A Phase 1, Open-label, Single Ascending and Multiple Set Dose Study to Evaluate the Safety, Tolerability, Immunogenicity, Pharmacokinetics, and Pharmacodynamics of ALXN1210 Administered Intravenously to Healthy Japanese Subjects

Unique Protocol ID:	ALXN1210-HV-104
NCT Number:	NCT05288816
EudraCT Number:	2015-005468-40
Date of SAP:	09 October 2016

9. DOCUMENTATION OF STATISTICAL METHODS

- Statistical Analysis Plan, Final Version 2.0, Dated 09 Oct 2016

Statistical Analysis Plan	RICHMOND Pharmacology

SPONSOR'S REFERENCE NUMBER: ALXN1210-HV-104

EUDRACT NUMBER: 2015-005468-40

RPL STUDY CODE: C15045

STATISTICAL ANALYSIS PLAN

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FINAL VERSION 2.0, 09 OCT 2016

Issued by: PPD
Richmond Pharmacology
Statistician
Signature.. PPD
Date.....14/10/2016

Approved by: PPD
Richmond Pharmacology (Consultant - ICRC)
Statistician
Signature.. PPD
Date.....18 OCT 2016

Approved by: PPD
Richmond Pharmacology
Research Director
Signature.... PPD
Date.....18.10.2016

Approved by: PPD
Senior Medical Director
Alexion Pharmaceuticals, Inc
Signature.....
Date.....

Approved by: PPD
Director, Biostatistics
Alexion Pharmaceuticals, Inc
Signature.....
Date..... PPD

Approved by: PPD
Associate Director, Clinical Pharmacology
Alexion Pharmaceuticals, Inc
Signature.. PPD
Date.....13 OCT 2016

Statistical Analysis Plan	RICHMOND Pharmacology

SPONSOR'S REFERENCE NUMBER: ALXN1210-HV-104

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Date 13-Oct-2016

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Associate Director, Clinical Pharmacology
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Signature.....
Date.....

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
λ_z	apparent terminal- elimination rate constant
ADA	antidrug antibody
AE	adverse event
AUC_∞	area under the serum concentration versus time curve from time 0 extrapolated to infinity
AUC_t	area under the serum concentration versus time curve from time 0 to the last quantifiable concentration
AUC_τ	area under the serum concentration versus time curve from time 0 to the end of the dosing interval (tau)
BLQ	below the level of quantification
BMI	body mass index
CL	total body clearance
C_{max}	maximum observed serum concentration
C_{min}	minimum observed serum concentration
CSR	clinical study report
cRBC	chicken red blood cell
CV	coefficient of variation
ECG	electrocardiogram
IMP	Investigational Medicinal Product
IV	intravenous
LLQ	lower limit of quantification
MedDRA	medical dictionary for regulatory activities
PD	pharmacodynamic(s)
PI	principal investigator
PK	pharmacokinetic(s)
PT	preferred term
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
R	accumulation ratio
RPL	Richmond Pharmacology Ltd
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis software
SD	standard deviation
SOC	system organ class
SRC	safety review committee
TEAE	treatment-emergent adverse event
TFL	tables figures and listings
$t_{½}$	terminal elimination half-life
t_{max}	time to maximum observed serum concentration
V_{ss}	volume of distribution at steady state
WHO	world health organization

TABLE OF CONTENTS

1. INTRODUCTION

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

Final Protocol Amendment 1 dated 24 Aug 2016 was used in the preparation of this SAP.

Pharmacokinetic parameters will be calculated by Alexion or its designee. Richmond Pharmacology Ltd (RPL) is responsible for performing statistical analyses. Tables, figures, and listings will be produced using Statistical Analysis Software (SAS) V9.2 or higher.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study objectives

The objectives of this study are:

Primary

- To evaluate the safety and tolerability of single and multiple doses of ALXN1210 following intravenous (IV) administration to healthy Japanese subjects.

Secondary

- To investigate the immunogenicity of ALXN1210 in healthy Japanese subjects.
- To characterize the pharmacokinetics (PK) of single and multiple doses of ALXN1210 in healthy Japanese subjects.
- To evaluate the pharmacodynamics (PD) effects of ALXN1210 as assessed by total and free C5 concentrations and chicken red blood cell (cRBC) hemolysis in healthy Japanese subjects.

2.2 Endpoints

Safety, immunogenicity, PK, and PD endpoints are described in the sections to follow. Timing of assessments is displayed in the Schedules of Assessments.

Safety Endpoints

Safety endpoints include the following:

- Change from baseline in physical examination assessments
- Change from baseline in vital signs
- Incidence of antidrug antibody (ADA) measured via immunogenicity testing
- Change from baseline in electrocardiogram (ECG) parameters
- Change from baseline in laboratory measurements
- Incidence of Adverse Events (AE) and Serious Adverse Events (SAE)

Pharmacokinetic Endpoints

The following PK parameters will be evaluated:

- Observed maximum serum concentration following all ALXN1210 doses (C_{max}) following single dose (Cohort 1 and 2) and doses 1 and 5 (Cohort 3);
- Dose-normalized C_{max}, following single dose (Cohort 1 and 2) and doses 1 and 5 (Cohort 3);
- Time to maximum observed serum concentration (t_{max}) following single dose (Cohort 1 and 2) and doses 1 and 5 (Cohort 3);
- Trough serum concentrations (C_{trough}) just prior to Doses 2 to 5, and 28 days after the 5th dose (Cohort 3);
- Area under the serum concentration versus time curve from time 0 to the last quantifiable concentration (AUC_t) after single dose (Cohort 1 and 2) and after dose 5 (Cohort 3);
- Dose-normalized AUC_t after single dose (Cohort 1 and 2) and following dose 5 (Cohort 3);
- AUC from time 0 (dosing) to the end of the dosing interval (AUC_τ) following doses 1 and 5 (Cohort 3). Following Dose 5, calculated over dosing interval (28 days);
- Terminal-phase elimination rate constant (λ_z) after single dose (Cohort 1 and 2) and after dose 5 (Cohort 3);
- Terminal elimination half-life ($t_{½}$) after single dose (Cohort 1 and 2) and after dose 5 (Cohort 3);
- Total body clearance of drug from the serum (CL) after single dose (Cohort 1 and 2) and after dose 5 (Cohort 3);
- Volume of distribution at steady state (V_{ss}) (Cohort 3);
- Assessment of steady state (Cohort 3);
- Accumulation at steady state (R) after the fifth dose (Cohort 3).

Pharmacodynamic Endpoints

Pharmacodynamic effects will be evaluated as follows:

- Change in serum total and free C5 concentration over time
- Change in cRBC hemolysis over time
- ALXN1210 concentration required for complete terminal complement inhibition based on PD effects evaluated.

3. NUMBER OF SUBJECTS AND RANDOMIZATION

3.2 Number and Source of Subjects

Up to 16 subjects are planned for evaluation of the primary and secondary objectives, and a maximum of 22 subjects could be enrolled and dosed. The total number of subjects dosed (including potential added subjects) will remain within a maximum of 6 subjects each in Cohorts 1 and 2 and 10 subjects in Cohort 3, for a maximum of 22 subjects in this study.

3.3 Randomization and Blinding

This is an open-label study (subjects and on-site medical/nursing staff and pharmacy staff are aware of study drug/dose assignment). Eligible subjects who meet the inclusion/exclusion criteria will be sequentially enrolled and assigned to

receive ALXN1210. Once a subject identification number has been assigned to 1 subject, it may not be assigned to another subject.

4. STATISTICAL ANALYSES

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

Descriptive statistics for PK parameters will include number of observations, arithmetic mean, SD, arithmetic coefficient of variation (CV), geometric mean, geometric CV, median, minimum and maximum, by treatment group.

Descriptive statistics for PD parameters will include number of observations, arithmetic mean, SD, median, minimum, and maximum, by treatment group.

Categorical variables will be summarized using frequency counts and percentages by treatment group.

Treatment group refers to all dose cohorts of ALXN1210.

Baseline will be defined as the last value of the assessment recorded prior to first administration of Investigational Medicinal Product (IMP). For post-dose assessments the first scheduled value will be used for summary analysis if repeated measurements are made at a time-point.

Deviations from the planned analyses will be described in the final integrated clinical study report.

4.1. Analysis Populations

The safety population will consist of all subjects who receive at least 1 dose of study drug. Subjects in this population will be used for the safety analysis.

The PK population will consist of all subjects who have sufficient serum concentration data to enable the calculation of PK parameters. The PK population will be used for PK analysis.

The PD population will consist of all subjects who have sufficient total and free C5 concentration data and cRBC hemolysis data. The PD population will be used for PD analysis.

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

Inclusion and exclusion from each analysis set will be decided at the Data Review Meeting prior to database lock.

4.2. Sample Size and Power

The sample size of 4 subjects in each of the single-dose cohorts (Cohorts 1 and 2) and 6 to 8 subjects in the 800 mg multiple-dose cohort will allow for the characterization of the central tendency of PK parameters as they relate to ALXN1210 and to gain initial knowledge of PK/PD relationships in Japanese subjects. To ensure future modeling and simulations are accurate, it is preferred to estimate the PK parameters with a maximum imprecision of < 25% following the IV administration of ALXN1210. Six subjects in Cohort 3 will provide 23.3%

maximum imprecision (Table 1) for the estimation of area under the serum concentration versus time curve from time 0 extrapolated to infinity (AUC∞), in terms of the relative distance of the lower 90% confidence limit from the observed PK parameter that will be obtained with 80% assurance and assuming the within-subject SD of the log-transformed AUC∞ is as much as 0.19.

Table 1: Estimation of the Maximum Imprecision in the Estimate of PK Parameters for Selected Sample Sizes

Number of Subjects on Active	Maximum Imprecision (%)
4	33.6
6	23.3
8	18.9

4.3. Demographics, Baseline Characteristics, and Subject Disposition

All subjects will be included in the summary of subject disposition, which will summarize the frequency and percentage of subjects screened and treated who completed or discontinued from the study, along with reason for discontinuation, by treatment group. Demographics and baseline characteristics will be summarized for all subjects by each treatment dose and overall on the safety population. If the remaining populations are different from the safety population, separate demographic tables will be produced. Continuous variables will be summarized using n, arithmetic mean, standard deviation, median, minimum, and maximum whereas categorical variables will be summarized by frequency and percentage by treatment group.

4.4. Safety Analysis

Safety analyses will be performed on the safety population, and will be reported by each treatment dose. Safety analyses will include an analysis of all AEs, ECGs, clinical laboratory data, physical examinations, and vital sign measurements and will be presented using descriptive statistics. No inferential statistical analyses are planned on the safety parameters of this study.

Adverse Events

The incidence of treatment-emergent (after dosing) AEs (TEAEs) will be summarized using the safety population. The Medical Dictionary for Regulatory Activities (MedDRA®) dictionary Version 19.0 (or higher) will be used to classify all AEs reported during the study by System Organ Class (SOC) and preferred term (PT). A summary of adverse events including the incidence of subjects who experience TEAEs and incidence of TEAEs (number of events) will be presented for each treatment dose and overall, by severity and by relationship to study drug. SAEs will be summarized by system organ class and preferred term for each treatment dose and overall, by severity, and by relationship to study drug.

SAEs and AEs resulting in withdrawal from the study will be listed. Subjects having multiple AEs within a category (e.g., overall, system organ class 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. In each table,

SOC will be presented in descending order of overall incidence rate (alphabetical order will be used in case of equal rates).

Medical history

Medical history data will be coded using MedDRA® dictionary Version 19.0 (or higher) and listed individually.

Study drug administration

Study drug administration data will be listed individually.

Vital signs

Vital signs data (systolic and diastolic blood pressure, heart rate, oral temperature, and respiration rate) will be listed for individual subjects. Summary statistics (n, arithmetic mean, SD, median, minimum, and maximum) of absolute values and changes from baseline will be calculated for each parameter by each treatment dose.

Laboratory data

Safety Laboratory parameters (blood chemistry hematology, coagulation and urinalysis) will be listed and abnormal parameters flagged as high (H) or low (L). Changes from baseline (continuous variables) will be summarized by each treatment dose based on scheduled values.

For summary statistics, the lab value with "<" will be replaced with 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 National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE; v4.03, published June 14, 2010). Parameters, not present in the above referenced document will not be graded. Shift tables by treatment group will be produced for these laboratory parameters by grade. These tables will summarize the number of subjects with each baseline grade relative to the normal ranges and changes to the worst highest grade assessed post-dose during the study.

Individual profiles will be presented for the following laboratory parameters: GGT, ALT, AST, Hb, Creatinine, RBC, WBC, Potassium, Sodium, Uric Acid, Albumin, Total Protein and neutrophils.

ECG

The ECG parameters will be measured at the specified time-points, including heart rate, PR, RR, QRS, QT and QTcF intervals. For summary statistics the average of all time-point ECG readings will be calculated, as well as changes from pre-treatment baseline values will be assessed by each treatment dose.

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 as follows:

- 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

Previous and concomitant medications

All previous and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary version June 1, 2015 and the frequency and percentage of concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) and Preferred name.

Physical examination

Physical examination data will be listed. Change from baseline to each visit will be presented for each item of the Physical Examination separately, using shift tables.

Infusion site evaluation

Data from the Infusion site evaluations will be listed individually.

Visual assessment scale for pain at infusion site

Data from the Pain at infusion site will be listed.

4.5 Pharmacokinetic Analysis

All serum concentration data will be listed for each individual subject and summarized at each time point by treatment group using the following descriptive statistics.

- N (the number of subjects)
- Arithmetic mean
- SD
- Arithmetic CV (inter-subject coefficients of variation)
- Geometric mean
- Geometric CV (inter-subject coefficients of variation)
- Median
- Minimum
- Maximum.

When a Below the Level of Quantification (BLQ) value occurs in a profile before the first measurable concentration, it is assigned a value of zero concentration. When a BLQ value occurs after a measurable concentration in a profile and is followed by a value above the Lower Level of Quantification (LLQ), then the BLQ will be omitted following visual inspection of the serum concentration versus time profile to assess the appropriateness of this assignment. When a BLQ value occurs at the end of a collection profile (after the last quantifiable concentration), the value is treated as missing data. When two BLQ values occur in succession, the profile is deemed to have terminated at the first BLQ value and any subsequent concentrations are omitted from PK calculations.

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

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

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

The figures of individual and mean concentrations versus nominal time on linear and semi-log scale will be plotted.

The individual serum concentration data for ALXN1210-treated subjects, with actual sampling dates and times calculated relative to the start of the infusion, will be used to derive the PK parameters by non-compartmental analyses using Phoenix WinNonlin 6.3 or higher.

The following PK parameters will be estimated:

- Observed maximum serum concentration following all ALXN1210 doses (C_{max}) following single dose (Cohort 1 and 2) and doses 1 and 5 (Cohort 3);
- Dose-normalized C_{max}, following single dose (Cohort 1 and 2) and doses 1 and 5 (Cohort 3);
- Time to maximum observed serum concentration (t_{max}) following single dose (Cohort 1 and 2) and doses 1 and 5 (Cohort 3);
- Trough serum concentrations (C_{trough}) just prior to Doses 2 to 5, and 28 days after the 5th dose (Cohort 3);
- Area under the serum concentration versus time curve from time 0 to the last quantifiable concentration (AUC_t) after single dose (Cohort 1 and 2) and after dose 5 (Cohort 3);
- Dose-normalized AUC_t after single dose (Cohort 1 and 2) and following dose 5 (Cohort 3);
- AUC from time 0 (dosing) to the end of the dosing interval (AUC_τ) following doses 1 and 5 (Cohort 3). Following Dose 5, calculated over dosing interval (28 days);
- Terminal-phase elimination rate constant (λ_z) after single dose (Cohort 1 and 2) and after dose 5 (Cohort 3);
- Terminal elimination half-life ($t_{½}$) after single dose (Cohort 1 and 2) and after dose 5 (Cohort 3);
- Total body clearance of drug from the serum (CL) after single dose (Cohort 1 and 2) and after dose 5 (Cohort 3);
- Volume of distribution at steady state (V_{ss}) (Cohort 3);
- Assessment of steady state (Cohort 3);
- Accumulation at steady state (R) after the fifth dose (Cohort 3).

All pharmacokinetic parameters will be listed for each individual subject and summarized by treatment group using the following descriptive statistics.

- N (the number of subjects)
- Arithmetic mean
- SD
- CV
- Geometric mean
- Geometric CV

- Median
- Minimum
- Maximum

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 may be provided in the Clinical Study Report (CSR).

4.6 Dose Proportionality

Dose proportionality of the 400mg and 800mg ALXN1210 doses may be assessed for the following PK parameters:

- dose-normalized AUC_t
- dose-normalized C_{max} (Cohort 1, 2 and Cohort 3 after first dose)

The parameters will be analyzed using the power model [1], where the ratio of geometric means and the corresponding 90% confidence interval will be derived. Dose proportionality will be concluded if the 90% confidence interval of the ratio contains 1.

4.7. Pharmacodynamic Analyses

The PD effects of ALXN1210 administered IV will be evaluated as follows:

- Changes and percent changes in serum Total C5 and Free C5 concentration over time.
- Change and percent change in cRBC hemolysis over time.
- ALXN1210 concentration required for complete terminal complement inhibition based on PD effects evaluated.

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 dose using the following descriptive statistics.

- N (the number of subjects)
- Arithmetic mean
- SD
- Median
- Minimum
- Maximum.

Individual percent change from baseline versus actual time and mean percent change from baseline versus nominal time will be presented for each PD parameter.

4.8. Immunogenicity Analyses

Immunogenicity, as measured by anti-drug antibodies, will be summarized in tabular form (number and percentage of subjects developing ADA) by treatment dose and will be presented in by-subject listings.
Immunogenicity data will be listed for each individual subject and will be summarized at each time point by treatment dose using the following descriptive statistics, if applicable.

- N (the number of subjects)
- Arithmetic mean
- SD
- Median
- Minimum
- Maximum.

4.9 Methods for Withdrawals, Missing Data, and Outliers

The individual serum concentration data, and the actual time for IMP administration and blood sampling will be used throughout the analyses. If there is any doubt in the actual time a sample is taken, then the scheduled time will be used. For PK data analysis, please see Section 4.5 Pharmacokinetic Analysis for the handling of missing and BLQ 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 IMP. 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. If a subject is withdrawn from study treatment but continues to participate in the study, the data collected will be included according to the treatment initially received for the Safety set.

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).

4.10 Protocol deviations

A protocol deviation is defined as a lack of compliance with the protocol which may interfere with the outcome of the trial. The protocol deviations will be identified and reviewed throughout the study, reviewed by PI/Sponsor and graded as minor or major. The final review will be performed at the Data Review Meeting prior to database lock. The protocol deviations will be listed.

5. CONVENTIONS

All listings will be ordered by treatment and subject number and will include all enrolled subjects. All data will be presented by the dose level of treatment.

For all tables, except PK parameter tables, descriptive statistics for min, max will be presented with the same number of decimal digits as the original values, and with one more decimal digit than the original data for mean and median; standard deviation will be reported with 2 or more decimal digits than the original.

For PK, the individual and summaries of PK parameter results will be reported in 3 significant digits in the listings and in the tables with the following exceptions:

- Tmax will be presented as follows: individual minimum, and maximum values will be reported exactly as the raw data are reported
- % CV will be presented to 1 decimal place

Page layout of tables and listings in landscape mode will be produced in Microsoft Word. Details of page layout will be provided in the tables figures and listings (TFL) shell document.