Statistical Analysis Plan	RICHMOND Pharmacology

SPONSOR'S REFERENCE NUMBER: WTX101-HV-106

EUDRACT NUMBER: 2018-004483-57

RPL STUDY CODE: C18055

STATISTICAL ANALYSIS PLAN

An Open-Label, Two-Single-Dose, Two-Period, Parallel Group Study to Assess the Pharmacokinetics and Safety of ALXN1840 in Healthy Adult Japanese and non-Japanese Subjects

FINAL VERSION 1.0 08 MAY 2019

Created by: PPD
Richmond Pharmacology
Biostatistician

Signature. PPD

Date...15MAY2019.

Approved by: PPD
ICRC-Weyer
Senior Biostatistician

Signature. PPD ....

Date...16 May 2019.

Approved by: PPD Ph.D.
Alexion Pharmaceuticals, Inc
Associate Director, Biostatistics

Signature.....

Date.....

Approved by: PPD Ph.D.
Alexion Pharmaceuticals, Inc
Director, Clinical Pharmacology

Signature.....

Date.....

Approved by: PPD MD
Alexion Pharmaceuticals, Inc
Executive Director, Medical Sciences

Signature.....

Date.....

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
%CV	Coefficient of Variation
AE	Adverse Event
ANOVA	Analysis of variance
AUC	Area under the Concentration Time Curve
AUC_{∞}	Area under the Concentration versus Time Curve from Time Zero Extrapolated to Infinity
AUC_t	Area under the Concentration versus Time Curve from Time Zero to the Last Quantifiable Concentration
BLQ	Below the Level of Quantification
BDRM	Blind Data Review Meeting
BMI	Body mass index
CI	Confidence Interval
CL	Total Body Clearance
C_{max}	Maximum Observed Concentration
Cp	Ceruloplasmin
CpC	Ceruloplasmin-bound copper
CRU	Clinical research unit
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria For Adverse Events
Cu	Copper
EC	Enteric-coated
ECG	Electrocardiogram
EOS	End of Study
EC	Enteric coating
ET	Early Termination
F_{rel}	Relative Bioavailability
HIV	Human immunodeficiency virus
ICF	Informed consent form
λ_z	Terminal Elimination Rate Constant
MedDRA	Medical Dictionary for Regulatory Activities
Mo	Molybdenum
NCC	Non-ceruloplasmin-bound copper
PD	Pharmacodynamic(s)
PDF	Portable Document Format
PK	Pharmacokinetic(s)
PT	Preferred term
PUF	Plasma ultrafiltrate
QTcF	QT interval corrected using Fridericia's formula
RPL	Richmond Pharmacology Ltd
RTF	Rich-Text Format
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software

SD	Standard Deviation
SI	Systeme Internationale
SOC	System Organ Class
SRC	Safety Review Committee
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
$t_{½}$	Terminal Elimination Half-Life
TFLs	Tables, Figures and Listings
T_{max}	Time to Maximum Observed Concentration
TPC	Cu-tetrathiomolybdate-albumin tripartite complex with ALXN1840 administration
V_d (V_d/F)	Apparent Volume of Distribution
WHO-DD	World Health Organisation – Drug Dictionary

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.

The protocol WTX101-HV-106 Amendment 1, dated 05 February 2019 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 Software (SAS), Version 9.3 or higher.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study objectives

The objectives of this study are:

Primary

- To evaluate the ALXN1840 PK in Japanese and non-Japanese healthy subjects.

Secondary

- To assess the safety and tolerability of ALXN1840 in Japanese and non-Japanese healthy subjects.

Exploratory

- To assess dose-proportionality of ALXN1840 PK of the 15 mg and 60 mg doses within each cohort and with combined cohort data;
- To explore PD and biomarkers of ALXN1840 in Japanese and non-Japanese healthy subjects.

2.2 Endpoints

Primary

- PK parameters calculated based on the measurements of plasma total molybdenum (Mo) concentrations (C_{max}, AUC_t, and AUC_∞).

Secondary

- Safety assessed by incidence of TEAEs and TESAEs, physical examination, vital sign measurements, clinical laboratory and ECG results.

Exploratory

- PK parameters calculated based on the measurements of plasma total molybdenum (Mo) concentrations (C_{max}, AUC_t, and AUC_∞).
- Absolute and percent changes of plasma ceruloplasmin (Cp) and copper (Cu) levels (total Cu, Cp, CpC and NCC);
- The NCC level will be corrected for the amount of Cu bound to the TPC ($NCC_{corrected}$).

3. TRIAL DESIGN

This is a single-center, open-label, two-single-dose, two-period, parallel group study evaluating PK and safety of ALXN1840 in healthy subjects. Pharmacokinetic parameters will be calculated based on the measurement of plasma total Mo concentration.
Approximately 24 healthy (12 Japanese and 12 non-Japanese), non-tobacco using, adult male and female subjects who complete the study screening assessments and meet all eligibility criteria will be enrolled to allow for a minimum of 20 subjects to complete the study (10 subjects in each cohort).

Cohort 1: Japanese subjects (defined as those subjects whose parents and grandparents are both Japanese and who have spent less than 5 years outside of Japan).

Cohort 2: Non-Japanese subjects.

The study will be conducted at a single site in the UK.

A Safety Review Committee may be used to evaluate the study data for subject safety and make recommendations on dose modification or termination of the study.

3.1 Overall Design

The study has a screening phase (Days -28 to -2), 2 Dosing Periods (Day -1 to Day 11 each), and an end-of-study (EOS) visit.

After completing the screening phase, enrolled subjects will be admitted to an inpatient facility (CRU) on Day -1 for dosing on Day 1 in Dosing Period 1.

Subjects will be then be readmitted to the CRU for Dosing Period 2 dosing, at least 14 days following the 15 mg dose.
Subjects are confined to the CRU from Days 1 to Day 11 for both Dosing Periods and have samples obtained for PK/PD assessments as well as safety evaluations performed (as detailed in Tables 1 and 2 of the trial protocol). Subjects are discharged 10 days after dosing with Period 1 and Period 2 following the 240 hour post dose procedures, unless medically necessary to extend their confinement.

The subjects in each cohort will follow the dosing regimen as follows:

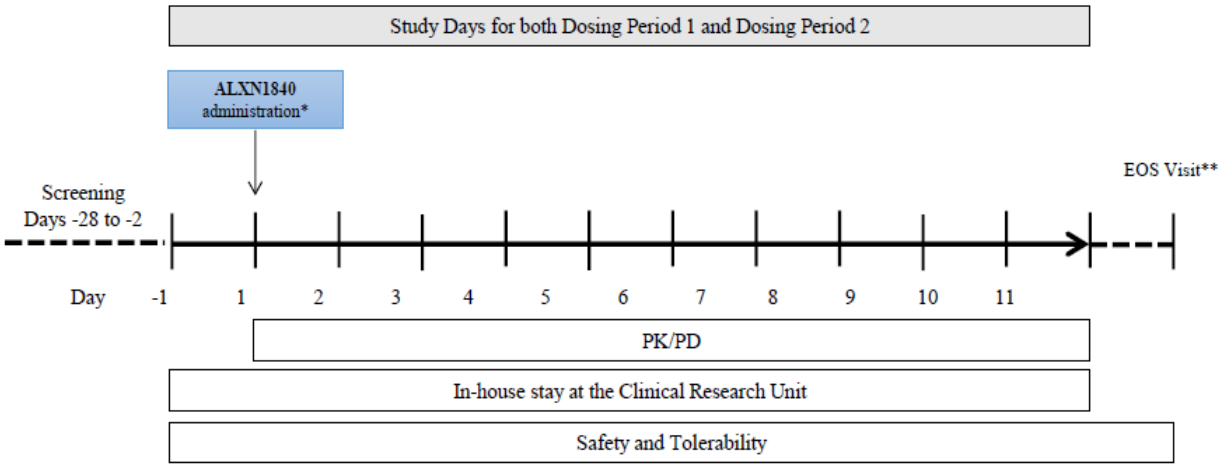
Dosing Period	**Planned dose**
Dosing Period 1	Subjects will receive a single dose of one 15 mg ALXN1840 enteric-coated (EC) tablet at Hour 0 on Day 1 of Period 1 following an overnight fast.
Dosing Period 2	Subjects will receive a single dose of 4 × 15 mg (for a total of 60 mg) ALXN1840 EC tablets at Hour 0 on Day 1 of Period 2 following an overnight fast.

Table 1: WTX101-HV-106 Study Drug Dosing Periods

Subjects will return to the CRU 14 days (+2 days) after the 60 mg dose in Dosing Period 2 for the EOS visit with follow-up procedures, and to determine if any AE had occurred since the last study visit. If subjects withdraw from the study early, they will be seen and assessed by the Investigator or designee, whenever possible, to undergo the procedures associated with the EOS visit. Subjects may be replaced at the discretion of the Sponsor.

3.2 Duration of Study

The planned study duration for each subject is approximately 56 days; up to 27 days for screening and approximately 29 days for dosing and follow-up.



* In Dosing Period 1 and Dosing Period 2, subjects will receive 15 mg and 60 mg of ALXN1840, respectively. Subjects will be readmitted to the CRU for Dosing Period 2 dosing after a minimum of 14 days after the 15 mg dose.

** EOS visit to take place 14 days (+2 days) following 60 mg dose of study drug.

Abbreviations: CRU = Clinical Research Unit; EOS = end of study, PD = pharmacodynamics; PK = pharmacokinetics.

Figure 1: Study WTX101-HV-106 Schematic

3.3 Sample Size

The study sample size is not based on hypothesis testing with statistical considerations. A sample size of 20 subjects (10 subjects in each cohort) has been selected based on practicality and convention for this type of study. Considering potential for subject drop-out of the study, a total of 24 subjects will be enrolled with 12 Japanese and 12 non-Japanese. The between-subject coefficient of variation (CV) in a previous bioavailability study using 2 × 30 mg EC tablets (Study WTX101-102) was 35%, which can be used to approximate the standard deviation (SD). Two cohorts of 10 subjects produce a two-sided 90% confidence interval with a distance from the difference in means to the limits that is equal to 0.271. For example, if the difference of means is zero and the ratio of means is 1, this level of precision corresponds to an interval from 0.76 to 1.31 on the ratio scale.

3.4 Randomization and Blinding

This is an open-label study.

Eligible subjects who meet all inclusion and no exclusion criteria will be assigned unique numbers for enrollment. In order to minimize selection bias in treatment assignment, subjects who are assigned subject numbers will have them assigned consecutively at the point of study drug dosing, in the same order as they have become eligible.

Study subject numbers will not be reallocated once assigned.

In an effort to achieve balance between the number of males and females in Cohorts 1 and 2, the maximum split in either direction will be 60%:40%.

4. STATISTICAL ANALYSES

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

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 %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: C_{max} and T_{max} will be presented as given in the raw data; AUC_t, AUC_∞, λz , $t_{1/2}$, CL or CL/F, and V_d or V_d/F will be presented with 3 decimal places. Special characters (including subscripts) will not be presented in the tables, listings or figures. Descriptive statistics for PK parameters will be presented with decimal places as appropriate for the particular parameter and cohort.

The analyses will be presented by cohort and period. All collected data will be presented in by-subject listings. Listings will be ordered by cohort, period and subject number and will include all randomized subjects. Deviations from this scheme, if any, will be specified in the relevant section.

Baseline will be defined as the last non-missing value among assessments recorded prior to administration of study drug within respective period. Changes from baseline values will be calculated by period as the post-baseline assessment value minus the baseline value. Only observed values from scheduled time points will be used to create summary tables.

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

Deviations from the planned analyses 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. 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 for this study.

4.2 Analysis Populations

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

Enrolled

All subjects who sign the ICF.

Safety Population

The safety population will consist of all subjects who receive at least 1 dose of the study drug.

PK Population

The PK population will consist of all subjects who have sufficient plasma samples to enable the calculation of PK parameters of at least Area Under the Curve (AUC) for at least one period.

PD Population

The PD population will consist of all subjects who have sufficient plasma samples which will enable the evaluation of the PD effects, i.e. who have at least one change from baseline value available of either plasma Cp or copper levels (total Cu, Cp, CpC and NCC).

4.3 Subject Disposition

All subjects will be included in the summary of subject disposition. This will present the overall number of subjects screened. It will also present by cohort and overall the frequency and percentage of subjects randomized, treated, and who completed or discontinued from the study, along with the 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, ethnicity) and body measurement data (height, body weight and body mass index) at screening will be listed and summarized for each cohort and overall for the safety population. If

the remaining populations are different from the safety population by more than 5%, separate demographic tables will be produced.

For the Japanese cohort, information about the Japanese criteria information (descent, place of birth and residence) will be listed.

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

4.5 Baseline and Other Safety Characteristics

Data collected from serology (HIV and Hep) tests, 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.

4.8 Medical History

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary Version 21.1 (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

Prior and concomitant medication will be coded using the World Health Organization drug dictionary (WHO-DD) version June 1, 2018 or higher.

Prior and concomitant non-drug therapies will be coded using the MedDRA version 21.1 or higher.

Prior medications/therapies 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/therapies are defined as those with start date and time on or after the date and time of first study drug administration, or those with start date and time prior to the first study drug administration but with end date and time on or after the date and time of first study drug administration. Concomitant medications will further be assigned to the Period in which they commence. Concomitant medications of Period 1 are defined as those with start date and time on or after the date and time of study drug administration in Period 1 and before study drug administration in Period 2. Concomitant medications of Period 2 are defined as those with start date and time on or after the date and time of study drug administration in Period 2.

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

All prior and concomitant medications/therapies will be listed by subject using reported name, ATC Term and WHO-DD Preferred Name, indication, dose, dose unit, frequency, route of administration, start date and end date or 'ongoing' flag and duration of use. Concomitant medications will be flagged.

The number and percentage of subjects with concomitant medication/therapy will be summarised overall and by WHO-DD Preferred Name and ATC Term using the safety population.

Non-pharmacologic therapies and procedures and prophylactic antibiotic treatment will be listed.

4.11 Safety Analysis

All safety analyses will be performed on the Safety Population.

Safety analyses will include an analysis of all AEs, ECGs, clinical laboratory data, physical examinations, and vital sign measurements using descriptive statistics.

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

4.11.1 Adverse Events

A Treatment Emergent Adverse Event (TEAE) is any adverse event that commences after the start of administration of study drug. TEAEs will further be classified by the Period in which they commenced. A TEAE will be classified as Period 1 if the AE start date/time is on or after the date and time of drug administration in Period 1, and Period 2 if the AE start date/time is on or after the date and time of drug administration in Period 2.

The incidence of TEAEs (after dosing) will be summarized using the safety population. The MedDRA dictionary Version 21.1 (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 cohort and overall, by severity and by relationship to study drug.

TEAEs and serious TEAEs will be summarized by SOC and Preferred Term for each cohort 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.

All adverse events will be listed. Serious TEAEs and AEs resulting in withdrawal from the study will be listed.

4.11.2 Laboratory Data

Clinical laboratory parameters (including chemistry, hematology (including RBC indices and WBC count with differentials), coagulation and urinalysis) 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 cohort and period. The last 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 (CTCAE). Shift tables by cohort and by period will be produced for laboratory parameters graded by CTCAE. 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 period.

Laboratory parameters planned in the study are outlined in Table 10 of the protocol. Any additional parameters collected as part of investigations will be listed only. Laboratory parameters will be presented in SI units, BUN will be converted to SI unit (mmol/L).

4.11.3 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.

Absolute (observed) values and changes from baseline in the ECG variables will be summarized by cohort, period 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 cohort and period:

- QT, QTcF interval > 450 msec to ≤ 480 msec
- QT, QTcF interval > 480 msec to ≤ 500 msec
- QT, QTcF interval > 500 msec
- QT, QTcF interval increases from baseline > 30 msec to ≤ 60 msec
- QT, QTcF interval increases from baseline > 60 msec

4.11.4 Vital Signs

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

4.11.5 Physical Examination

Physical examination data will be listed individually over time.

4.12 Pharmacokinetic Data Analysis Plan

All plasma concentration data will be listed for each individual subject and summarized at each time point by cohort and period. Individual and mean concentrations versus nominal time on linear and semi-log scales will be presented graphically by period.

The PK population will be used to present the summary of PK parameters.

4.12.1 Values Below the Limit of Quantification and Missing Values

If a Below the Limit of Quantification (BLQ) value occurs in a profile before the first measurable concentration, it will be assigned a value of zero concentration. If a BLQ value occurs after a measurable concentration in a profile and is followed by a value above the lower limit of quantification, then the BLQ value will be omitted following visual inspection of the plasma concentration versus time profile to assess the appropriateness of this assignment. If a BLQ value occurs at the end of a collection profile (after the last quantifiable concentration), the value will be treated as missing data. If 2 BLQ values occur in succession, the profile will be deemed to have terminated at the first BLQ value and any subsequent concentrations will be omitted from PK calculations following visual inspection of the plasma concentration versus time profile to assess the appropriateness of this assignment.

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. If a subject vomited following dose administration, then their profile will be examined to determine the impact of this on PK parameter estimation.

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 2 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.

4.12.2 Pharmacokinetic Parameters

Individual plasma concentration data for ALXN1840, assessed as plasma total Mo concentration-time data, with actual sampling dates and times calculated relative to the actual date and time for the start of dose administration in each Dosing Period, will be used to derive the PK parameters. PK parameters will be calculated

using non-compartmental analyses with Phoenix® WinNonlin® Version 8.0 or higher. If missing actual sampling dates and times, then the nominal time relative to the start time of the administration will be used.

The following plasma total Mo PK parameters will be derived for each subject and period:

- **C_{max} [ng/mL]:** Maximum observed plasma concentration
  - For multiple peaks, the highest post-dose concentration will be reported as C_{max}
- **C_{max}_n[ng/mL]/[mg]:** Dose normalized maximum observed plasma concentration
  - Calculated as C_{max} /dose
- **T_{max} [h]:** Time to maximum observed plasma concentration
  - In case that multiple peaks are available of equal magnitude at the highest post-dose concentration, the earliest T_{max} will be reported
- **AUC_t [h* ng/mL]:** Area under the plasma concentration versus time curve from time zero (dosing) to the last quantifiable concentration
- **AUC_t_n [h* ng/mL]/[mg]:** Dose normalized area under the plasma concentration versus time curve from time zero (dosing) to the last quantifiable concentration
  - Calculated as AUC_t /dose
- **AUC_∞ [h* ng/mL]:** Area under the plasma concentration versus time curve from time zero (dosing) extrapolated to infinity
- **AUCextr (%):** The percentage of AUC_∞ extrapolated.
  - Subjects with an AUCextrap > 20% will be flagged, and parameters that are dependent on AUC_∞ will also be flagged (AUC_∞, **AUC_∞ _n,** CL/F, Vd/F and Frel).
- **AUC_∞_n [h* ng/mL]/[mg]:** dose normalized area under the plasma concentration versus time curve from time zero (dosing) extrapolated to infinity
  - Calculated as AUC_∞ /dose
- **λ_z [1/h]:** Apparent terminal-phase elimination rate constant
  - 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 terminal phase
  - Calculated as dose/(λ_z*AUC_∞)
- **F_{rel}:** Relative bioavailability defined as the ratio of the geometric means for the dose normalized AUC_∞ parameter for the ALXN1840 Japanese cohort over the ALXN1840 non-Japanese cohort by dose strength of 15 mg or 60 mg.

PK parameters will be listed for each individual subject and summarized by cohort and period. 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 %CV, median, minimum and maximum.

For the relative bioavailability, a 95% CI for the ratio of the geometric means will be provided. To calculate CIs of geometric mean ratios, dose normalized AUC_∞ will be log-transformed and CIs will be constructed for the mean difference of log-transformed parameters, assuming that log-transformed parameters are normally distributed. The CIs are then back-transformed to receive CIs for the geometric mean ratios. The geometric mean ratios and their 95% CIs will be tabulated.

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. Subjects who vomit post-dose will have their plasma concentration profile evaluated for inclusion in the PK analysis.

Analyses of other PK data including, but not limited to those, of PUF Mo may be conducted.

4.12.3 Pharmacokinetic Analysis for Ethnic Difference

The PK parameters for total Mo (C_{max}, AUC_t, and AUC_∞) will be evaluated for Japanese and non-Japanese cohorts, using an analysis of variance (ANOVA) statistical model [1,2] with cohort and period as the fixed effects, and subject as a random effect, using the natural logarithms of the data. The within-subject CV for the C_{max}, AUC_t, and AUC_∞ will be estimated using the mean squared error from the ANOVA. The mean between-group differences and their 90% and 95% CIs are back-transformed to the linear scale and represent estimates of ratios of geometric means.

In addition, the Japanese versus non-Japanese cohorts will be evaluated using descriptive statistics: for each cohort, the geometric means and the associated 95% confidence intervals of C_{max}_n, AUC_t_n, and AUC_∞_n will be reported at each dose.

4.13 Exploratory Analyses

4.13.1 Dose Proportionality

Dose proportionality for each cohort and cohorts combined will be assessed graphically and using power models [1,2]. The log (PK parameters) is included as

a response variable and log (dose) is included as a fixed effect in the power model. The following PK parameters will be assessed for dose proportionality: dose-normalized C_{max} (C_{max}_n), dose-normalized AUC_t (AUC_t_n), dose-normalized AUC_∞ **(**AUC_∞**_n)**. The ratio of geometric means will be estimated with its 2-sided 90% and 95% confidence intervals.

4.13.2 CL/F and Body Size

Relationships between CL/F and body size (body weight [kg] and BMI [kg/m²]) will be evaluated graphically for the Japanese and non-Japanese cohorts and with combined cohort data. If suggested by the graphs, regression models may be fit to the data

4.13.3 Pharmacodynamic and Biomarker Analyses

Individual ALXN1840 PD and biomarkers, assessed as plasma total Cu (PD), NCC (PD), $NCC_{corrected}$ (PD), Cp (biomarker), and CpC (biomarker) concentration-time data (including measured, absolute and percent changes from baseline) will be listed and summarized at each time point by cohort and period with descriptive statistics. The NCC level will be corrected for the amount of Cu bound to the TPC (NCCcorrrected).

Individual subject data (and change from baseline) of plasma Cp and copper levels (total Cu, Cp, CpC and NCC) will be presented graphically for each cohort and period. Mean plots (for measured and change from baseline value) of cohort and dose will be overlaid (separately for PD and biomarker parameters) and presented over time.

Analyses of other biomarker data including, but not limited to, those of PUF Cu may be conducted.

4.14 Methods for Withdrawals, Missing Data and Outliers

The individual plasma 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 4.12.1 regarding the handling of missing and BLQ values. For PD data analysis, there will be no imputation for missing values.

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).

5. References

[1] Amy Newlands, "Statistics and Pharmacokinetics in Clinical Pharmacology Studies", PhUSE 2006, Dublin, Ireland.

[2] European Medicines Agency. Committee for medicinal products for human use (CHMP): Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1). Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf.