way.

Any quantitative laboratory parameters that are given as '<xx' or '>xx' in the database will be imputed with the absolute value of the number without the sign (e.g., <2.2 will be imputed as 2.2) for the calculation of the changes from baseline and for the descriptive statistics. In the listings, no imputations will be performed, and all data will be displayed as recorded in the database.

Each laboratory result will be classified as low (L), normal (N), or high (H) at each time point according to the laboratory supplied reference ranges. For hematology and biochemistry, shift tables will be presented showing the number and percentage of participants with shifts from baseline to each postdose time point. Tabulations will be presented by treatment cohort.

Measurements obtained at Screening and EOS will not be included in the shift tables.

Frequency tabulations of qualitative clinical laboratory variables (urinalysis) will be presented by treatment cohort and time-point.

All laboratory data will be displayed in listings.

Laboratory abnormalities that are considered clinically significant (CS) are recorded in the database as AEs.

Results of pregnancy tests (females only), serology, drugs of abuse and alcohol tests will be listed only.

4.13.4 Vital Signs

A by-participant listing of all vital sign measurements (including weight) and change from baseline will be presented.

This listing will include a flag for measurements identified as treatment-emergent markedly abnormal (TEMA)/potentially clinically significant (PCS) as calculated by the criteria outlined in Table 4.

Measured (observed) values including changes from baseline will be summarized by cohort and time point and by vital sign parameter (Oral temperature, pulse rate, respiratory rate, and systolic and diastolic blood pressure (mm Hg)).

Measurements obtained at Screening will not be included in the shift tables or in the tabulations of descriptive statistics.

Measurements obtained prior to dosing will be included in the tabulations for the treatment received in that specific treatment cohort.

Table 4 TEMA/PCS Criteria for Vital Signs

Variable	Unit	Criterion	
		Low	High
Systolic blood pressure	mmHg	≤ 80 mmHg and ≥ 20 mmHg decrease from Baseline	≥ 140 mmHg and ≥ 20 mmHg increase from Baseline
Diastolic blood pressure	mmHg	Value ≤ 60 and ≥ 15 decrease from Baseline	Value ≥ 90 and ≥ 15 increase from Baseline
Pulse rate	bpm	Value ≤ 40 and ≥ 15 decrease from Baseline	Value ≥90 and ≥15 increase from Baseline

Note: The change in measurement (increase or decrease) will be calculated relative to the value obtained at baseline.

Both conditions must be satisfied for a measurement to be considered potentially clinically significant; bpm = Beats per minute.

Box plot of vital sign parameters over time will be presented for systolic BP, diastolic BP, and pulse rate.

4.13.5 ECG

Standard safety 12-lead ECGs will be performed as shown in the Section 6.1.

The following ECG parameters will be recorded:

Heart rate (HR) (beats per minute [bpm])

PR interval (msec)

QRS interval (msec)

QT interval (msec)

QTc interval (msec)

QTcF interval (msec)

The ECG will be evaluated by the Investigator as 'Normal', 'Abnormal, NCS' or 'Abnormal, CS'.

All ECG parameters will be listed by participant including changes from baseline by dose cohort, including pooled placebo, pooled active treatment across cohorts, pooled IV cohorts, pooled SC cohorts and overall.

Baseline is defined in Section 4.2.4.

Descriptive statistics for absolute values and changes from baseline will be presented by cohort. A categorical QTc analysis will also be performed.

Measurements obtained at Screening will not be included in the shift tables.

A summary of the number and percentage of participants with the following QT/QTc intervals of ECG parameters will be displayed in a frequency table at each visit by dose cohort, including pooled placebo, pooled active treatment across cohorts, pooled IV cohorts, pooled SC cohorts and overall cohort:

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

The listing of ECG abnormality will be presented separately.

Mean of the triplicates for ECG measurements will also be presented in the listing and used for deriving baseline and change from baseline.

4.13.6 12-Lead Holter ECG

Not applicable.

4.13.7 Physical Examination

Physical examinations will be performed as shown in the Section 6.1.

The full physical examination includes an assessment of general appearance and a review of systems (dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, neurologic systems).

The brief physical examination includes an assessment of the general appearance, skin, abdomen, cardiovascular system and lungs.

Clinically significant physical examination findings will be listed.

4.13.8 Daylight Saving Time (DST):

DST is not implemented at clinbase level, hence not applicable.

4.13.9 Safety Monitoring (Safety Review Committee)

The blinded SRC, consisting of the Investigator, Medical Monitor, Drug 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. Decisions to continue, modify (explore the dose cohort further), or escalate dosing will be made by the Investigator and/or SRC.

The SRC will meet at minimum to support each cohort dose escalation after review of blinded data. Where review of unblinded data may be necessary in the event of emerging safety signals, additional ad hoc meetings will be scheduled without the Investigator/site staff in attendance. If dosing is stopped because of a safety event, continuation of the cohort and/or study will require a substantial amendment.

4.14 Immunogenicity Analysis

All ADA analyses will be performed on the Immunogenicity Analysis Set Population .

Participants in the placebo group will be pooled from each cohort for the summary analysis. ADA titer values will be summarized descriptively by dose cohort, including pooled placebo, pooled active treatment across cohorts, pooled IV cohorts, pooled SC cohorts and overall , by visit. Summary of ADA response to investigation product by visit and dose cohort, including pooled placebo, pooled

active treatment across cohorts, pooled IV cohorts, pooled SC cohorts and overall ADA response will be provided. A listing for immunogenicity analysis which including sampling date, time, day, ADA response category, ADA titer level and ADA maximum titer level will be presented.

4.15 Biomarkers

Biomarker assays may be conducted as exploratory analyses on collected whole blood samples and the data used for research (eg, exploratory) related to ALXN1910. The results of biomarker analyses may be reported in the CSR or in a separate study summary.

4.16 Handling of Dropouts or Missing Data

No imputation of missing data will be performed except for partial dates imputation mention in Section 6.2.

4.17 Subgroup Analysis

No subgroup analysis is planned for the study.

4.18 Planned Interim Analyses

Interim analyses will not be conducted for this study.

4.19 Changes in the Conduct of the Study or Planned Analysis

The ADA titer categories analysis is removed as categories based on quartiles is not informative due to the small number of study participants.

5 REFERENCES

Software:

[4] SAS® Version 9.4 of the SAS System for Personal Computers. Copyright © 2002-2003. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

[5] Phoenix®WinNonlin® Software Version 8.0 or higher. https://www.certara.com

6 APPENDICES

6.1 Schedule of Assessments

Table 5 Schedule of Assessments-Single Ascending Dose Cohorts (Screening through Day 5)

Study Day[a]	**Screen -ing**	**Day -1**	**Day 1**							**Day 2**		**Day 3**		**Day 4**		**Day 5**
Assessments	**D -29 to D-2**	**Admit**	**Predose**	**0 h I/ SOI**	**30 min post I/SOI**	**2 h post I/SOI**	**4 h post I/SOI**	**8 h post I/SOI**	**12 h post I/SOI**	**24 h post I/ SOI**	**36 h post I/ SOI**	**48 h post I/ SOI**	**60 h post I/ SOI**	**72 h post I/ SOI**	**84 h post I/ SOI**	**96 h post I/SOI**
Status (OP or CRU)	**OP**	**CRU**														
Admission		X														
Discharge																X[b]
Informed consent[c]	X															
Inclusion/exclusion[d]	X	X														
Medical history[e]	X															
Demographics	X															
Height, weight, and BMI[f]	X	X														
Hepatitis B and C screen	X															
HIV (Types 1 and 2) screen	X															
Follicle-stimulating hormone[g]	X															
Urine alcohol test	X	X														
Urine drug screen	X	X														
Serum pregnancy test[h]	X															
Urine pregnancy		X														

test[h]																
Study Day[a]	**Screen -ing**	**Day -1**	**Day 1**							**Day 2**		**Day 3**		**Day 4**		**Day 5**
Assessments	**D -29 to D-2**	**Admit**	**Predose**	**0 h I/ SOI**	**30 min post I/SOI**	**2 h post I/SOI**	**4 h post I/SOI**	**8 h post I/SOI**	**12 h post I/SOI**	**24 h post I/SOI**	**36 h post I/SOI**	**48 h post I/SOI**	**60 h post I/SOI**	**72 h post I/SOI**	**84 h post I/SOI**	**96 h post I/SOI**
Status (OP or CRU)	**OP**	**CRU**														
Randomization[i]			X													
Study intervention administration (ALXN1910 or placebo)				X												
Injection/infusion site evaluation[j]				X			X			X		X		X		X
Physical examination	X	X														
Brief physical examination[k]										X		X				X
Vital sign measurements[l]	X		X		X	X	X	X	X	X		X		X		X
ECG[m]	X		X		X	X	X	X	X	X	X	X		X		X
Chemistry[n]	X	X								X						X
Hematology[n]	X	X								X						X
Coagulation[n]	X	X								X						X
Urinalysis[n]	X	X								X						X
PK[o]			X		X	X	X	X	X	X		X		X		X

PD (PPi, PLP, PL, and PA)			X							X		X				X

Study Day[a]	**Screen -ing**	**Day -1**			**Day 1**					**Day 2**		**Day 3**		**Day 4**		**Day 5**
Assessments	**D -29 to D-2**	**Admit**	**Predose**	**0 h I/ SOI**	**30 min post I/SOI**	**2 h post I/SOI**	**4 h post I/SOI**	**8 h post I/SOI**	**12 h post I/SOI**	**24 h post I/SOI**	**36 h post I/SOI**	**48 h post I/SOI**	**60 h post I/SOI**	**72 h post I/SOI**	**84 h post I/SOI**	**96 h post I/SOI**
Status (OP or CRU)	**OP**				**CRU**											
Urine for calcium, phosphorus, and creatinine[p]			X							X		X				X
Immunogenicity samples[q]			X													
Hypersensitivity reactions[r]				←Monitor continuously after dose→												
Hypersensitivity reaction laboratory tests (tryptase & complement C5b-9)[s]			X	←See footnote[r]→												
Concomitant medications	←Monitor continuously (after ICF is signed at Screening)→															
Adverse events review and evaluation	←Monitor continuously (after ICF is signed at Screening)→															

Note: When scheduled at the same timepoint, the triplicate ECG should be performed first, followed by vital signs assessments, and then PK/PD sampling.

[a] Permissible window for study assessments are described in the Windows Allowance Document.
[b] Participants will be discharged from the CRU after completing all Day 5 assessments. Due to the time needed for turnaround of laboratory test results, discharge will actually occur on Day 6.
[c] A signed and dated IEC-approved ICF must be obtained before any study-specific screening procedures are performed.
[d] Recheck clinical status before randomization and/or dose of study intervention.
[e] Including substance usage (drugs, alcohol, tobacco, and caffeine) and past/current medical conditions.
[f] Height and BMI only at Screening.
[g] Only female participants claiming postmenopausal status will have a follicle-stimulating hormone test to confirm postmenopausal status.
[h] All female participants will have a pregnancy test (serum at Screening and urine on Day -1) to confirm the participant is not pregnant. Any female participant who becomes pregnant while participating in the study will be withdrawn.
[i] Randomization will occur predose on Day 1.
[j] Injection/infusion site evaluations will be performed within 15 minutes after I/SOI and ± 15 minutes at 4 and 24 hours post I/SOI. See Protocol Section 10.5 for additional details.
[k] Brief physical examination to be conducted at discharge from the CRU.
[l] At Screening, supine and standing (orthostatic) blood pressures will be performed according to the CRU's typical procedure to exclude participants who are prone to orthostatic hypotension.
[m] Each ECG timepoint during the study will be 12-lead and performed in triplicate sequentially within 5 minutes, at least 1 minute apart after 10 minutes of bedrest in supine position (note, no bedrest is required post ECG), at 90, 75, and 60 minutes before dosing. ECGs should not be performed after any major meal (i.e., major meals should be withheld until after ECG assessments).
[n] Investigators should review Day 5 laboratory results to ensure each participant is suitable for discharge.
[o] The IV dose cohorts will also have an end-of-infusion PK time point.
[p] Spot urine collection.
[q] Sample for ADA assessments will be collected prior to administration of the drug. In the event of suspected SAE like hypersensitivity or anaphylaxis, additional samples may be collected for ADA assessments at or near the event.
[r] See Protocol Section 10.4 for details.
[s] Collect 3 lab samples after a suspected hypersensitivity reaction: as soon as possible and at 2 and 8 hours after the suspected reaction (+ 1 hour window for each sample). If the suspected hypersensitivity reaction persists beyond 8 hours, the CRU should contact the Medical Monitor for guidance. Predose samples will only be analyzed for participants with a reported suspected hypersensitivity reaction.
Abbreviations: ADA = antidrug antibody; BMI = body mass index; C5b-9 = terminal complement complex; CRU = clinical research unit; ECG = electrocardiogram; h = hours; HIV = human immune deficiency virus; I = injection; ICF = informed consent form; IEC = Independent Ethics Committee; OP = outpatient; min = minutes; PA = pyridoxic acid; PD = pharmacodynamic; PK = pharmacokinetic; PL = pyridoxal; PLP = pyridoxal 5′-phosphate; PPi = inorganic pyrophosphate; SOI = start of infusion; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event

Schedule of Activities – Single Ascending Dose Cohorts (Day 6 through Day 75)

Study Day[a]	**Day 6 post I/SOI**	**Day 7 post I/SOI**	**Day 8 post I/SOI**	**Day 15 post I/SOI**	**Day 22 post I/SOI**	**Day 29 post I/SOI**	**Day 36 post I/SOI**	**Day 43 post I/SOI (EOS/ED**[b]**)**	**Day 75 post I/SOI (EOS/ED**[b]**)**
Status (OP or CRU)	**OP**								
Full physical examination								X	X
Brief physical examination			X	X		X			
Vital sign measurements[c]			X	X		X		X	X
12-lead ECG (triplicate)[d]	X	X	X	X				X	X
Chemistry			X	X	X	X	X	X	X
Hematology			X	X	X	X	X	X	X
Coagulation			X	X	X	X	X	X	X
Urinalysis (via dipstick)			X	X	X	X	X	X	X
Urine pregnancy test[e]						X			
Serum pregnancy test[e]								X	X
PK	X	X	X	X	X	X	X	X	X
PD (PPi, PLP, PL, and PA)			X	X	X	X	X	X	X
Immunogenicity samples[f]						X		X	X
Urine for calcium, phosphorus, and creatinine[g]			X	X		X		X	X
Hypersensitivity reactions[h]	←Monitor continuously after dose→								
Hypersensitivity reaction laboratory tests (tryptase and complement C5b-9)[i]	←See footnote[h]→								
Concomitant medications	←Monitor continuously (after ICF is signed at Screening)→								
Adverse event review and evaluation	←Monitor continuously (after ICF is signed at Screening)→								

Note: When scheduled at the same timepoint, the triplicate ECG should be performed first, followed by vital signs assessments, and then PK/PD sampling.

[a] Permitted windows for study assessments are described in the Windows Allowance Document.

[b] EoS procedures will be performed on Day 75.. If possible, participants who withdraw/are withdrawn from the study should have an ED visit conducted at the time of discontinuation that includes the EoS assessments. All efforts will be made to contact participants who ED from the study via phone for a safety follow-up call approximately 30 days (4.5 half-lives) after their dose to assess AEs.

[c] Vital signs taken postdose will be performed before the coinciding blood collection, whenever possible.

[d] Each ECG will be 12-lead and performed in triplicate sequentially within 5 minutes, at least 1 minute apart after 10 minutes of bedrest in supine position (note, no bedrest is required post ECG). ECGs should not be assessed after any major meal (i.e., major meals should be withheld until after ECG assessments).

[e] Only female participants of childbearing potential will have a pregnancy testing to confirm the participant is not pregnant.

[f] Sample for ADA assessments will be collected prior to administration of the drug. In the event of suspected SAE like hypersensitivity or anaphylaxis, additional samples may be collected for ADA assessments at or near the event.

[g] Spot urine collection.

[h] See Protocol Section 10.4 for details.

[i] If the participant is in the clinic, collect the first sample as soon as possible (preferred) or within 1 hour of the suspected hypersensitivity reaction, and 2 additional samples at 2 and 8 hours after the suspected hypersensitivity reaction (+ 1 hour window for each sample). If the participant is not in the clinic, these samples do not need to be collected and suspected hypersensitivity reactions will be reported as TEAEs/TESAEs only. If the suspected hypersensitivity reaction persists beyond 8 hours, the CRU should contact the Medical Monitor for guidance.

Abbreviations: ADA = anti-drug antibody; C5b-9 = terminal complement complex; CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; EOS = end of study; h = hours; I = injection; ICF = informed consent form; OP = outpatient; PA = pyridoxic acid; PD = pharmacodynamic; PK = pharmacokinetic; PL = pyridoxal; PLP = pyridoxal 5′-phosphate; PPi = inorganic pyrophosphate; SOI = start of infusion; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event

6.2 Imputation Rules for Partial Dates

Imputed dates and time will NOT be presented in the listings.

Table 6 and Table 7 present algorithm for imputing partial dates for TEAE and prior/concomitant medication respectively.

Table 6 Algorithm for Treatment-Emergent Adverse Events:

Start/Increase Severity Date	Stop Date	Action
Known	Known	Considered as a treatment-emergent adverse event (TEAE) if start date on or after the date of the first dose of investigational product (IP)
	Partial	Considered as a TEAE if start date on or after the date of the first dose of IP. The last day of the month and the last month (ie, December) will be used if the stop day/month is missing.
	Missing	Considered as a TEAE if start date on or after the date of the first dose of IP
Partial, but known components show that it cannot be on or after first IP taken date	Known	Not a TEAE. The first day of the month and January will be used if the start day/month is missing.
	Partial	Not a TEAE. The first day of the month and January will be used if the start day/month is missing. The last day of the month and the last month (ie, December) will be used if the stop day/month is missing.
	Missing	Not a TEAE. The first day of the month and January will be used if the start day/month is missing.
Partial, could be on or after first IP taken date	Known	Considered as TEAE, if stop date is after first IP taken date. The first IP taken date will be used if start date is in the same month/year with first IP taken date, or the first day of the month and January will be used if the start day/month is after first IP taken date Considered as not TEAE, if stop date is prior to first IP taken date. The first day of the month and January will be used if the start day/month is missing.
	Partial	Considered as TEAE. The first IP taken date will be used if start date is in the same month/year with first IP taken date, or the first day of the month and January will be used if the start day/month is after first IP taken date. The last day of the month and the last month (ie, December) will be used if the stop day/month is missing.
	Missing	Considered as TEAE. The first IP taken date will be used if start date is in the same month/year with first IP taken date, or the first day of the month and January will be used if the start day/month is after first IP taken date.
Missing	Known	Considered as TEAE if stop date is on or after the date of the first dose of IP.

Start/Increase Severity Date	Stop Date	Action
	Partial	The last day of the month and the last month (ie, December) will be used if the stop day/month is missing. If the imputed stop date is on or after the first dose of IP considered as a TEAE; if the year is missing, considered as a TEAE
	Missing	Considered as a TEAE

Table 7 Algorithm for Prior/Concomitant Medications Categorization:

Start Date	Stop Date	Action
Known	Known	If stop date is prior to the date for the first dose of IP, considered as prior; if stop date is on or after the date for the first dose of IP, considered as concomitant.
	Partial	The last day of the month and the last month (ie, December) will be used if the day/month of stop date is missing. If the impuated stop date is prior to the date for the first dose of IP, considered as prior; if the imputed stop date is on or after the date for the first dose of IP, considered as concomitant.
	Missing	Considered as concomitant.
Partial	Known	If stop date is prior to the date for the first dose of IP, considered as prior; If stop date is on or after the date for the first dose of IP, considered as concomitant. The first day of the month and January will be used if the start day/month is missing.
	Partial	The last day of the month and the last month (ie, December) will be used if the day/month of stop date is missing. If the impuated stop date is prior to the date for the first dose of IP, considered as prior; if the imputed stop date is on or after the date for the first dose of IP, considered as concomitant. The first day of the month and January will be used if the start day/month is missing.
	Missing	Considered as concomitant. The first day of the month and January will be used if the start day/month is missing.
Missing	Known	If stop date is prior to the date for the first dose of IP, considered as prior; if stop date is on or after the date for the first dose of IP, considered as concomitant.
	Partial	The last day of the month and the last month (ie, December) will be used if the day/month of stop date is missing. If the impuated stop date is prior to the date for the first dose of IP, considered as prior; if he imputed stop date is on or after the date for the first dose of IP, considered as concomitant.
	Missing	Considered as concomitant.

6.3 Laboratory Test Parameters

Category	Lab Parameter
Hematology	Red blood cell count
	Hematocrit
	Red blood cell indices:
	Mean corpuscular volume
	Mean corpuscular Hemoglobin
	Mean corpuscular hemoglobin concentration
	Reticulocytes
	Monocytes
	Eosinophils
	Basophils
	Platelet count
	Mean platelet volume
	White blood cell count
	Neutrophils
Clinical Chemistry	Blood urea nitrogen/urea
	Potassium
	Creatinine
	Sodium
	Chloride
	HbA1c
	Creatine kinase
	AST/SGOT
	ALT/SGPT
	Gamma-glutamyltransferase
	Alkaline phosphatase
	Total and direct bilirubin
	Indirect bilirubin
	Total protein
	Albumin
	Calcium including ionizedcalcium
	Phosphate
	Urea
	Magnesium
	Bicarbonate
Coagulation	Prothrombin time
	Partial thromboplastin time
	International normalized ratio
Other safety laboratory tests	Antidrug antibodies (Alexion)
	The following tests are to be conducted in case of an acute injection/infusion-associated reaction:
	Tryptase (Alexion)
	C5b-9 (Alexion)
	Hematology, chemistry, and urinalysis panels
Routine urinalysis (by dipstick)	Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, erythrocytes, and leukocyte esterase

	Microscopic examination (if any leukocytes, trace protein, nitrites, and blood [if not menstruating] are abnormal)
Urine electrolyte	Urine for calcium, phosphorus, and creatinine
Other screening tests	Urine drug and alcohol tests
	FSH (confirmation of postmenopausal state)
	HIV-1 and HIV-2 antibodies, HbsAg, anti-HBC IgG + IgM (if IgG positive), and anti-HCV
	Serum human chorionic gonadotropin pregnancy test Serum or urine pregnancy tests

Abbreviations: ALT = alanine aminotransferase; anti-HBC = hepatitis B core antibody; anti-HCV = hepatitis C virus antibody; AST = aspartate aminotransferase; C5b-9 = terminal complement complex; FSH = follicle-stimulating hormone; HbsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IgM = immunoglobulin M; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase

6.4 ECG Notable Criteria

ECG Parameters	**Definition/threshold**
QT, QTcF	QTcF interval ≤ 450 msec
	450 msec < QT, QTcF interval ≤ 480 msec
	480 msec < QT, QTcF interval ≤ 500 msec
	QT, QTcF interval > 500 msec
	QT, QTcF interval increases from baseline ≤ 30 msec
	30 msec < QT, QTcF interval increases from baseline ≤ 60 msec
	QT, QTcF interval increases from baseline > 60 msec

ECG = electrocardiogram; bpm = beats per minute; QTcF = QT corrected using Fridericia's formula

6.5 Sample SAS Code for statistical analysis

Dose proportionality analysis

```
ODS OUTPUT parameterestimates=est FitStatistics=fit;
PROC REG DATA = PP ALPHA=0.05 PLOTS=ALL;
    BY PARAMCD PARAM;
    MODEL LNAVAL=LNDOS/CLB;
RUN;
```

where:

LNAVAL: natural log-transformed PK parameter

LNDOS: natural log-transformed dose level of ALXN1910

PARAM: PK parameter

SUBJECT: participant

Absolute Bioavailability analysis

```
ODS SELECT NOPRINT(NOWARN);
  ODS OUTPUT CovParms= Cv1 lsmeans=lsm estimates=est Diffs=diff1;
  PROC MIXED DATA=DATA1 NOITPRINT;
  BY COMPOUND PPSPEC PARAMN PARAMCD PARAM;
  CLASS SUBJID TRTA;
  MODEL LN_PK = TRTA/DDFM=KR;
  RANDOM SUBJID ;
  LSMEANS TRTA/PDIFF ALPHA=0.05 CL;
  ESTIMATE "SC vs IV" TRTA 1 -1 /CL ALPHA=0.05;
  RUN;
```

where:

COMPOUND: compound used in the study

PPSPEC : Specification (Serum)

PARAMN : numerical order of PK parameter

PARAMCD :short name of PK parameter

PARAM: PK parameter

LN_PK; natural log transformed value of PK parameter

SUBJID: Participant

TRTA: actual treatment

Ethnicity Comparison

Sample SAS Code:

```
ODS SELECT NOPRINT(NOWARN);
ODS OUTPUT CovParms= Cv1 lsmeans=lsm estimates=est Diffs=diff1;
PROC MIXED DATA=DATA1 NOITPRINT;
BY COMPOUND ANALYTE PPSPEC PARAMN PARAMCD PARAM;
CLASS SUBJID ETHNICITY;
MODEL LN_PK = ETHNICITY/DDFM=KR;
RANDOM INT SUBJID ;
LSMEANS ETHNICITY/PDIFF ALPHA=0.05 CL;
ESTIMATE "JAPANESE vs NON-JAPANESE" ETHNICITY 1 -1 /CL ALPHA=0.05;
RUN;
```

where:

COMPOUND: compound used in the study

ANALYTE : analyte of the drug (can be parent or metabolite)

PPSPEC : Specification (serum)

PARAMN : numerical order of PK parameter

PARAMCD :short name of PK parameter

PARAM: PK parameter

LN_PK; natural log transformed value of PK parameter

SUBJID: Participant

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