A Phase 1, Randomized, 2-Period, 2-Way Cross-over Study to Assess the Single-Dose Pharmacokinetics of ALXN1840 Enteric-Coated Tablets at 2 Dose Strengths in Healthy Adult Subjects

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Statistical Analysis Plan

RICHMOND Pharmacology

SPONSOR'S REFERENCE NUMBER: ALXN1840-HV-104

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STATISTICAL ANALYSIS PLAN

A Phase 1, Randomized, Open-Label, 2-Way Crossover Study to Assess the Single-Dose Pharmacokinetics of ALXN1840 Enteric-Coated Tablets at 2 Dose Strengths in Healthy Adult Subjects.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Explanation
AE	Adverse Event
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
AUC	Area under the Plasma Concentration Time Curve
AUC_{extr}	The percentage of AUC_{∞} extrapolated
AUC_t	Area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration
AUC_{∞}	Area under the plasma Concentration versus Time Curve from Time Zero Extrapolated to Infinity
BDRM	Blind Data Review Meeting
BLQ	Below the Level of Quantification
BMI	Body Mass Index
CL/F	Clearance/Bioavailability
C_{max}	Maximum Observed Plasma Concentration
Cp	Ceruloplasmin
CpC	Ceruloplasmin-bound copper
CSR	Clinical Study Report
CRU	Clinical Research Unit
CTCAE	Common Terminology Criteria for Adverse Events
Cu	Copper
CV	Coefficient of Variation
EC	Enteric-Coated
ECG	Electrocardiogram
EOS	End of Study
ET	Early Termination
F_{rel}	Relative Bioavailability
GMR	Geometric Mean Ratio
ICF	Informed Consent Form
λ_z	Apparent Terminal-Phase Elimination Rate Constant
MedDRA	Medical Dictionary for Regulatory Activities
Mo	Molybdenum
NCC	Non-Ceruloplasmin-Bound Copper
$NCC_{corrected}$	Corrected NCC
PD	Pharmacodynamic(s)
PDF	Portable Document Format
PK	Pharmacokinetic(s)
PUF	Plasma Ultrafiltrate

QT	Interval between the start of the Q wave and the end of the T wave in an ECG
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
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TESAE	Serious Treatment-Emergent Adverse Event
$t_{½}$	Terminal Elimination Half-Life
TFLs	Tables, Figures and Listings
T_{max}	Time to Maximum Observed Plasma Concentration
TPC	Cu-Tetrathiomolybdate-Albumin Tripartite Complex Formed after ALXN1840 Administration
V_d/F	Apparent Volume of Distribution
WHO-DD	World Health Organization 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 dated 09 Apr 2019, Amendment 1, was used in the preparation of 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 assess the relative bioavailability of ALXN1840 administered orally as 3 × 5 mg enteric-coated (EC) tablets (test) versus 1 × 15 mg EC tablet (reference).

Secondary

- To assess the overall safety and tolerability of ALXN1840.

Exploratory

- Relationships between Clearance/bioavailability (CL/F) and body size, body weight (kg) and body mass index (BMI kg/m²).
- To explore pharmacodynamics (PD) and biomarkers of 15 mg ALXN1840 among the following dosing regimens: either as a single 15 mg EC tablet (Treatment A) or 3 EC tablets of 5 mg (Treatment B).

2.2 Endpoints

Primary

- PK parameters for plasma total molybdenum (Mo) including the maximum observed plasma concentration (C_{max}), the area under the plasma concentration versus time curve from zero to the last quantifiable concentration (AUC_t), and extrapolated to infinity (AUC_∞).

Secondary

- Safety assessed by incidence of treatment emergent adverse events (TEAEs) and serious TEAEs (TESAEs), physical examination, vital signs measurements, clinical laboratory, and 12-lead electrocardiogram (ECG) results.

Exploratory

- CL/F, body weight, and body mass index.
- Absolute and percent changes of plasma copper (Cu) levels including total Cu, ceruloplasmin (Cp), ceruloplasmin-bound copper (CpC) and non-ceruloplasmin-bound copper (NCC).
- The NCC level will be corrected for the amount of Cu bound to the TPC resulting in corrected NCC ($NCC_{corrected}$).

3. STUDY DESIGN

This is a single-center, randomized, open-label, 2-way crossover study to assess the single-dose pharmacokinetics (PK) of ALXN1840 EC tablets at 2 dose strengths in healthy male and female adult subjects under fasting conditions. Pharmacokinetic parameters will be calculated based on the measurement of plasma total Mo concentration. A total of 48 healthy, adult participants (20-28 male and 20-28 female) who complete the study screening assessments and meet all eligibility criteria will be enrolled to allow for a minimum of 40 subjects to complete the study (20-24 subjects in each sequence, 10-14 of each sex in each sequence).

3.1 Overall Design

The study has a Screening Period (Days -28 to -2), 2 Dosing Periods (Day -1 to Day 11 each) and an end-of-study (EOS) visit 14 days (+2 days) post final dose. After completing the Screening Period, enrolled subjects will be admitted to an inpatient facility (Clinical Research Unit [CRU]) on Day -1 for dosing on Day 1 in Dosing Period 1. Subjects will be readmitted to the CRU for Dosing Period 2 following a minimum of 14 days after the previous dose. In each Dosing Period, subjects will receive 1 of the 2 treatments as illustrated below:

Treatment A (reference)	1 x 15 mg ALXN1840 EC tablet
Treatment B (test)	3 x 5 mg ALXN1840 EC tablets

Table 1: Treatments

Subjects will return to the CRU 14 days (+2 days) after the final dose of study drug for the EOS visit with follow-up procedures, and to determine if any adverse event (AE) has occurred since the last study visit. If subjects withdraw from the study early, they will be seen and assessed by the Investigator, whenever possible, to undergo the procedures associated with the EOS visit.

Subjects may be replaced at the discretion of the Sponsor.

A total of 48 subjects will be enrolled (20-28 male subjects and 20-28 female subjects) to ensure a minimum sample size of 40 subjects (20-24 subjects in each sequence, 10-14 of each sex in each sequence) complete the study.

Each subject will receive both treatments in 1 of the 2 sequences as defined in the table below according to the study drug dosing regimen outlined above, where the single 15 mg EC tablet (Treatment A) is the "reference" dose and the 3 EC tablets of 5 mg (Treatment B) are the "test" dose.

Sequence Number	**Treatment Sequence**		**Male**	**Female**	**Total**
	Period 1	**Period 2**			
1	A	B	10-14	10-14	24
2	B	A	10-14	10-14	24
Total			20-28	**20-28**	**48**

Table 2: Treatment Sequence

3.2 Duration of Study

The planned study duration is approximately 70 days; up to 27 days for screening, approximately 29 days for dosing and follow-up, and an interval of at least 14 days between the 2 Dosing Periods.

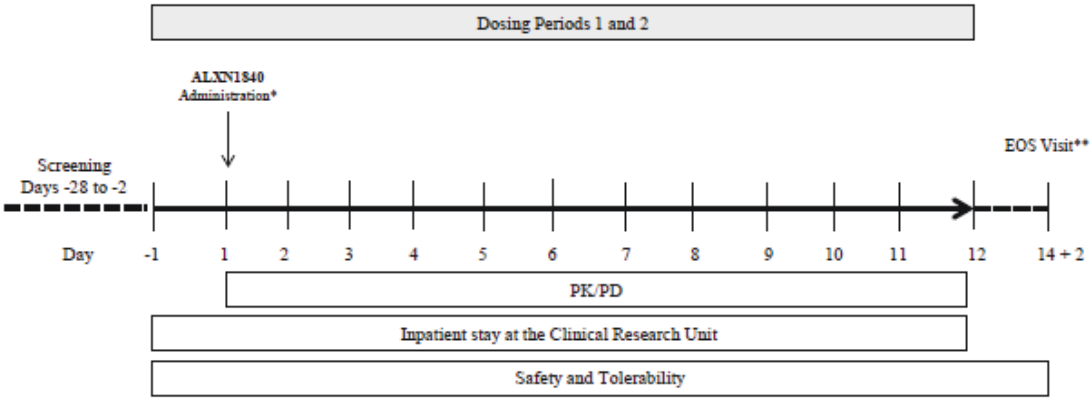

Figure 1: Study ALXN1840 Schematic

* Subjects will leave the Clinical Research Unit on Day 11 of Dosing Period 1 and will be readmitted following a minimum of 14 days after the dose of study drug for Dosing Period 2.

** EOS visit to be performed 14 days (+2 days) after the final dose of study drug.

Abbreviations: EOS = end of study, PD = pharmacodynamics; PK = pharmacokinetics.

3.3 Sample size

The study sample size is not based on hypothesis testing with statistical considerations. A sample size of 40-48 subjects (20-24 subjects in each sequence; 10-14 male and female subjects in each sequence, with a maximum split in either direction of approximately 60%:40%) 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 48 subjects will be enrolled with 20-28 male subjects and 20-28 female subjects.

3.4 Randomization and Blinding

This is an open-label study where, in order to minimize selection bias in treatment assignment, subjects will be randomized to 2 treatment sequences.

- Eligible subjects who meet all inclusion and no exclusion criteria will be assigned unique numbers for enrollment.
- Study subject numbers will not be reallocated once assigned.
- To achieve balance between the number of males and females in the 2 treatments sequence the maximum split in either direction will be approximately 60%:40% (10-14 of each sex in each sequence).
- Subjects randomized to Treatment A will receive 1 × 15 mg ALXN1840 EC tablet, whilst subjects randomized to Treatment B will receive 3 x 5 mg ALXN1840 EC tablets.

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 non-missing observations (n), arithmetic mean, 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. Descriptive statistics and percentages and frequency counts will be summarized by sex, treatment, period and sequence, where appropriate.

PK parameters will be presented as follows in the listing: C_{max} and time to maximum observed plasma concentration (T_{max}) will be presented as given in the raw data; AUC_t, AUC_∞, the apparent terminal-phase elimination rate constant (λ_z), the terminal elimination half-life ($t_{1/2}$), CL/F, and the apparent volume of distribution (Vd/F) will be presented with 3 decimal places. Descriptive statistics for PK parameters will be presented with decimal places as appropriate for the parameter and treatment.

The analyses will be presented by treatment, sex, period and sequence where appropriate. All collected data will be presented in by-subject listings. Listings will be ordered by treatment sequence and subject number and will include all randomized subjects.

Baseline will be defined as the last non-missing value among assessments recorded prior to first administration of study drug per period, where unscheduled assessment at the respective scheduled study are also taken into account. Changes from baseline values will be calculated as the post-baseline assessment value minus the baseline value per period. In general, only observed values from scheduled time points will be used to create summary tables, with the exception of unscheduled assessments on the respective study day. It is assumed that unscheduled assessments on scheduled study days are repetitions of potentially invalid scheduled assessments, and thus those unscheduled assessments will replace the respective scheduled assessments for summary tables and further statistical analyses.

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 as RTF files in Microsoft Word. Final TFLs will additionally be created in bookmarked portable document format (PDF). Further details of page layout will be provided in the TFL shell document.

All statistical analyses will be conducted using SAS® for Windows® Version 9.3 or higher.

4.1 Interim Analysis

No interim analyses are planned for this study.

4.2 Analysis Populations

Inclusion and exclusion from each analysis population will be decided at the Blind Data Review Meeting (BDRM) prior to database lock. Further exclusions may be made from PK and PD populations based on the plasma concentration data.

Randomized Population

The randomized population consists of all enrolled subjects who sign the informed consent form (ICF), and randomised in the study, regardless of whether subjects received a dose of study drug. Subjects who prematurely withdraw from the study for any reason and for whom an assessment is not performed will still be included in the randomized population. Subjects will be summarized according to their randomized treatment group.

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 data to enable the calculation of at least one of the following PK parameters: C_{max}, AUC_t or AUC_∞ for plasma total Mo under both treatments, A and B. Subjects who did not receive the full dose of study drug will be excluded from the PK population.

PD Population

The PD population will consist of all subjects who have sufficient plasma samples which will enable the evaluation of the PD effects, that is for whom at least one absolute and percentage change of plasma copper levels in terms of either Cu, Cp, CpC or NCC is available under both treatments, A and B.

4.3 Subject Disposition

All subjects enrolled will be included in the summary of subject disposition. This will present the overall number of subjects screened and by treatment sequence 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 analysis population will be tabulated. Discontinued subjects will be listed. Subject assignment to analysis 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), body measurement data (height, body weight and body mass index) at screening and menstruation information (regular cycle, first day of last cycle, average cycle length) will be listed and summarized (excluding menstruation information) by each treatment sequence and overall for the safety population. If the remaining analysis populations are different from the safety population by more than 5%, separate demographic tables will be produced. Height will be measured in centimetres and weight in kilograms. Body mass index will be given in kg/m^2.

4.5 Baseline and Other Safety Characteristics

Data collected from 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 and the frequency of failed inclusion or exclusion criteria will be summarized.

4.7 Protocol Deviations

The final review of protocol deviations will be performed prior to database lock. The protocol deviations will be listed and summarized by treatment sequence.

4.8 Medical History

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary Version 21.0 (or higher). Medical and surgical history data will be listed individually and summarized by treatment sequence.

4.9 Study Drug Administration and Meals

As per protocol, study drug dosing will occur with the subject being in a fasted state.

Study drug administration data will be listed individually.

Meal (breakfast, lunch, dinner, snacks) times and consumption grade will be listed.

4.10 Prior and Concomitant Medications

All prior and concomitant medications will be coded using the World Health Organization Drug Dictionary version June 1, 2018 or higher and will be listed individually.

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 either 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 and continuing at the time of first dose of study drug administration.

If medication/therapy dates or times 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, anatomical therapeutic chemical (ATC) Term and World Health Organization drug dictionary (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. Prior medication will be summarized in the same way as concomitant medication.

Non-pharmacologic therapies and procedures will be listed separately.

4.11 Safety Analyses

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 21.0 (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 period, treatment and overall, by toxicity and by relationship to study drug.

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

Subjects having multiple AEs within a category (e.g., overall, SOC and Preferred Term) will be counted once in that category.

For toxicity tables, a subject's worst toxicity 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 and AEs resulting in withdrawal from the study will be listed separately.

Adverse events during screening will be summarized by treatment sequence and overall.

4.11.2 Laboratory Data

Clinical laboratory parameters (including blood chemistry, haematology, 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. 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) and summarized by CTCAE grade. Non-protocol parameters will only be listed, in a separate listing, if required. Shift tables by treatment will be produced for all other laboratory parameters. 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. Similarly, shift tables from baseline based on NCI toxicity grade will be created.

As per the study protocol, any laboratory tests with values considered clinically significantly abnormal are to be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or medical monitor. For all summary analyses, only the last available of all repeated measurements is to be used.

4.11.3 Electrocardiograms

ECG parameters will be measured at the time points specified in the study protocol and will at least include heart rate, PR interval, RR interval, QRS duration, interval between the start of the Q wave and the end of the T wave in an ECG (QT), and corrected QT interval corrected using Fridericia's formula (QTcF), where 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 per period.

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

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

- 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

As per the clinical study protocol, recorded ECGs will be reviewed by the Investigator, or qualified designee, and abnormal ECGs may be followed by additional safety recordings. For summary analyses, the additional safety ECGs will be used only, and will replace the initial ECGs that were reviewed as abnormal.

4.11.4 Vital Signs

Vital signs data (systolic and diastolic blood pressure, heart rate, temperature, respiration rate, and if available orthostatic drop calculated as standing minus supine value) 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 treatment.

As per the study protocol, out of range blood pressure or heart rate measurements are to be repeated by the Investigator's discretion, and for summary statistics any such repeated measurement is to be used instead of the initial out of range measurement.

4.11.5 Physical Examination

Physical examination data will be listed individually and abnormal findings will be summarized by period and treatment.

4.12 Pharmacokinetic Analyses

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

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 within period, 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

The plasma total Mo PK parameters will be summarized with descriptive statistics.

Analyses of other PK data including, but not limited to those, of PUF Mo may be conducted. PK parameters will be calculated using Phoenix® WinNonlin®.

The following PK parameters will be derived for each subject:

- **C_{max} [ng/mL]:** Maximum observed plasma concentration
    - for multiple peaks, the highest post-dose concentration will be reported as C_{max}
- **T_{max} [h]:** Time to maximum observed plasma concentration
    - in case that multiple peaks are of equal magnitude, 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_∞ [h*ng/mL]:** Area under the plasma concentration versus time curve from time zero (dosing) extrapolated to infinity
- **AUC_{extr} (%):** The percentage of AUC_∞ extrapolated
    - Subjects with an AUC_{ext} > 20% will be flagged, and parameters that are dependent on AUC∞ will also be flagged (AUC_∞, AUC_∞ _n, CL/F, Vd/F and F_{rel})
- **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_{∞}.
- **Vd/F [L]:** Apparent volume of distribution during terminal phase
  - Calculated as dose / (λ_z*AUC_{∞})
- **Relative Bioavailability (F_{rel})**: defined as the ratio of the geometric means of PK parameter (C_{max}, AUC_t and AUC_{∞}) for the test (= treatment B = 3 x 5 mg ALXN1840 EC tablets) over the reference (= treatment A = 1 x 15 mg ALXN1840 EC tablet) treatment, for details see section 4.12.3

PK parameters will be listed for each individual subject and summarized by period and treatment. Descriptive statistics for PK parameters will include number of observations (n), arithmetic mean (Mean), SD, arithmetic coefficient CV, geometric mean, geometric CV, median, minimum and 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 will be provided in the CSR. Additional PK parameters may be calculated, as appropriate.

4.12.3 Bioavailability Analysis

The PK parameters for total Plasma and Plasma Ultrafiltrate Mo (C_{max}, AUC_t, and AUC_{∞}) will be evaluated using an Analysis of Variance (ANOVA) statistical model with dosing period, treatment, and sequence as the fixed effects, and subject as a random effect, using the natural logarithms of the data. Confidence intervals (90%) will be constructed for the least squares geometric mean ratios (GMR) for the 3 × 5 mg ALXN1840 (test) versus 1 × 15 mg ALXN1840 (reference) dose for all 3 parameters using the natural log-transformed data. The GMRs and associated 90% confidence limits will be exponentiated back to the original scale. The within-subject coefficient of variation for the C_{max}, AUC_t, and AUC_{∞} will be estimated using the mean squared error from the ANOVA. In addition, the geometric means and the associated 95% confidence intervals of C_{max}, AUC_t, and AUC_{∞} will be reported for each treatment.

4.12.4 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 two treatment sequences and with combined data. If suggested by the graphs, regression models may be fit to the data.

4.13 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 treatment with descriptive statistics.

NCC is calculated by subtracting the amount of Cu bound to ceruloplasmin from the total plasma Cu level:

$$NCC[\mu mol/L] = \frac{Total\ plasma\ Cu\ [\mu g/L] - (3.15 * ceruloplasmin\ [mg/L])}{63.5\ [\mu g/\mu mol]}$$

For subjects dosed with ALXN1840, there is also Cu bound in the tetrathiomolybdate-Cu-albumin tripartite complex which is addressed by the NCC correction method:

$$NCC_{corrected} = \left(\sqrt{NCC} - 0.993\sqrt{Mo}\right)^2$$

In the calculation of NCC and NCCcorrected, the following adjustments will be made:

- Copper values < lower limit of quantification (LLOQ) are set to missing and NCC will not be derived;
- Ceruloplasmin <LLOQ are set to 0;
- Molybdenum <LLOQ are set to 0;
- Negative NCC values are not utilized and NCCcorrected will not be derived;
- NCCcorrected will be set to 0 when 0.993√Mo > √NCC.

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

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 below level of quantification (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 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).

Certificate Of Completion

Envelope Id: PPD
Status: Completed
Subject: Please DocuSign: C18054 ALXN1840-HV-104 SAP Final 1.0 11Nov2019_signed.pdf
Source Envelope:
Document Pages: 20
Signatures: 2
Envelope Originator:
Certificate Pages: 2
Initials: 0
PPD
AutoNav: Enabled
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Status: Original
19-Nov-2019 | 12:54
Holder: PPD
Location: DocuSign

Signer Events	Signature	Timestamp
PPD Alexion Pharmaceuticals Inc. Security Level: Email, Account Authentication (Required), Digital Certificate **Signature Provider Details:** Signature Type: Alexion Pharmaceuticals, Inc. (Regulated) (Client ID: PPD Signature Issuer: Alexion Pharmaceuticals Issue 2 CA **Electronic Record and Signature Disclosure:** Not Offered via DocuSign	Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD Signature Provider Location: https://dswebapp.alexion.com/takepen/signenvelope With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 19-Nov-2019 | 13:00 Viewed: 19-Nov-2019 | 13:20 Signed: 19-Nov-2019 | 13:21
PPD Alexion Pharmaceuticals, Inc. (Regulated) Security Level: Email, Account Authentication (Required), Digital Certificate **Signature Provider Details:** Signature Type: Alexion Pharmaceuticals, Inc. (Regulated) (Client ID: PPD Signature Issuer: Alexion Pharmaceuticals Issue 2 CA **Electronic Record and Signature Disclosure:** Not Offered via DocuSign	Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD Signature Provider Location: https://dswebapp.alexion.com/takepen/signenvelope With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 19-Nov-2019 | 13:00 Viewed: 19-Nov-2019 | 13:06 Signed: 21-Nov-2019 | 08:33

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	19-Nov-2019 | 13:00
Certified Delivered	Security Checked	19-Nov-2019 | 13:20
Signing Complete	Security Checked	21-Nov-2019 | 08:33
Completed	Security Checked	21-Nov-2019 | 08:33

Payment Events	Status	Timestamps