Statistical Analysis Plan

NCT #: NCT05254613

SPONSOR'S REFERENCE NUMBER: ALXN1830-HV-105

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STATISTICAL ANALYSIS PLAN

A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Ascending Dose Study of Subcutaneous ALXN1830 in Healthy Participants

FINAL VERSION 1.0, 24MAR2021

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
%CV	Coefficient of Variation
ADA	Antidrug Antibodies
AE	Adverse Event
AESI	Adverse events of special interest
AUC	Area under the Concentration Time Curve
$AUC_{0-\infty}$	Area under the Serum Concentration versus Time Curve from Time Zero Extrapolated to Infinity
AUC_{0-t}	Area under the Serum Concentration versus Time Curve from Time Zero to the Last Quantifiable Concentration
AUC_{tau}	Area under the Serum Concentration during the dosing interval
BLQ	Below the Level of Quantification
BDRM	Blind Data Review Meeting
BMI	Body Mass Index
CI	Confidence Interval
CL	Total Body Clearance
CL/F	Apparent total clearance
C_{max}	Maximum Observed Serum Concentration
COVID-19	Novel Coronavirus (previously 2019 n-CoV)
CSR	Clinical Study Report
ECG	Electrocardiogram
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IRR	Infusion-related Reactions
λ_z	Terminal Elimination Rate Constant
MAD	Multiple Ascending Dose
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralizing Antibody
PD	Pharmacodynamic(s)
PDF	Portable Document Format
PK	Pharmacokinetic(s)
QTcF	QT interval corrected using Fridericia's formula
RPL	Richmond Pharmacology Ltd
RTF	Rich Text Format
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SC	Subcutaneous
SD	Standard Deviation
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SOC	System Organ Class
SRC	Safety Review Committee
TEAE	Treatment-Emergent Adverse Event

$t_{½}$	Terminal Elimination Half-Life
TFLs	Tables, Figures and Listings
T_{max}	Time to Maximum Observed Serum Concentration
V_d	Volume of Distribution
V_d/F	Apparent Volume of Distribution

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1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to define the variables and analysis methodology to address the study objectives.

The protocol dated 24 January 2020, Amendment 2 was used to prepare this SAP.

Pharmacokinetic (PK) parameters calculations and statistical analyses will be the responsibility of Richmond Pharmacology Ltd (RPL). Tables, figures, and listings (TFLs) will be produced using Statistical Analysis System (SAS), Version 9.4 or higher.

Early Termination of Study

ALXN1830-HV-105 was placed on hold in FEB2020 and the decision was made by Alexion in FEB2021 to prematurely discontinue the study due to Covid-19. Twelve subjects were enrolled and completed the study. There are no further subject visits expected. The study has been terminated and no additional subjects will be dosed under this protocol.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study objectives

The objectives of this study are:

Primary

- To assess the safety and tolerability of single and multiple doses of ALXN1830 SC.

Secondary

- To assess the PK of single and multiple doses of ALXN1830 SC.
- To explore the PD effects of single and multiple doses of ALXN1830 SC.
- To assess the immunogenicity of ALXN1830 SC.

2.2 Endpoints

Primary

- Safety assessed by the incidence and relatedness of TEAEs, SAEs, AESIs, physical examination, vital sign measurements, clinical laboratory and ECG results.

Secondary

- ALXN1830 PK profiles and PK parameters.
- Change in IgG levels.
- Measurement of ADA levels and Nabs.

3. TRIAL DESIGN

This is a Phase 1 study in up to 56 healthy adult participants (42 on active treatment, 14 on placebo) conducted at a single site in the United Kingdom. Eight participants will be randomly assigned in a 6:2 ratio to each of up to 7 cohorts to receive either single or multiple doses of ALXN1830 SC (n = 6 per cohort) or single or multiple doses of placebo (n = 2 per cohort). Cohort 7 is optional. If Cohort 6 is terminated early due to safety or IgG stopping rules, then Cohort 7 may be dosed at a < 1500 mg lower weekly dose for 4 doses. If Cohort 6 does not reach the expected IgG reduction, and no safety or IgG stopping rules are met, then Cohort 7 may be dosed at higher dose > 1500 mg (but not to exceed 2250 mg) weekly for 4 doses).

3.1 Overall Design

Initially, the first 4 participants randomized to each cohort will be dosed with 3 participants on ALXN1830 and 1 participant on placebo. The dosing will be staggered, with an interval of at least 3 days for the SAD cohorts and at least 7 days for the MAD cohorts, before dosing the rest of the participants in the cohort. The shorter interval of staggered dosing for the SAD cohorts compared to the MAD cohorts is considered appropriate as the expected PK exposure of the ALXN1830 SC doses will be a fraction of that of the IV dose demonstrated to be safe and well tolerated in previous IV studies. The reduction of IgG after a single SC dose will be well within the observed IgG reduction observed in previous IV studies; and in general, there will be low risk of immunogenicity and infusion related reactions after a single dose. All participants will be observed during the drug administration and for 2 hours after dosing for safety and participants will be encouraged to report any discomfort immediately, especially within 24 hours post dosing. At no time will more than 4 participants per cohort be dosed on a given day.

A Safety Review Committee (SRC), consisting of the Investigator, safety monitor, 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. Relevant safety data from any other studies ongoing with ALXN1830 will be made available to the SRC. At Alexion's discretion, and after consultation with the SRC, additional participants may be enrolled as replacement participants if a participant discontinues within 3 weeks of the last dose for reasons other than drug-related AEs.

Table 1: ALXN1830-HV-105 Dosing Cohorts

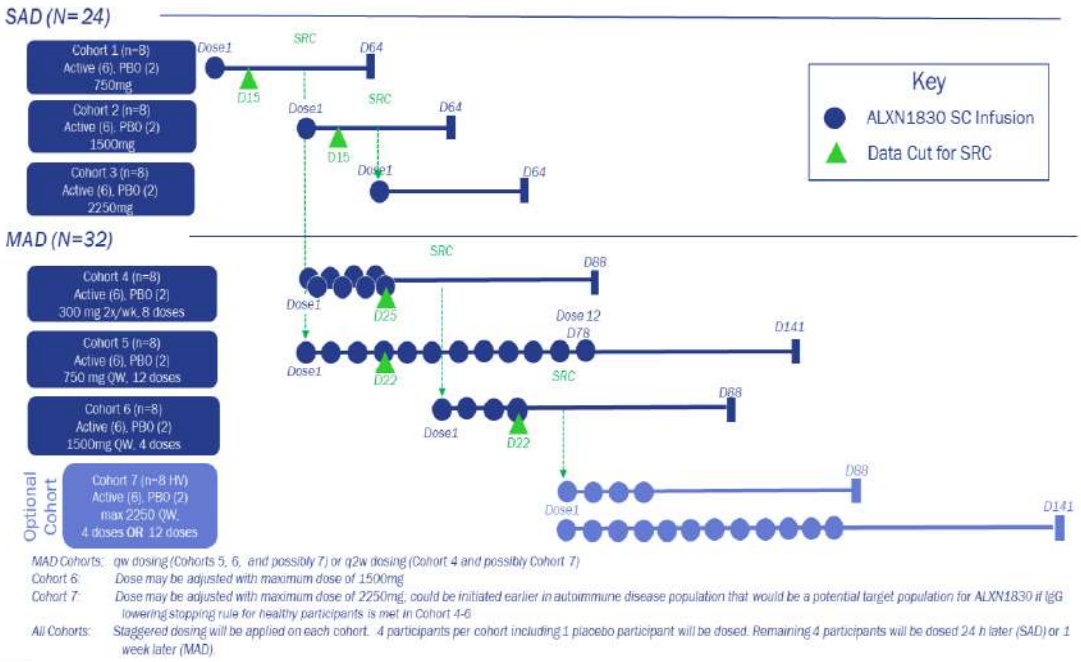
Cohort (n)	Regimen/Route of Administration	Study Drug (N)
1	1 Single dose SC	ALXN1830 750 mg (6 active/2 placebo)
2	1 Single dose SC	ALXN1830 1500 mg (6 active/2 placebo)
3	1 Single dose SC	ALXN1830 up to 2250 mg (6 active/2 placebo)
4	8 doses biw SC	ALXN1830 300 mg (6 active/2 placebo)
5	12 doses qw SC	ALXN1830 750 mg (6 active/2 placebo)
6	4 doses qw SC	ALXN1830 1500 mg (6 active/2 placebo)
7 (Optional)	4 or 12 doses qw SC	ALXN1830 2250mg (6 active/2 placebo)

Abbreviations: biw = twice weekly; qw = weekly; SC = subcutaneous.

3.2 Duration of Study

The planned study duration is approximately 183 days: up to 42 days for screening and approximately 141 days for dosing and follow up.

Figure 1: Study ALXN1830-HV-105 Schematic



3.3 Sample Size

Up to 56 participants will be enrolled. Participants will be randomly assigned in a 6:2 ratio to up to 7 planned cohorts to receive either single or multiple doses of ALXN1830 SC (n = 6 per cohort) or single or multiple doses of placebo (n = 2 per cohort). Cohort 7 is optional.

Progression to the next dosing cohort will be gated by review of initial dosing data by an SRC.

Formal sample size calculation has not been performed. The number of participants has been chosen based on feasibility and are considered adequate to meet the study objectives.

3.4 Randomization and Blinding

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

On Day 1 participants will be assigned a randomization number in ascending numerical order. The randomization number encodes the participant's assignment to one of the 7 cohorts of the study, according to the randomization schedule generated prior to the study by the Statistics Department at Alexion (or designee).

Participants will be randomly assigned in a 6:2 ratio to receive ALXN1830 or placebo. The Investigator will remain blinded to each participant's assigned study drug throughout the course of the study. To maintain this blind, site's pharmacy staff will be responsible for the reconstitution and dispensation of all study drug.

3.5 Early Termination

Due to the outbreak of COVID-19, it was decided by the Sponsor as per study protocol section 7.5 that the study will be discontinued. Prior to termination, 8 subjects from Cohort 1 and 4 subjects from Cohort 2 were dosed. The statistical analyses outlined in this SAP will be presented for Cohort 1, single dose SC ALXN1830 750 mg (6 active/2 placebo) and Cohort 2, single dose SC ALXN1830 1250mg (3 active/1 placebo). The statistical analysis described, and the associated summary tables may not be presented due to the unavailability of data where necessary. In these cases, a blank table with corresponding table number(s) will be created with the words "No data match the criteria for this report."

4. STATISTICAL ANALYSES

In general, descriptive statistics for continuous variables will include number of non-missing values (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum.

Descriptive statistics for PK parameters will include number of observations (n), arithmetic mean, standard deviation (SD), arithmetic coefficient of variation (%CV), geometric mean, geometric %CV, median, minimum and maximum.

Categorical variables will be summarized using frequency counts and percentages.

For all tables, except PK parameter tables, descriptive statistics for minimum and maximum will be presented with the same decimal digits as the original data, and with 1 more decimal place than the original data for mean and median; SD will be reported with 2 more decimal places than the original data.

PK parameters will be presented as follows in the listing:

Parameters	Definitions
C_{max}	Maximum observed serum concentration
t_{max}	Time to maximum observed serum concentration
AUC_t	Area under the concentration-time curve from time 0 to the last quantifiable concentration
$AUC_{0-\infty}$	Area under the concentration-time curve from time 0 (dosing) to time infinity
$t_{½}$	Terminal elimination half-life
λ_z	Terminal-phase elimination rate constant
CL/F	Total body clearance or apparent clearance

Vd/F	Volume of distribution or apparent volume of distribution

C_{max} and T_{max} will be presented as given in the raw data; $AUC_{t,}$ $AUC_{0-\infty}$, λ_z , $t_{1/2}$, CL/F, and V_d/F data permitting, will be presented with 3 significant figures, where appropriate in the tables, listings or figures. The rounding of pharmacokinetic results will be undertaken only after the final calculation of PK parameters. Descriptive statistics for PK parameters will be presented to 3 significant figures for all parameters. Due to early termination, the particular pharmacokinetic parameters to be derived will be determined based on the available concentration data.

The analyses will be produced for cohorts 1 and 2. They will be presented by treatment group (dose levels and placebo). Placebo subjects will be pooled across cohorts. All collected data will be presented in by-subject listings. Listings will be ordered by treatment group and subject number and will include all randomized subjects.

Baseline will be defined as the last non-missing value among assessments including unscheduled visits recorded prior to first administration of study drug. Changes from baseline values will be calculated as the post-baseline assessment value minus the baseline value. Only observed values from scheduled time points will be used to create summary tables (except for baseline).

Early Termination (ET) visits will be recoded to ET visits where necessary and reported as ET.

Deviations from the planned analyses mentioned in this SAP will be described in the final clinical study report (CSR).

Page layout of the TFLs will be in landscape mode and will be provided in Microsoft Word file format. Final TFLs will additionally be created as bookmarked PDF. Further details of page layout will be provided in the TFL shell document. Individual RTF files for tables may be provided to assist medical writing. RTF files will not be compiled into a single document.

4.1 Interim Analysis

No Interim analyses are planned.

4.2 Analysis Populations

Inclusion and exclusion from each analysis set will be decided at the Blind Data Review Meeting (BDRM) prior to database lock. Further exclusions may be made from PK/PD/Immunogenicity sets based on the concentrations of ALXN1830.

Enrolled Population

The enrolled population will consist of all participants who sign the ICF and were randomized.

Safety Population

The safety population will consist of all participants who receive at least 1 dose of study drug. Participants will be analyzed according to the study drug they received.

PK Population

The PK population will consist of all participants who have at least one post-dose measurable serum ALXN1830 concentration data to evaluate PK parameters. Participants will be analysed according to the study drug they received.

PD Population

The PD population will consist of all participants who have at least one serum IgG data to evaluate PD effects. Participants will be analysed according to the study drug they received.

Immunogenicity Population

The immunogenicity population will consist of all participants who have ADA sample collected.

4.3 Subject Disposition

All subjects will be included in the summary of subject disposition. The summary will present the overall number of subjects enrolled, the number of subjects by treatment group and overall, the frequency and percentage of subjects randomized and treated, and who completed or discontinued from the study, along with reason for discontinuation.

Furthermore, the number and percentage of subjects in each study population will be tabulated. Discontinued subjects will be listed. Subject assignment to study populations will be listed.

Screen Failures will not be listed or included in summary tables.

4.4 Demographic Characteristics

Individual subject demographics (including age, sex, race and ethnicity) and body measurement data (height, body weight and body mass index (BMI)) at baseline will be listed and summarized by each treatment group and overall, for the safety population and the PK population. If the remaining populations are different from the safety population by more than 5%, separate demographic tables will be produced.

Height will be measured in centimeters and weight in kilograms. BMI will be given in kg/m^2.

4.5 Baseline and Other Safety Characteristics

Data collected from vaccine and antibiotic prophylaxis, vaccine titer, virus serology, serum pregnancy test, alcohol breath test and urine drug screen will be listed by subject.

4.6 Inclusion and Exclusion Criteria

The inclusion and exclusion criteria will be listed together with the overall eligibility for each subject.

4.7 Protocol Deviations

The final review of protocol deviations will be performed at the BDRM prior to database lock. The protocol deviations will be listed and summarized by deviations category.

4.8 Medical History

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary Version 22.0 (or higher) and listed individually. Surgical histories will be listed separately.

4.9 Study Drug Administration

Study drug administration data will be listed individually.

4.10 Prior and Concomitant Medications

All prior and concomitant medications will be coded using the World Health Organization Drug Dictionary version March 1, 2018 (or higher) and will be listed individually. The frequency and percentage of prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical and Preferred Name. Separate tables will be given for prior and concomitant medications. Prior medications are defined as those for which the end date and time is prior to the date, and time of first study drug administration. Concomitant medications are defined as those with start date and time on or after the date and time of first study drug administration, or ongoing medications with start date and time prior to the first study drug administration. The end date and time of concomitant medications may fall on or after the date and time of first study drug administration. Non-pharmacologic therapies and procedures and prophylactic antibiotic treatment will be listed.

In case of partially missing start (end) date or time, the available information will be used, as much as possible, to classify the medication as prior or concomitant.

4.11 Infusion Site (Pain) Evaluation

Data from the infusion site evaluations and from pain at infusion/injection site will be listed individually. Infusion site evaluations will be summarized by treatment group.

4.12 Safety Analysis

Safety analyses will be performed on the safety population and will be reported at each time point by treatment group.

Safety analyses will include an analysis of all TEAEs, AESIs, ECGs, clinical laboratory data, physical examinations, and vital sign measurements using descriptive statistics. No inferential statistical analyses are planned on the safety parameters of this study.

4.12.1 Adverse Events

A Treatment-Emergent Adverse Event (TEAE) is any adverse event that commences after the start of administration of study drug.

An AESI is an AE of scientific or medical concern specific to the Sponsor or the product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate.

The AESIs for ALXN1830 include the following:

- Any infusion-related reactions (IRRs) equal to or higher than Grade 3; or any IRR that may jeopardize the participant and requires immediate intervention to prevent it from leading to severe outcomes.
- Potential cases of any delayed hypersensitivity reactions, equal to or higher than Grade 2.

The incidence of TEAEs and AESIs (after dosing) will be summarized using the safety population. The MedDRA dictionary Version 22.0 (or higher) will be used to classify all AEs reported during the study by System Organ Class (SOC) and Preferred Term. A summary of TEAEs including the incidence of subjects who experienced TEAEs (number and percentage of subjects) and incidence of TEAEs (number of events) will be presented for each treatment group and overall, by severity and by relationship to study drug.

TEAEs, AESIs and serious TEAEs will be summarized by SOC and Preferred Term for each treatment group and overall, and by relationship to study drug.

Subjects having multiple AEs within a category (e.g., overall, SOC and Preferred Term) will be counted once in that category. For severity tables, a subject's most severe event within a category will be counted. For relationship tables, a subject's

event with greatest relationship to study drug within a category will be counted. In each table, SOC and Preferred Term will be presented in descending order of overall incidence rate (alphabetical order will be used in case of equal rates).

All adverse events will be listed. Serious TEAEs will be listed.

4.12.2 Laboratory Data

Clinical laboratory parameters (including blood chemistry, hematology, coagulation, urinalysis and other laboratory results) will be listed and abnormal parameters will be flagged as high (H) or low (L) according to reference ranges. Absolute (observed) values and changes from baseline (continuous variables) will be summarized for each parameter and scheduled time point by treatment group. The last non-missing lab value will be used for summary analysis if repeated measurements are made at any time point.

For summary statistics, a lab value with "<" will be replaced with a numeric value by removing the "<" sign. In the listings, the values will be displayed as originally reported by the laboratory.

Laboratory parameter values will be graded according to the Common Terminology Criteria for Adverse Events v5.0. Non-protocol parameters will only be listed, in a separate listing, if required.

4.12.3 Electrocardiograms

ECG parameters will be measured at the specified time points and will include heart rate, PR, RR, QRS, QT, and corrected QT interval corrected using Fridericia's formula (QTcF)(QTcF=QT/RR^1/3). The variables will be listed individually.

Three or more replicate measurements are taken at each protocol time point and the arithmetic mean of the evaluable/available measurements will be taken as the measurement to be used for summary statistics. Arithmetic mean values will also be included into the listings.

For ECG variables, the change from baseline will be derived using the arithmetic mean value of each time-point triplicate minus the arithmetic mean of baseline triplicate values. The baseline is the arithmetic mean of all pre-dose measurements observed prior to dosing on Day 1.

Absolute (observed) values and changes from baseline in the ECG variables will be summarized by treatment group and time point.

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

- QT, QTcF interval > 450 msec
- QT, QTcF interval > 480 msec

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

The summary of outliers for QT and QTcF will be presented using the following groupings:

- > 450 msec to ≤ 480 msec
- > 480 msec to ≤ 500 msec
- > 500 msec

And the corresponding group for QT and QTcF interval increases:

- > 30 msec to ≤ 60 msec
- > 60 msec

4.12.4 Telemetry and Holter

Cardiac telemetry and Holter data will be listed individually.

4.12.5 Vital Signs

Vital signs data (systolic and diastolic blood pressure, heart rate, temperature, oxygen saturation and respiration rate) will be listed for individual subjects. Summary statistics of absolute (observed) values and changes from baseline will be calculated and presented for each parameter at scheduled time point by treatment group.

4.12.6 Physical Examination

Physical examination data will be listed individually.

4.13 Pharmacokinetic Analysis

All serum concentration data may be listed for each individual subject and summarized at each time point by treatment group. Individual and mean concentrations versus time on linear and semi-log scales may be presented graphically. Individual concentration plots will be based on actual sampling time relative to the actual start of dosing time. Overlaid individual plots by treatment group will be presented using graphically using nominal time. PK parameters will be summarized by treatment group. The PK population will be used to conduct all PK analysis.

4.13.1 Values Below the Limit of Quantification and Missing Values

Parameter Estimation

Concentrations that are below limit of quantitation (BLQ) and are associated with time-points prior to the first quantifiable concentration in a profile are replaced with zero for the non-compartmental analysis. A BLQ value between two non-BLQ values will be set as missing for the estimation of the pharmacokinetic parameters. Any BLQ value that occurs after the last quantifiable concentration will be set as zero. If more than one BLQ values occur in succession between two non BLQ values, the situation will be considered on a case-by-case basis.

Summary Statistics

When calculating the mean or median value for a concentration at a given time point, all BLQ values will be set to half the Lower Limit of Quantification, except when an individual BLQ falls between two quantifiable values, in which case it will be omitted.

Samples with no reportable value due to a bioanalytical issue or missing samples will be set to missing and will not be included in the PK calculations.

For tabulation, graphical representation, and calculation purposes, all samples with no reportable value (or missing samples) observed after dosing will be set to missing.

4.13.2 Pharmacokinetic Parameters

Individual ALXN1830 serum concentration data along with actual dosing and sampling times will be used to derive pharmacokinetic (PK) parameters by non-compartmental analysis (NCA) using Phoenix WinNonlin software (Version 6.3 or higher). If actual sampling or dosing times are missing, then the nominal times will be used. Dose-normalized parameters will be derived using the actual dose; the nominal dose will be used if the actual dose is not available. PK parameters will be summarized by cohort.

Descriptive statistics for PK parameters will include number of observations (n), arithmetic mean (mean), standard deviation (SD), arithmetic coefficient of variation (%CV), geometric mean, geometric coefficient of variation (%CV), median, minimum and maximum.

The following PK parameters will be derived for each subject in Cohorts 1 and 2:

- **C_{max} (µg/mL):** Maximum observed serum concentration
- **T_{max} (h):** Time to maximum observed serum concentration
- **$AUC_{0-Tlast}$ (h*µg/mL):** Area under the serum concentration versus time curve from time zero (dosing) to the last quantifiable concentration
- **$AUC_{0-\infty}$ (h*µg/mL):** Area under the serum concentration versus time curve from time zero (dosing) extrapolated to infinity
- **λ_z (1/h):** Apparent terminal-phase elimination rate constant

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  - Only those data points that are judged to describe the terminal log-linear decline will be used in the regression
  - A minimum number of 3 data points in the terminal phase will be used in calculating λ_z, with the line of regression starting at any post-C_{max} data point (C_{max} should not be part of the regression slope)
- **$t_{½}$ (h):** Terminal elimination half-life
  - Calculated as ln(2)/ λ_z
- **CL/F (L/h):** Apparent total clearance
  - Calculated as dose/AUC_{∞}
- **V_d/F (L)**: Apparent volume of distribution during the terminal phase
  - Calculated as dose/(λ_z*AUC_{∞})

Some PK parameters may not be calculated for all or some subjects 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 CSR.

Additional PK parameters may be calculated, as appropriate.

4.14 Pharmacodynamic Analyses

The pharmacodynamic endpoints will be evaluated using the PD population as follows:

- Actual values, changes and percent changes in IgA, IgG and IgM concentration over time.
- Actual values, change and percent change IgG subtypes (1-4) over time.
- Actual values, change and percent change in CIC over time.

PD data will be listed for each individual subject and absolute (observed) values as well as changes and percent changes from baseline will be summarized at each time point by treatment group. For summary statistics, BLQ values will be assigned a value of half the Lower Limit of Quantification.

Individual and mean percent change from baseline versus time profiles may be presented graphically for each PD parameter. Individual plots will be based on actual sampling time relative to dosing time. The mean plots will be based on nominal time. More figures may be presented if necessary.

Baseline is defined as the last observed (scheduled or unscheduled) value collected prior to first dose administration. If a baseline value is missing, no change from baseline is to be calculated and the subject excluded from the summary statistics for change from baseline.

4.15 Immunogenicity Analyses

Immunogenicity, as measured by ADA to ALXN1830 (all formulations), will be listed, and summarized over time by treatment group using the Immunogenicity population.

A summary of the number and proportion of patients who are ever positive and always negative will also be provided by treatment group.

4.17 Methods for Withdrawals, Missing Data and Outliers

The individual serum concentration data and the actual timing of study drug administration and blood sampling will be used throughout the analyses. If there is any doubt about the actual time at which a sample was taken, then the scheduled time will be used. For PK data analysis, please see Section 4.13.1 regarding the handling of missing values. For PD data analysis, there will be no imputation for missing values.

If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

AEs with unknown start date/time will be assumed to be treatment-emergent unless the end date/time is known to be before the first administration of study drug. Otherwise, missing or partial dates will be listed as such.

There will be no further imputation of missing data (i.e., subjects who prematurely discontinue from the study will not be included in summary statistics or analyses beyond the time of discontinuation).

Depending on the extent of missing values, the appropriateness of the methods described for handling missing data may be reassessed prior to database lock (to examine the sensitivity of results to handling of missing data).