Alexion Pharmaceuticals, Inc.

ALXN1850-HPP-101

A Phase 1, Open-label, Dose-escalating Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ALXN1850 in Adults with Hypophosphatasia

26/04/2022

Final Statistical Analysis Plan

Version 1.0

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List of Abbreviations

Abbreviation	Term
25-OH	25- hydroxy
ADA	antidrug antibody
AE	Adverse event
ALP	alkaline phosphatase
AUC	area under the curve
AUC_{inf}	area under the curve from time 0 extrapolated to infinity
AUC_t	area under the curve from time 0 to the last quantifiable concentration
AUC_{tau}	area under the plasma concentration versus time curve within the dosing interval
bHCG	human chorionic gonadotropin
BLQ	below the limit of quantification
BMI	body mass index
Ca	calcium
CI	confidence interval
CL	total body clearance
CL/F	apparent total body clearance
C_{max}	maximum observed plasma concentration
CSR	clinical study report
CTX-1 (sCTX)	serum C-telopeptide cross-link of type 1 collagen
CV	coefficient of variation
ECG	electrocardiogram
ED	early discontinuation
EoS	end of study
F	absolute bioavailability after subcutaneous administration
FSH	follicle stimulating hormone
eCRF	electronic case report form
HIV	human immunodeficiency virus
HPP	hypophosphatasia
ICF	informed consent form
IgG	immunoglobulin G
IQR	interquartile range
IV	Intravenous(ly)

MedDRA	Medical Dictionary for Regulatory Activities
n	number of non-missing values
N	number of participants
NAb	neutralizing antibody
P1NP	N-terminal propeptide of type I procollagen
PA	pyridoxic acid
PD	pharmacodynamic(s)
PEA	phosphoethanolamine
PK	pharmacokinetic(s)
PL	pyridoxal
PLP	pyridoxal-5'-phosphate
PPi	inorganic pyrophosphate
PT	preferred term
PTH	parathyroid hormone
Q1	quartile 1
Q3	quartile 3
QTcF	QT interval corrected for heart rate using Fridericia's formula
R	subcutaneous accumulation ratio
Rsq	the coefficient of determination
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SD	standard deviation
SOC	system organ class
SRC	Safety Review Committee
$t_{1/2}$	apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TNSALP	tissue-nonspecific alkaline phosphatase
T_{max}	time of maximum observed concentration
V_d	volume of distribution during the terminal phase
V_d/F	apparent volume of distribution during the terminal phase
$\%AUC_{extrap}$	percentage of AUC_{inf} due to extrapolation
%CV	percent coefficient of variation
λ_z	terminal phase elimination rate constant

1. Introduction

Hypophosphatasia (HPP) is a rare, inherited, metabolic disease caused by deficient activity of the tissue non-specific isoenzyme of alkaline phosphatase, typically due to loss-of-function mutation(s) in the *ALPL* gene. ALXN1850 is an investigational enzyme replacement therapy that addresses the underlying cause of HPP by replacing the defective enzyme, thus reversing the mineralization defects of the skeleton and improving systemic manifestations of HPP.

The purpose of this statistical analysis plan (SAP) is to define the planned statistical analysis of the study data consistent with the study objectives. This SAP is written based on protocol ALXN1850-HPP-101, version Amendment 5, dated 11 Mar 2022. Any deviations/changes from the planned analyses described in this SAP will be identified, with justification, in the appropriate section of the clinical study report.

2. Objectives and Endpoints

The study objectives and corresponding endpoints are presented in Table 1.

Table 1: Objectives and Endpoints

Objective	Endpoints
Primary	
Assess the safety and tolerability of ALXN1850 given IV as a single dose and given SC 1 dose per week for 3 weeks	Incidence of TEAEs and TESAEs
Secondary	
Assess the PK of single IV and multiple SC doses of ALXN1850	ALXN1850 PK (activity) over time profiles and PK parameters
Assess the absolute bioavailability of ALXN1850 SC	AUC_{tau} values of the first SC versus IV administration
Assess the PD effects of single IV and multiple SC doses of ALXN1850	Absolute change and percent change from baseline in plasma concentrations of PPi and PLP and PLP/PL ratio over time
Assess the immunogenicity potential of ALXN1850	Incidence of ADAs and NAbs
Exploratory	
Explore role of ALXN1850 on calcium and bone homeostasis and other PD biomarkers	Absolute, change, and percent change from baseline in ionized Ca, phosphorus, magnesium, PTH, CTX-1 (sCTX), P1NP, osteocalcin, and PA over time

Abbreviations: ADA = antidrug antibody; AUC_{tau} = area under the plasma concentration versus time curve within the dosing interval; Ca = calcium; IV = intravenous; NAb = neutralizing antibody; P1NP = N-terminal propeptide of type I procollagen; PA = pyridoxic acid; PD = pharmacodynamics(s); PK = pharmacokinetic(s); PL = pyridoxal; PLP = pyridoxal-5'-phosphate; PPi = inorganic pyrophosphate; PTH = parathyroid hormone; SC = subcutaneous; CTX-1 (sCTX) = serum C-telopeptide cross-link of type 1 collagen; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event

3. Study Design

This is an open-label, dose-escalating study to assess safety, tolerability, PK, PD, bioavailability, and immunogenicity of ALXN1850 when given IV and SC to adults with HPP.

Study participants will be enrolled into 3 cohorts in a sequential fashion. The first participant in each cohort will begin dosing before the rest participants of the cohort. A Safety Review Committee (SRC) wi ll convene after the first participant in each cohort has completed the first IV dose to assess safety and tolerability, and to endorse initiation of SC study drug administration to the first participant as well as IV and SC study drug administration to the remaining number of participants in the cohort. Once at least 3 participants in Cohort 1 participants have received a single IV dose and 3 weekly SC doses, the SRC will convene again to review safety and tolerability data, and to determine if the dose escalation may proceed. If the SRC endorses dose escalation, Cohort 2 will begin dosing at the next dosing level. Cohort 3 will begin dosing after the SRC has reviewed all relevant safety, tolerability, and PK data from participants in Cohorts 1 and 2 and endorsed dose escalation. The study design is presented in Figure 1.

Participants who are positive for ADAs at the last assessment of the study will be given options to enable further monitoring of their ADA values after the end of the study; these options may include enrollment in the Global HPP Registry.

4. General Statistical Considerations

All statistical analyses will be conducted using statistical analysis system SAS® Version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina) a nd Phoenix® WinNonlin® Version 8.0 or higher (Certara USA, Inc., Princeton, New Jersey) .

Descriptive statistics for continuous variables will include number of participants (N), number of non-missing values (n), a rithmetic mean, geometric mean (for PK analysis only) , standard deviation (SD), pe rcent coefficient of variation (%CV; for PK analysis only) , geometric %CV (for PK analysis only) , median, quartile 1 (Q1, for safety analysis only) , quartile 3 (Q3, for safety analysis only), i nterquartile range (IQR, for safety analysis only) , minimum, and maximum, unless otherwise noted. For categorical variables, frequencies and percentages will be presented. Descriptive statistics will be summarized by cohort and overall and by timepoint, unless otherwise noted. In the case where N is an even number, the median will be calculated as the average of the 2 middle numbers of the ordered samples or parameter estimates.

For the summary statistics of all continuous variables unless otherwise specified, for absolute value, minimum and maximum will be presented to the same number of decimal places as the raw data, mean, median, Q1, Q3, and IQR will be presented to one more decimal places than the raw data, SD will be presented to two more decimal places than the raw data; for percent change, minimum and maximum will be presented to one decimal place, mean, median, Q1, Q3, and IQR will be presented to two decimal places, and SD will be presented to three decimal places. %CV and geometric %CV will be presented to one decimal place, and N and n will be presented to integer.

Percentages will be suppressed when the count is zero and will be presented to one decimal place. The denominator for all percentages will be the number of participants in the cohort for the population of interest, unless otherwise specified.

All tables, listings, and figures will be presented by cohort, unless otherwise specified.

All data listings will be sorted by cohort, participant number, and date-time if applicable.

No algorithm for imputation of missing data will be employed but will be analyzed as missing.

Study days are calculated with respect to the first dose date as below:

- If the assessment/observation date is on or after the first dose date, then Study Day = Assessment/Observation Date – First Dose Date + 1;
- Otherwise, Study Day = Assessment/Observation Date – First Dose Date

Study weeks are calculated with respect to the first dose for the assessment/observation occurred on or after the first dose as below, unless otherwise specified:

- Study Week = Integer part of (Assessment/Observation Date – First Dose Date)÷7+1

Baseline will be defined as the last non-missing assessment (including repeated and unscheduled assessments) before the first dose of study drug administration, unless otherwise specified.

For summary of safety assessments, if there are repeated measurements at a time point, the first non-missing assessment at that time point will be used in the summary tables.

Unscheduled results will not be included in the summary tables, except for determining Baseline, but will be presented in data listings.

For safety laboratory evaluations, for the purpose of summarization, any numeric values recorded below the lower limit or above the upper limit of quantification will be set to the respective limit for all related summaries. In listings, original results containing inequality sign will be displayed, unless otherwise specified.

The methodology and data handling specifications for PK data are detailed in Section 8.

4.1. Statistical Hypotheses

No statistical hypotheses are planned for this study.

4.2. Sample Size

The sample size is empiric and selected to support assessment of safety, tolerability, and PK parameters. Approximately 15 participants will be enrolled to allow for at least 9 participants (3 per cohort) to “complete” (ie. participant completed EoT assessments, all PK/PD sampling was performed within window, and all doses were received per the SoA) the study.

4.3. Randomization, Stratification, and Blinding

This is a Phase 1, open-label study; therefore, there will be no randomization, stratification, and blinding of study participants in this study.

4.4. Analysis Sets

The following analysis sets will be used in the statistical analyses:

- Safety Set: The Safety Set will include all participants who receive any amount of study drug. Participants will be analyzed according to the study drug received.
- Pharmacokinetic Set: The PK Set will include all treated participants for whom the PK profile of ALXN1850 can be adequately characterized. Pharmacokinetic analyses will be based upon the study drug received.
- Pharmacodynamic Set: The PD Set will include all treated participants for whom the PD profile of ALXN1850 can be adequately characterized.
- Immunogenicity Analysis Set: The Immunogenicity Analysis Set will include all treated participants who received any study drug and who after the first dose have at least one reportable result in the ADA assay. Anti-drug antibody analysis will be conducted based on the actual treatment they receive.

5. Participant Disposition

5.1. Disposition

Using the enrolled set, the screen failure of participants will be summarized with counts and percentages by overall. A summary table will include the following:

- Number of participants in the enrolled set (ie, all participants who signed the informed consent form [ICF])
- Number of participants who were screen failures
- Number of participants who received a dose
- Number of participants who failed screening due to COVID-19 related reasons
- Reason for screen failure that was not due to eligibility
- Reason for screen failure that was due to eligibility

Based on the Safety Set, the analysis sets will be summarized with counts and percentages by cohort and overall. A summary table will include the following:

- Number of participants included in PK Set
- Number of participants excluded from the PK Set
- Reason for exclusion from the PK Set
- Number of participants included in PD Set
- Number of participants excluded from the PD Set
- Reason for exclusion from the PD Set
- Number of participants included in Immunogenicity Set
- Number of participants excluded from the Immunogenicity Set
- Reason for exclusion from the Immunogenicity Set

Using the Safety Set and PK Set, the disposition of participants will be summarized with counts and percentages by cohort and overall. A summary table will include the following:

- Number of participants who completed the study
- Number of participants who discontinued the study
- Reasons for discontinuation
- Number of participants who discontinued the treatment
- Reasons for treatment discontinuation
- Number of participants who were discontinued due to COVID-19

Screen failure data will be presented in a data listing for all screen failure participants. Participant disposition data and analysis sets will be presented in separate data listings for the Safety Set.

5.2. Protocol Deviations

The protocol deviations will be summarized by cohort and overall for the Safety Set. Protocol deviations will be classified as important and not important.

All protocol deviations will be presented in a data listing for the Safety Set.

5.3. Inclusion and Exclusion Criteria

Inclusion and exclusion criteria deviations will be presented in a data listing for the Safety Set.

6. Demographics and Baseline Characteristics

6.1. Demographics

Age, sex, race, ethnicity, height, and body mass index (BMI) will be collected at Screening only; weight will be collected at Screening, on Day -1, and on Day 14, Day 21, and Day 28 for first participant within each cohort, and on Day 7, Day 14, and Day 21 for subsequent participants within each cohort.

Descriptive statistics will be calculated for the following continuous demographic characteristics:

- Age (years)
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)

Frequency counts and percentages will be tabulated for the following categorical variables:

- Sex
- Race
- Ethnicity

The summaries will be presented by cohort and overall for the Safety Set. The last weight measurement collected before the first dose will be used as baseline for the summary.

Demographic characteristics will be presented in a data listing for the Safety Set.

6.2. Alcohol Test and Urine Drug Screen

An alcohol test will be performed at Screening. A urine drug screen (includes amphetamines; barbiturates; benzodiazepines; cocaine; opiates; phencyclidine; methamphetamine; 3,4 methylenedioxy-methamphetamine; and methadone) will be performed at Screening, on Day -1, and on Day 14, Day 21, and Day 28 for first participant within each cohort, and at screening, Day -1, Day 7, Day 14, and Day 21 for subsequent participants within each cohort.

Urine alcohol and drug screen results will be presented in a separate data listing.

6.3. Medical History

Medical history data will be collected at Screening.

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version to be delineated in the clinical study report [CSR]) and presented in a data listing for the Safety Set.

6.4. Genetic

To confirm eligibility, genetic testing for *ALPL* gene variant may be performed during the Screening.

Genetic testing results will be listed for the Safety Set.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

Medications that stop prior to the first dose of study drug will be classified as prior medication. Medications that start on or after the first dose of study drug will be classified as concomitant. If a medication starts before the first dose of study drug and stops on or after the first dose of study drug, then the medication will be classified as both prior and concomitant.

All prior and concomitant medications will be coded according to the World Health Organization Drug Dictionary (version to be delineated in the CSR).

Prior concomitant medications will be summarized by cohort and overall for the Safety Set. Concomitant medications will be summarized by cohort and overall for the Safety Set.

All prior and concomitant medications will be presented in a data listing for the Safety Set.

7.2. Medical or Surgical Treatment Procedures

Medical or surgical treatment procedures will be coded using the MedDRA (version to be delineated in CSR) a nd will be presented in a data listing for the Safety Set.

7.3. Study Treatment

The study drug composition and doses to be administered in this study are presented in the protocol. Decisions to continue, modify (explore the dose cohort further), o r escalate dosing will be made by the SRC.

The study drug administration and drug accountability data as collected on electronic case report form (eCRF) will be presented in the data listings for the Safety Set.

8. Pharmacokinetics

The Safety Set will be used for PK concentration listings and individual figures, and the PK Set will be used for PK parameter listings, all summary tables, mean figures and statistical analyses.

8.1. Data Handling

Plasma concentrations that are below the limit of quantification (BLQ) will be treated as zero for calculation of descriptive statistics. Individual values that are BLQ will be presented as "BLQ" in the concentration data listing. For the presentation of summary and order statistics, if at least 1 participant has a concentration value BLQ for the time point, then the minimum value will be displayed as "BLQ". If more than 25% of participants have a concentration data value of BLQ for a given time point, then the minimum and the first quartile [Q1] will be displayed as "BLQ". If more than 50% of the participants have a concentration data value of BLQ for a given time point, then the minimum and median values will be displayed as "BLQ". If more than 75% of the participants have a concentration value of BLQ for a given time point, the minimum, Q1, median, and third quartile [Q3] values will be displayed as "BLQ". If all participants have concentration data values BLQ for a given time point, then all order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as "BLQ", and the SD and coefficient of variation (CV) will be reported as not applicable, otherwise the calculated mean will be presented.

For PK parameter calculations, BLQ values will be treated as zero with the exception that a BLQ value between 2 quantifiable concentrations will be set as missing. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal phase, those concentrations after BLQ concentrations will be treated as missing.

Data rounding specifications for PK data are documented in the PK TLF shells.

8.2. Plasma Pharmacokinetic Concentrations

Blood samples for analysis of concentrations of ALXN1850 in plasma for each of the treatments will be collected at the following time points:

First participant within each cohort	Subsequent participants within each cohort
Day 1: pre-dose , EOI, and 2h, 6h, , and 12h post dose (IV dose)	Day 1: pre-dose , EOI, and 2h, 6h, , and 12h post dose (IV dose)
Day 2 (24 hours post IV dose)	Day 2 (24 hours post IV dose)
Day 3 (48 hours post IV dose)	Day 3 (48 hours post IV dose)
Day 5 (96 hours post IV dose)	Day 5 (96 hours post IV dose)
Day 8 (168 hours post IV dose)	
Day 15: pre-dose and 2h, 6h, and 12h post dose (SC dose 1)	Day 8: pre-dose and 2h, 6h, 8h, and 12h post dose (SC dose 1)
Day 16 (24 hours post SC dose 1)	Day 9 (24 hours post SC dose 1)
Day 17 (48 hours post SC dose 1)	Day 10 (48 hours post SC dose 1)
Day 19 (96 hours post SC dose 1)	Day 12 (96 hours post SC dose 1)
Day 22: pre-dose and 2h, 6h, and 12h post dose (SC dose 2)	Day 15: pre-dose and 2h, 6h, and 12h post dose (SC dose 2)
Day 23 (24 hours post SC dose 2)	Day 16 (24 hours post SC dose 2)

Day 29: pre-dose and 2h, 6h, and 12h post dose (SC dose 3)	Day 22: pre-dose and 2h, 6h, and 12h post dose (SC dose 3)
Day 30 (24 hours post SC dose 3)	Day 23 (24 hours post SC dose 3)
Day 31 (48 hours post SC dose 3)	Day 24 (48 hours post SC dose 3)
Day 36 (168 hours post SC dose 3)	Day 29 (168 hours post SC dose 3)
Day 51 (3 weeks post SC dose 3)	Day 43 (3 weeks post SC dose 3)
Day 65 (5 weeks post SC dose 3)	Day 57 (5 weeks post SC dose 3)
Day 85 (8 weeks post SC dose 3)	Day 78 (8 weeks post SC dose 3)

Individual plasma concentrations of ALXN1850 for each treatment will be presented in data listings and summarized separately using descriptive statistics (N, n [non-missing values within the population], arithmetic mean, SD, %CV, median, minimum, and maximum) b y cohort, study day, and scheduled time point. All participants (first and subsequent) will be summarized together for Days 1-8 (predose) for each cohort, after Day 8 only subsequent participants data will be summarized and whereas first participant data will be presented separately. An additional sensitivity analysis will be performed by combining subsequent participants with the first participant (following each SC dosing, ie, SC Dose 1, SC Dose 2, and SC Dose 3) whe re data (corrected from prior carryover exposure post IV dose) is summarized by cohort and scheduled timepoints relative to each dose.

Individual plasma concentrations for ALXN1850 will be plotted for each participant by actual time on both linear and semi-logarithmic scales. Mean plasma concentrations of ALXN1850 versus nominal time will be plotted for each treatment on both linear and semi-logarithmic scales. In addition, mean plasma concentrations of ALXN1850 versus nominal time will be plotted for each treatment by ADA status on both linear and semi-logarithmic scales. The definition of ADA status (ADA negative and ADA positive, and/or pre-existing immunogenicity, treatment-emergent ADA responses, and treatment-boosted ADA responses if data permits, the definition for the ADA response categories is described in the Section 11 of Immunogenicity Analysis).

Individual and mean plasma trough concentrations (C_{trough}) fo r ALXN1850 versus day following subcutaneous dose administration will be plotted on both linear and semi-logarithmic scales. Time to reach steady state will be graphically assessed by plotting mean plasma C_{trough} concentration versus study day in both linear and semilogarithmic scales.

In addition, attainment of steady state will be assessed via stepwise, linear mixed regression models with a random subject effect among subsequent participants. The analysis will be stratified by cohort. This approach involves an examination of Ctrough concentrations over time using mixed regression models and calculating a slope and corresponding 95% CI. Predose assessments on day 8, day 15, and day 22 will be used. The model results will be evaluated to see if 0 is included in the 95% CI which indicates that the steady state was achieved.

Plasma PK concentrations of ALXN1850 will be reported to 3 significant figures in summary statistics except for %CV which will be reported to 1 decimal place and N and n which will be reported as integers.

8.3. Plasma Pharmacokinetic Parameters

The plasma concentration-time data for ALXN1850 will be analyzed by non-compartmental analysis using Phoenix® WinNonlin® Version 8.0 or higher (Certara USA, Inc., Princeton, New Jersey). The following PK parameters will be derived for ALXN1850 based on actual date and times calculated relative to the actual date and time from the start of dose administration (for example, start of infusion) in each dosing period, where data permit. If missing actual sampling dates and times, then the nominal time relative to the start time of the administration will be used.

C_{max}	Maximum observed plasma concentration
$C_{max\_corrected}$	Maximum observed plasma concentration (for SC dose only if carryover from IV exposure is observed)
C_{trough}	Trough (predose) concentration observed at the start of the dosing interval (C_{trough})
T_{max}	Time of maximum observed concentration
AUC_t	Area under the curve (AUC) from time 0 to the last quantifiable concentration, calculated using the linear trapezoidal rule
AUC_{168h}	Area under the curve (AUC) from time 0 to 168h, calculated using the linear trapezoidal rule (for IV dose only)
AUC_{inf}	AUC from time 0 extrapolated to infinity, calculated using the linear trapezoidal method (IV dose only)
AUC_{tau}	AUC within the dosing interval, calculated using the linear trapezoidal method (SC dose only)
$AUC_{tau\_corrected}$	AUC within the dosing interval, calculated using the linear trapezoidal method (for SC dose only if carryover from IV exposure is observed)
$t_{1/2}$	Apparent terminal elimination half-life, calculated as: ln (2) / Kel
CL	Total body clearance calculated as: Dose / AUC_{inf} (For IV dose only)
CL/F	Apparent total body clearance calculated as: Dose / AUC_{tau} at steady state (For SC dose and only if C_{trough} can attain steady state)
V_d	Volume of distribution during the terminal phase, calculated as: Dose / [λ_z * AUC_{inf}] (For IV dose only)
V_d/F	Apparent volume of distribution during the terminal phase, calculated as: Dose / [λ_z * AUC_{tau} at steady state] (For SC dose and only if C_{trough} can attain steady state)
R	Subcutaneous accumulation ratio (AUC_{tau_SC} 3rd dose / AUC_{tau_SC} 1st dose)
F	Absolute bioavailability after subcutaneous administration, F = AUC_{tau} (SC) / AUC_{inf} (IV)

In addition to the above PK parameters, which will be listed and summarized, the following parameters will also be listed to document the selection of data points used to estimate $T_{1/2}$ using non-compartmental procedures:

λ_z	Terminal phase elimination rate constant
Number points	Number of data points used to estimate λ_z; a minimum of 3 data points must be used, and C_{max} must not be included
λ_z lower	Lower bound used for the estimation of λ_z
λ_z upper	Upper bound used for the estimation of λ_z
Rsq	r^2, the coefficient of determination (goodness of fit statistic); λ_z and all associated parameters will only be reported where $r^2 \geq 0.80$
$\%AUC_{extrap}$	Percentage of AUC_{inf} due to extrapolation; If $\%AUC_{extrap}$ >20% then, AUC_{inf}, CL, and V_d, will not be summarized

Additional plasma PK parameters may be calculated if deemed appropriate.

Plasma PK parameters for ALXN1850 will be presented in data listings and summarized separately using descriptive statistics (n, arithmetic mean, SD, %CV, geometric mean, geometric %CV, median, minimum, and maximum) by treatment. T_{max} will be summarized using the descriptive statistics median, minimum, and maximum only. Plasma PK will be presented by ADA status in figures. In addition, the Plasma PK parameters and ADA titers will be presented in the overlay figures for each subject overtime.

Plasma PK parameters of ALXN1850 will be reported to 3 significant figures in summary statistics except for %CV which will be reported to 1 decimal place and N and n which will be reported as integers.

8.4. Pharmacokinetic Statistical Analyses

Dose-proportionality of plasma ALXN1850 PK parameters, C_{max}, AUC_{168h}, AUC_{inf}, (IV dose only), and AUC_{tau} (SC dose only) for both IV and SC treatments over the dose range tested will be investigated. A power model will be fitted to describe the relationship between Y (C_{max}, AUC_{168h}, AUC_{inf}, and AUC_{tau}) and X (dose) using the least squares linear regression model:

- $\ln(Y) = \ln(\alpha) + \beta \ln(X)$, which is the logarithmic form of $Y = \alpha X^{\beta}$, where Y is PK parameter and X is dose.

The intercept of regression line, α, and the slope of the regression line, β, will be presented along with the 90% confidence interval (CI) of the slope. Dose proportionality will be concluded when the 90% CI of the slope (beta) lies entirely within $[(1+\ln(0.8)/\ln(r), 1+\ln(1.25)/\ln(r))]$, where r is the dose range (highest dose/lowest dose) .

Dose-proportionality of plasma ALXN1850 PK parameters, C_{max}, AUC_{168h}, AUC_{inf}, (IV dose only), a nd AUC_{tau} (SC dose only) for both IV and SC treatments over the dose range tested will be investigated based on ADA status (ADA negative and ADA positive, and/or pre-existing immunogenicity, treatment-emergent ADA responses, and treatment-boosted ADA responses if data permits) usi ng a similar model.

Absolute bioavailability of ALXN1850 following SC administration will be assessed by comparing AUC_{tau} values of the first SC dose versus AUC_{inf} of the IV dose for the similar dose

cohorts. Log-transformed AUC_{tau} and AUC_{inf} estimates will be analyzed using an analysis of variance model with group (IV vs SC) as a factor. The parameter estimates results will be exponentiated and the ratio of geometric means and 90% CIs will be presented. Analysis will be repeated by ADA status.

9. Safety Analysis

All safety summaries and analyses will be based upon the Safety Set.

9.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention, whether or not considered related to the study intervention.

Adverse events will be analyzed in terms of TEAEs which are defined as any AEs that begin or worsen on or after the first dose of treatment until the final follow-up visit. If the onset date/time of an AE is missing and AE end date is on or after the first dose of treatment, the AE will be defined as treatment-emergent.

A treatment-related TEAE is defined as a TEAE that is considered to be related to the treatment.

A serious AE (SAE) is defined as any untoward medical occurrence that, at any dose, results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent disability/incapacity, is a congenital anomaly/birth defect, or are other situations (medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious).

The AE's relationship to study treatment will be evaluated by the investigator. The following relationships will be collected on eCRF: related or not related.

The AEs that are evaluated as related will be considered treatment-related AEs for summary purpose.

The severity of AEs will be classified by the investigator as mild (Grade 1), moderate (Grade 2), severe (Grade 3), l ife-threatening (Grade 4), or fatal (Grade5) .

Injection/infusion-site reactions are defined as AEs localized to the site of IV or SC route of study drug administration, occurring at any time during study participation that are assessed by the Investigator to be related to study drug.

Injection/infusion-associated reactions are defined as systemic AEs (eg, fever, chills, flushing, alterations in heart rate and blood pressure, dyspnea, nausea, vomiting, diarrhea, and generalized skin rashes) oc curring during or within 24 hours of the start of IV or SC injection/infusion that are assessed by the Investigator to be related to the study drug.

An overview summary of TEAEs will be provided and will include number and percentage of participants:

- With at least 1 TEAE
- With at least 1 TEAE related to study drug
- With at least 1 TESAE
- With at least 1 TESAE related to study drug
- Drug withdrawn due to a TEAE
- Drug withdrawn due to a TEAE related to study drug
- Who died
- With at least 1 injection/infusion-site reactions
- With at least 1 injection/infusion-associated reactions
- With at least 1 hypersensitivity reaction

All AE summary tables will be summarized by the most recent type of administration (IV or SC), cohort, and overall (within each cohort and all cohorts combined)

All AEs will be coded using MedDRA (version to be delineated in the CSR). The summary will be presented according to the most recent type of administration (ie, IV or SC) be ing received prior to the AE onset regardless of when the AE ended, and by cohort and overall.

The TEAEs will also be summarized by system organ class (SOC), p referred term (PT) , by severity and relationship to study treatment. The TESAEs will also be summarized by SOC, PT, and by relationship to study treatment.

Adverse events of special interest including injection/infusion-site reactions and hypersensitivity including anaphylaxis (injection/infusion-associated reactions [IAR] + hypersensivity) wi ll also be summarized by SOC and PT.

The summary of TEAE, TESAE, and AE of special interest including injection/infusion-site reactions and hypersensitivity including anaphylaxis by SOC and PT will also be repeated by ADA status (ADA negative and ADA positive, and/or pre-existing immunogenicity, treatment-emergent ADA responses, and treatment-boosted ADA responses if data permits).

In the summary tables where both SOC and PT are presented, the default ordering of SOC will be alphabetical and the default ordering for PT will be most prevalent (using percentage) PT within each SOC based on Total column. For PTs with the same number of participants, they should be further sorted by number of events and then alphabetically.

All summary tables will include number and percentage of participants and number of events, unless otherwise stated. For the number of AEs, each occurrence will be counted once. Percentages will be based upon the number of participants in the Safety Set.

In the by participant analyses, a participant having the same event more than once within the same level of summarization will be counted only once within the same administration (ie, IV or SC) using the most intense or severe event (for by toxicity grade summary) or the most related event (for by relationship summary) .

All AEs will be listed from the signing of the ICF until the final follow-up visit.

Treatment-emergent AEs, TESAEs, TEAEs resulting in withdrawal from the study, injection/infusion-site reactions, hypersensitivity including anaphylaxis will be listed separately.

9.2. Clinical Laboratory Evaluations

The following laboratory tests will be performed:

- Hematology: red blood cell count, hematocrit, red blood cell indices (mean corpuscular volume, mean corpuscular hemoglobin, %reticulocytes, and glycated hemoglobin), and white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count)
- Chemistry: blood urea nitrogen, potassium, creatinine, sodium, chloride, glucose (fasting), total carbon dioxide, aspartate aminotransferase/serum glutamic-oxaloacetic transaminase, gamma glutamyl transferase, alanine aminotransferase/serum glutamic-pyruvic transaminase, ALP (screening only), total and direct bilirubin, indirect bilirubin, total protein, albumin, calcium (including ionized calcium), phosphate, and magnesium
- Coagulation: prothrombin time, partial thromboplastin time, and international normalized ratio
- Routine urinalysis (by dipstick): specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, erythrocytes, calcium, calcium/creatinine, and leukocyte esterase; microscopic examination (if any leukocytes, trace protein, nitrites, and blood [if not menstruating] are abnormal)

Chemistry, hematology, coagulation, and urinalysis will be performed at below timepoint (glycated hemoglobin HbA1c will only be required at screening):

First participant within each cohort	**Subsequent participants within each cohort**
Screening	Screening
Day -1	Day -1
Day 2 (24 hours post IV dose)	Day 2 (24 hours post IV dose)
Day 8 (1 week post IV dose)	Day 7 (1 week post IV dose)
Day 14 (2 weeks post IV dose)	
Day 16 (24 hours post SC dose 1)	Day 9 (24 hours post SC dose 1)
Day 21 (1 week post SC dose 1)	Day 14 (1 week post SC dose 1)
Day 23 (24 hours post SC dose 2)	Day 16 (24 hours post SC dose 2)
Day 28 (1 week post SC dose 2)	Day 21 (1 week post SC dose 2)
Day 30 (24 hours post SC dose 3)	Day 23 (24 hours post SC dose 3)
Day 36 (1 week post SC dose 3)	Day 29 (1 week post SC dose 3)
Day 65/EoT (6 weeks post SC dose 3)	Day 57/EoT (5 weeks post SC dose 3)

Chemistry laboratory tests at screening must include ALP and PLP.

Relative time to dose will be presented for summary statistics which includes: baseline, 24 hours post IV dose, 1 week post IV dose, 2 weeks post IV dose, 24 hours post SC dose 1, 1 week post SC dose 1, 24 hours post SC dose 2, 1 week post SC dose 2, 24 hours post SC dose 3, and 1 week post SC dose 3.

Summary statistics and change from baseline for chemistry, hematology, coagulation, and urinalysis will be presented by relative time to dose. Laboratory parameter values will be graded based on the National Cancer Institute CTCAE (v5.0, published 27 Nov 2017) grading for severity. Shift tables will be produced for chemistry, hematology, coagulation, and urinalysis. Shift from baseline grade tables will be presented by relative time to dose. Shift from baseline to post-baseline worst highest grade will be presented.

All clinical laboratory tests (including chemistry, hematology, coagulation, and urinalysis) will be presented in data listings.

9.3. Vital Sign Measurements

Vital sign measurements will include temperature (°C; tympanic or oral), respiratory rate, supine systolic and diastolic pressure, and pulse.

Vital sign measurements will be performed at below timepoint:

First participant within each cohort	**Subsequent participants within each cohort**
Screening	Screening
Day 1 (pre-dose, 2h, 6h, and 12h post IV dose)	Day 1 (pre-dose, 2h, 6h, and 12h post IV dose)
Day 2 (24 hours post IV dose)	Day 2 (24 hours post IV dose)
Day 3 (48 hours post IV dose)	Day 3 (48 hours post IV dose)
Day 5 (96 hours post IV dose)	Day 5 (96 hours post IV dose)
Day 8 (1 week post IV dose)	
Day 15 (pre-dose, 2h, 6h, and 12h post SC dose 1)	Day 8 (pre-dose, 2h, 6h, and 12h post SC dose 1)
Day 16 (24 hours post SC dose 1)	Day 9 (24 hours post SC dose 1)
Day 17 (48 hours post SC dose 1)	Day 10 (48 hours post SC dose 1)
Day 19 (96 hours post SC dose 1)	Day 12 (96 hours post SC dose 1)
Day 22 (pre-dose, 2h, 6h, and 12h post SC dose 2)	Day 15 (pre-dose, 2h, 6h, and 12h post SC dose 2)
Day 23 (24 hours post SC dose 2)	Day 16 (24 hours post SC dose 2)
Day 29 (pre-dose, 2h, 6h, and 12h post SC dose 3)	Day 22 (pre-dose, 2h, 6h, and 12h post SC dose 3)
Day 30 (24 hours post SC dose 3)	Day 23 (24 hours post SC dose 3)
Day 31 (48 hours post SC dose 3),	Day 24 (48 hours post SC dose 3)
Day 36 (168 hours post SC dose 3)	
Day 36 (1 week post SC dose 3)	Day 29 (168 hours/1 week post SC dose 3)
Day 51 (3 weeks post SC dose 3)	Day 43 (3 weeks post SC dose 3)
Day 65 (5 weeks post SC dose 3)	Day 57 (5 weeks post SC dose 3)
Day 85/ED/EoS (8 weeks post SC dose 3)	Day 78/ED/EoS (8 weeks post SC dose 3)

Relative time to dose will be presented for summary statistics which includes:

- Baseline, 2 hours post IV dose, 6 hours post IV dose, 12 hours post IV dose, 24 hours post IV dose, 48 hours post IV dose, 96 hours post IV dose, and 1 week post IV dose;
- Pre SC dose 1, 2 hours post SC dose 1, 6 hours post SC dose 1, 12 hours post SC dose 1, 24 hours post SC dose 1, 48 hours post SC dose 1, and 96 hours post SC dose 1;

- Pre SC dose 2, 2 hours post SC dose 2, 6 hours post SC dose 2, 12 hours post SC dose 2, 24 hours post SC dose 2;
- Pre SC dose 3, 2 hours post SC dose 3, 6 hours post SC dose 3, 12 hours post SC dose 3, 24 hours post SC dose 3, 48 hours post SC dose 3, 1 week post SC dose 3, 3 weeks post SC dose 3, 5 weeks post SC dose 3, and 8 weeks post SC dose 3.

Summary statistics and change from baseline for vital signs (temperature, respiratory rate, pulse, and systolic and diastolic blood pressure) will be presented by relative time to dose.

Vital sign measurement results, including height, weight, and BMI, will be presented in a data listing.

9.4. Physical Examination

A physical examination will include assessments of the general appearance; skin; head, ears, eyes, nose, and throat; neck; lymph nodes; chest; heart; abdominal cavity; limbs; central nervous system; and musculoskeletal system.

Physical examination will be performed at below timepoint:

First participant within each cohort	Subsequent participants within each cohort
Screening	Screening
Day -1/ Day 1	Day -1/ Day 1
Day 2/ Day 3 (48 hours post IV dose)	Day 2/Day 3 (48 hours post IV dose)
	Day 7 (1 week post IV dose),
Day 14 (2 weeks post IV dose)	
Day 17 (48 hours post SC dose 1)	Day 10 (48 hours post SC dose 1),
Day 21 (1 week post SC dose 1)	Day 14 (1 week post SC dose 1)
Day 28 (1 week post SC dose 2)	Day 21 (1 week post SC dose 2),
Day 31 (48 hours post SC dose 3)	Day 24 (48 hours post SC dose 3)

Relative time to dose will be presented for summary statistics which includes: baseline, 48 hours post IV dose, 1 week post IV dose, 2 weeks post IV dose, 48 hours post SC dose 1, 1 week post SC dose 1, 48 hours post SC dose 2, 1 week post SC dose 2, and 48 hours post SC dose 3.

Physical examination results will be classified as Normal, Abnormal Not Clinically Significant, Abnormal Clinically Significant, and Not Examined. The results will be summarized by relative time to dose and by cohort and overall.

Physical examination results will be presented in a data listing.

9.5. Electrocardiograms

Electrocardiogram (ECG) parameters will include heart rate, PR, RR, QRS, QT, and QTcF intervals.

Triplicate 12-lead ECGs will be obtained at below timepoint and at screening:

First participant within each cohort	Subsequent participants within each cohort
Day 1 (pre-dose, 2h, 6h, and 12h post IV dose)	Day 1 (pre-dose, 2h, 6h, and 12h post IV dose)
Day 2 (24 hours post IV dose)	Day 2 (24 hours post IV dose)

First participant within each cohort	Subsequent participants within each cohort
Day 3 (48 hours post IV dose)	Day 3 (48 hours post IV dose)
Day 5 (96 hours post IV dose)	Day 5 (96 hours post IV dose)
Day 8 (1 week post IV dose)	
Day 15 (pre-dose, 2h, 6h, and 12h post SC dose 1)	Day 8 (pre-dose, 2h, 6h, and 12h post SC dose 1)
Day 16 (24 hours post SC dose 1)	Day 9 (24 hours post SC dose 1)
Day 17 (48 hours post SC dose 1)	Day 10 (48 hours post SC dose 1)
Day 19 (96 hours post SC dose 1)	Day 12 (96 hours post SC dose 1)
Day 22 (pre-dose, 2h, 6h, and 12h post SC dose 2)	Day 15 (pre-dose, 2h, 6h, and 12h post SC dose 2)
Day 23 (24 hours post SC dose 2)	Day 16 (24 hours post SC dose 2)
Day 29 (pre-dose, 2h, 6h, and 12h post SC dose 3)	Day 22 (pre-dose, 2h, 6h, and 12h post SC dose 3)
Day 30 (24 hours post SC dose 3)	Day 23 (24 hours post SC dose 3)
Day 31 (48 hours post SC dose 3),	Day 24 (48 hours post SC dose 3)
Day 36 (1 week post SC dose 3)	Day 29 (1 week post SC dose 3)
Day 65/End of Treatment (EoT) (6 weeks post SC dose 3)	Day 57 EoT (5 weeks post SC dose 3)

Note: Predose triplicate 12-lead ECGs will be performed 3 times at approximately 2, 1, and 0.5 hours before the start of dosing.

The average of the triplicate ECG readings at the time points collected will be calculated and used in the summary statistics. The baseline will be defined as the average of the last non-missing assessment (including repeated and unscheduled assessments) before the first dose of study drug administration.

Relative time to dose will be presented for the summary statistics includes:

- Baseline, 2 hours post IV dose, 6 hours post IV dose, 12 hours post IV dose, 24 hours post IV dose, 48 hours post IV dose, 96 hours post IV dose, and 1 week post IV dose;
- Pre SC dose 1, 2 hours post SC dose 1, 6 hours post SC dose 1, 12 hours post SC dose 1, 24 hours post SC dose 1, 48 hours post SC dose 1, and 96 hours post SC dose 1;
- Pre SC dose 2, 2 hours post SC dose 2, 6 hours post SC dose 2, 12 hours post SC dose 2, 24 hours post SC dose 2;
- Pre SC dose 3, 2 hours post SC dose 3, 6 hours post SC dose 3, 12 hours post SC dose 3, 24 hours post SC dose 3, 48 hours post SC dose 3, 1 week post SC dose 3, and 8 weeks post SC dose 3.

Summary statistics and changes from baseline of calculated average for heart rate, PR, RR, QRS, QT, and QT interval corrected for heart rate using Fridericia's formula (QTcF) will be presented by relative time to dose and by each dose.

An outlier analysis will be performed. Summary table showing the frequency and percentage of participants who meet any of the following criteria at each relative time to dose will be produced.

- QT, QTcF interval:

- ≤ 450 msec
- > 450 and ≤ 480 msec
- > 480 and ≤ 500 msec
- > 500 msec

- QT, QTcF interval increases from baseline:
  - ≤ 30 msec
  - > 30 and ≤ 60 msec
  - > 60 msec

All ECG findings will be presented in a data listing.

9.6. Ophthalmological Examination

Ophthalmological examinations will be performed at the Screening and EoT.

Ophthalmological examinations results will be presented in a data listing.

9.7. Renal Ultrasound

A renal ultrasound will be performed at the Screening and EoT.

Renal ultrasound results will be presented in a data listing.

9.8. Injection or Infusion Site Evaluation

Subcutaneous injection- or IV infusion-site evaluations will be performed at below timepoint:

First participant within each cohort	Subsequent participants within each cohort
Day 1 (0h and EoI, every 15 minutes for first hour, 2h, 6h, and 12h post IV dose)	Day 1 (0h and EoI, every 15 minutes for first hour, 2h, 6h, and 12h post IV dose)
Day 2 (24 hours post IV dose)	Day 2 (24 hours post IV dose)
Day 3 (48 hours post IV dose)	Day 3 (48 hours post IV dose)
Day 8 (1 week post IV dose)	
Day 15 (0h and EoI, every 15 minutes for first hour, 2h, 6h, and 12h post SC dose 1)	Day 8 (0h and EoI, every 15 minutes for first hour, 2h, 6h, and 12h post SC dose 1)
Day 16 (24 hours post SC dose 1)	Day 9 (24 hours post SC dose 1)
Day 17 (48 hours post SC dose 1)	Day 10 (48 hours post SC dose 1)
Day 22 (0h and EoI, every 15 minutes for first hour, 2h, 6h, and 12h post SC dose 2)	Day 15 (0h and EoI, every 15 minutes for first hour, 2h, 6h, and 12h post SC dose 2)
Day 23 (24 hours post SC dose 2)	Day 16 (24 hours post SC dose 2)
Day 29 (0h and EoI, every 15 minutes for first hour, 2h, 6h, and 12h post SC dose 3)	Day 22 (0h and EoI, every 15 minutes for first hour, 2h, 6h, and 12h post SC dose 3)
Day 30 (24 hours post SC dose 3	Day 23 (24 hours post SC dose 3)
Day 31 (48 hours post SC dose 3)	Day 24 (48 hours post SC dose 3)
Day 36 (1 week post SC dose 3)	Day 29 (1 week post SC dose 3)

Hypersensitivity reaction labs (tryptase, IgE, C5b-9, chemistry, hematology, and urinalysis) will be performed at below timepoint:

First participant within each cohort	Subsequent participants within each cohort
Day 1 (predose)	Day 1 (predose)
During and postdose: within 1 hour of a hypersensitivity reaction. 2 hour and 8 after first sample	During and postdose: within 1 hour of a hypersensitivity reaction. 2 hour and 8 hour after first sample

Samples will only be analyzed for participants who experience systemic acute hypersensitivity reactions to study drug and assessed in select participants at the Sponsor's discretion.

Relative time to dose will be presented for summary statistics which includes:

For injection or infusion site evaluation:

- 0h and EoI, every 15 minutes for first hour, 2h, 6h, and 12h post IV dose, 24 hours post IV dose, 48 hours post IV dose, and 1 week post IV dose;
- 0h and EoI, every 15 minutes for first hour, 2h, 6h, and 12h post SC dose 1, 24 hours post SC dose 1, and 48 hours post SC dose 1;
- 0h and EoI, every 15 minutes for first hour, 2h, 6h, and 12h post SC dose 2, 24 hours post SC dose 2;
- 0h and EoI, every 15 minutes for first hour, 2h, 6h, and 12h post SC dose 3, 24 hours post SC dose 3, 48 hours post SC dose 3, and 1 week post SC dose 3.

For hypersensitivity reaction labs:

- Predose Day 1;
- During and postdose: As soon as possible (within 1 hour of reaction), and again at 2 and 8 hours after the first sample;
- As soon as possible (within 1 hour of reaction), and again at 2 and 8 hours after the first sample;

Summary statistics and change from baseline for SC injection- or IV infusion-site evaluations and hypersensitivity reaction will be presented by relative time to dose.

The results for SC injection- or IV infusion-site evaluations and hypersensitivity reaction will be presented in data listings.

9.9. Other Safety Data

The following other safety assessments will be performed:

- Other safety laboratory tests: intact 25-hydroxy (25-OH) Vitamin D; the following tests are to be conducted in case of an acute injection-associated reaction: tryptase (Alexion), terminal complement complex C5b-9 (Alexion), IgE (Alexion), hematology, chemistry, and urinalysis panels
- Urine electrolyte: urine for calcium, urine for phosphorus, and urine for creatinine
- Follicle stimulating hormone (FSH): confirmation of post-menopausal state

- Human immunodeficiency virus (HIV)-1 and HIV-2 antibodies, hepatitis B surface antigen (HbsAg), anti-hepatitis B core antigen immunoglobulin G (IgG) + immunoglobulin M (if IgG positive) and hepatitis C virus antibodies (anti-hepatitis C virus)
- Serum or urine human chorionic gonadotropin (bHCG) pregnancy test: as needed for women of childbearing potential
- Cross-reactive immunological material assay

Urine for calcium, phosphorus, and creatinine as well as optional phosphoethanolamine (PEA), samples will be collected on Day -1, Day 2, Day 3, Day 8, Day 16, Day 17, Day 23, Day 30, Day 31, and Day 36 for first participant within each cohort, and on Day -1, Day 2, Day 3, Day 9, Day 10, Day 16, Day 23, Day 24, and Day 29 for subsequent participants within each cohort. Optional PEA samples will additionally be collected at screening and Day 65 for first participants and at screening and day 57 for subsequent participants.

Pregnancy test will be performed at screening, Day -1, Day 14, Day 21, and Day 28 for first participant within each cohort, and at screening, Day -1, Day 7, Day 14, Day 21, Day 29, Day 43, Day 57, and Day 78/ED/EoS for subsequent participants within each cohort. A highly sensitive serum bHCG will be performed at Screening and on Day -1; urine tests will be performed during subsequent visits.

Hepatitis B and C, HIV, FSH, and 25-OH vitamin D will be performed at Screening.

Cross-reactive immunological material assay will be performed on Day 1.

Other laboratory tests (including hepatitis B and C, HIV, FSH, and 25-OH vitamin D, urine for calcium, phosphorus, PEA, and creatinine, and pregnancy) will be presented in a separate data listing.

Cross-reactive immunological material assay will be listed in a data listing.

10. Pharmacodynamic Analysis

All PD analyses will be performed on the PD Set and will be summarized by relative time to dose.

Pharmacodynamic analysis (PPi, PLP, and PL) will be performed at below timepoint:

First participant within each cohort	Subsequent participants within each cohort
Day 1 (pre IV dose); EoI (end of infusion)	Day 1 (pre IV dose); EoI (end of infusion)
Day 2 (24 hours post IV dose)	Day 2 (24 hours post IV dose)
Day 3 (48 hours post IV dose)	Day 3 (48 hours post IV dose)
Day 5 (96 hours post IV dose)	Day 5 (96 hours post IV dose)
Day 8 (1 week post IV dose)	
Day 15 (pre SC dose 1)	Day 8 (pre SC dose 1)
Day 16 (24 hours post SC dose 1)	Day 9 (24 hours post SC dose 1)
Day 17 (48 hours post SC dose 1)	Day 10 (48 hours post SC dose 1)
Day 19 (96 hours post SC dose 1)	Day 12 (96 hours post SC dose 1)
Day 22 (pre SC dose 2)	Day 15 (pre SC dose 2)
Day 23 (24 hours post SC dose 2)	Day 16 (24 hours post SC dose 2)
Day 29 (pre SC dose 3)	Day 22 (pre SC dose 3)

First participant within each cohort	Subsequent participants within each cohort
Day 30 (24 hours post SC dose 3)	Day 23 (24 hours post SC dose 3)
Day 31 (48 hours post SC dose 3),	Day 24 (48 hours post SC dose 3)
Day 36 (1 week post SC dose 3)	Day 29 (1 week post SC dose 3)
Day 51 (3 weeks post SC dose 3)	Day 43 (3 weeks post SC dose 3)
Day 65 (5 weeks post SC dose 3)	Day 57 (5 weeks post SC dose 3)
Day 85/ED/EoS (8 weeks post SC dose 3)	Day 78/ED/EoS (8 weeks post SC dose 3)

Relative time to dose includes:

- Baseline, 24 hours post IV dose, 48 hours post IV dose, 96 hours post IV dose, and 1 week post IV dose;
- Pre SC dose 1, 24 hours post SC dose 1, 48 hours post SC dose 1, and 96 hours post SC dose 1;
- Pre SC dose 2, 24 hours post SC dose 2;
- Pre SC dose 3, 24 hours post SC dose 3, 48 hours post SC dose 3, 1 week post SC dose 3, 3 weeks post SC dose 3, 5 weeks post SC dose 3, and 8 weeks post SC dose 3.

Summary statistics will be presented for absolute, change from baseline, and percent change from baseline for PLP, PLP/PL ratio, and PPi by cohort and relative time to dose for all participants, and will be further repeated by each ADA status (ADA negative and ADA positive, and/or pre-existing immunogenicity, treatment-emergent ADA responses, and treatment-boosted ADA responses if data permits). This summary table will be repeated including all participants up to 1 week post IV dose and subsequent participants for the remaining relative time to dose.

Absolute, change, and percent change from the baseline in mean plasma PLP, PLP/PL ratio, and PPi concentration versus time data will be presented graphically by cohort and by ADA status (ADA negative and ADA positive, and/or pre-existing immunogenicity, treatment-emergent ADA responses, and treatment-boosted ADA responses if data permits) over timepoints relative to dose for all participants. This mean figure will be repeated including all participants up to 1 week post IV dose and subsequent participants for the remaining relative time to dose. In addition, the value of plasma PLP, PLP/PL ratio, and PPi for each participant will be presented graphically overlaid with ADA status over timepoints relative to dose.

All data for PPi, PLP, and PL will be presented in data listings.

11. Immunogenicity Analysis

All immunogenicity analyses will be performed on the Immunogenicity Analysis Set.

Asfotase alfa ADA and NAb will only be tested in participants who have previously received asfotase alfa. Immunogenicity analyses (ALXN1850 ADA and NAb) will be performed on samples collected at timepoint shown below:

First participant within each cohort	Subsequent participants within each cohort
Day 1 (pre IV dose)	Day 1 (pre IV dose)
Day 8 (1 week post IV dose)	
Day 15 (pre SC dose 1)	Day 8 (pre SC dose 1)
Day 22 (pre SC dose 2)	Day 15 (pre SC dose 2)
Day 29 (pre SC dose 3)	Day 22 (pre SC dose 3)

First participant within each cohort	Subsequent participants within each cohort
Day 36 (1 week post SC dose 3)	Day 29 (1 week post SC dose 3)
Day 51 (3 weeks post SC dose 3)	Day 43 (3 weeks post SC dose 3)
Day 65 (5 weeks post SC dose 3)	Day 57 (5 weeks post SC dose 3)
Day 85/ED/EoS (8 weeks post SC dose 3)	Day 78/ED/EoS (8 weeks post SC dose 3)

Immunogenicity testing (asfotase alfa ADA and NAb) will be performed at Screening for participants who have previously received asfotase alfa.

Anti-drug antibody variables include ADA response category incidence and titer over the duration of the study will be defined as:

- ADA negative: ADA negative response in the ADA assay at all time points.
- ADA positive: include participant with a positive response in the ADA assay at any time point will be categorized as follows:
    - Pre-existing immunogenicity: Defined as ADA positive result in the assay at baseline with all post first dose ADA results negative or a positive result at baseline with all post first dose ADA results less than 4 folds over the baseline titer levels.
    - Treatment-emergent ADA responses: Defined as a positive result in the ADA assay post first dose, when baseline results are negative or missing.
    - Treatment-boosted ADA responses: Defined as a positive result in the ADA assay post first dose, that is greater than or equal to 4-fold over baseline titer levels, when baseline results are positive.

NAb response category will be defined as below

- NAb positives: a positive result in the NAb assay post first dose, in a participant with treatment-emergent or treatment-boosted ADA responses.
- Or will be NAb negative.

The incidence of ADA response categories (negative, pre-existing immunogenicity, treatment-emergent ADA responses, and treatment-boosted ADA response) wi ll be summarized as absolute occurrence (n) a nd percentage (%) by cohort. The summary statistics of maximum ADA titer levels will be summarized for ADA positive participants by cohort. Listing of maximum ADA titer level for ADA positive participants will be provided.

NAb positive and NAb negative will be summarized as absolute occurrence (n) a nd percentage (%) by cohort. Listing for NAb positive participants will be provided for treatment-emergent and treatment boosted participants.

The ADA titer will be summarized by cohort and relative to each dose. The mean and individual ADA titer will be presented graphically by cohort over time.

Relative time to dose includes: baseline; 1 week post IV dose, pre SC dose 1; pre SC dose 2; pre SC dose 3, 1 week post SC dose 3, 3 week post SC dose 3, 5 week post SC dose 3, and 8 week post SC dose 3.

All immunogenicity results will be presented in a data listing.

12. Exploratory Analysis

Blood for PTH will be performed at Screening, and on Day 36 (1 week post SC dose 3) for first participant within each cohort, and on Day 29 (1 week post SC dose 3) for subsequent participants within each cohort.

Bone biomarkers (sCTX, P1NP, osteocalcin) will be performed at below timepoint:

First participant within each cohort	Subsequent participants within each cohort
Day 1 (pre IV dose)	Day 1 (pre IV dose)
Day 36 (1 week post SC dose 3)	Day 29 (1 week post SC dose 3)
Day 65 (5 weeks post SC dose 3)	Day 57 (5 weeks post SC dose 3)
Day 85/ED/EoS (8 weeks post SC dose 3)	Day 78/ED/EoS (8 weeks post SC dose 3)

Pyridoxic acid will be performed at below timepoint:

First participant within each cohort	Subsequent participants within each cohort
Day 1 (pre IV dose)	Day 1 (pre IV dose)
Day 2 (24 hours post IV dose)	Day 2 (24 hours post IV dose)
Day 3 (48 hours post IV dose)	Day 3 (48 hours post IV dose)
Day 5 (96 hours post IV dose)	Day 5 (96 hours post IV dose)
Day 8 (1 week post IV dose)	
Day 15 (pre SC dose 1)	Day 8 (pre SC dose 1)
Day 16 (24 hours post SC dose 1)	Day 9 (24 hours post SC dose 1)
Day 17 (48 hours post SC dose 1)	Day 10 (48 hours post SC dose 1)
Day 19 (96 hours post SC dose 1)	Day 12 (96 hours post SC dose 1)
Day 22 (pre SC dose 2)	Day 15 (pre SC dose 2)
Day 23 (24 hours post SC dose 2)	Day 16 (24 hours post SC dose 2)
Day 29 (pre SC dose 3)	Day 22 (pre SC dose 3)
Day 30 (24 hours post SC dose 3)	Day 23 (24 hours post SC dose 3)
Day 31 (48 hours post SC dose 3),	Day 24 (48 hours post SC dose 3)
Day 36 (1 week post SC dose 3)	Day 29 (1 week post SC dose 3)
Day 51 (3 weeks post SC dose 3)	Day 43 (3 weeks post SC dose 3)
Day 65 (5 weeks post SC dose 3)	Day 57 (5 weeks post SC dose 3)
Day 85/ED/EoS (8 weeks post SC dose 3)	Day 78/ED/EoS (8 weeks post SC dose 3)

Relative time to dose for PTH will be presented for summary statistics will include baseline and 1 week post SC dose 3.

Relative time to dose for bone biomarkers will be presented for summary statistics will include: baseline; 1 week post SC dose 3, 5 week post SC dose 3, and 8 week post SC dose 3.

Relative time to dose will be presented for summary statistics for PA will include:

- Baseline, 24 hours post IV dose, 48 hours post IV dose, 96 hours post IV dose, and 1 week post IV dose;
- Pre SC dose 1, 24 hours post SC dose 1, 48 hours post SC dose 1, and 96 hours post SC dose 1;
- Pre SC dose 2, 24 hours post SC dose 2;

- Pre SC dose 3, 24 hours post SC dose 3, 48 hours post SC dose 3, 1 week post SC dose 3, 3 weeks post SC dose 3, 5 weeks post SC dose 3, and 8 weeks post SC dose 3.

Summary statistics will be presented for absolute, change from baseline, and percent change from baseline for PTH, sCTX, P1NP, and osteocalcin will be presented by relative time to dose and by cohort and overall.

Summary statistics will be presented for absolute, change from baseline, and percent change from baseline for PA will be presented by relative time to dose and by each dose.

Absolute, change, and percent change from the baseline in PTH, PA, sCTX, P1NP, and osteocalcin versus time will be presented graphically by cohort over time.

All data for PTH, PA, sCTX, P1NP, and osteocalcin will be presented in data listings.

13. Interim Analysis

No formal interim analyses will be planned in this study. Before dose escalation is allowed, a safety and PK data review for each dose Cohort will be performed. Database snapshot operational plan and dose selection plan will be referenced for creating the data snapshot.

14. Changes in the Planned Analysis

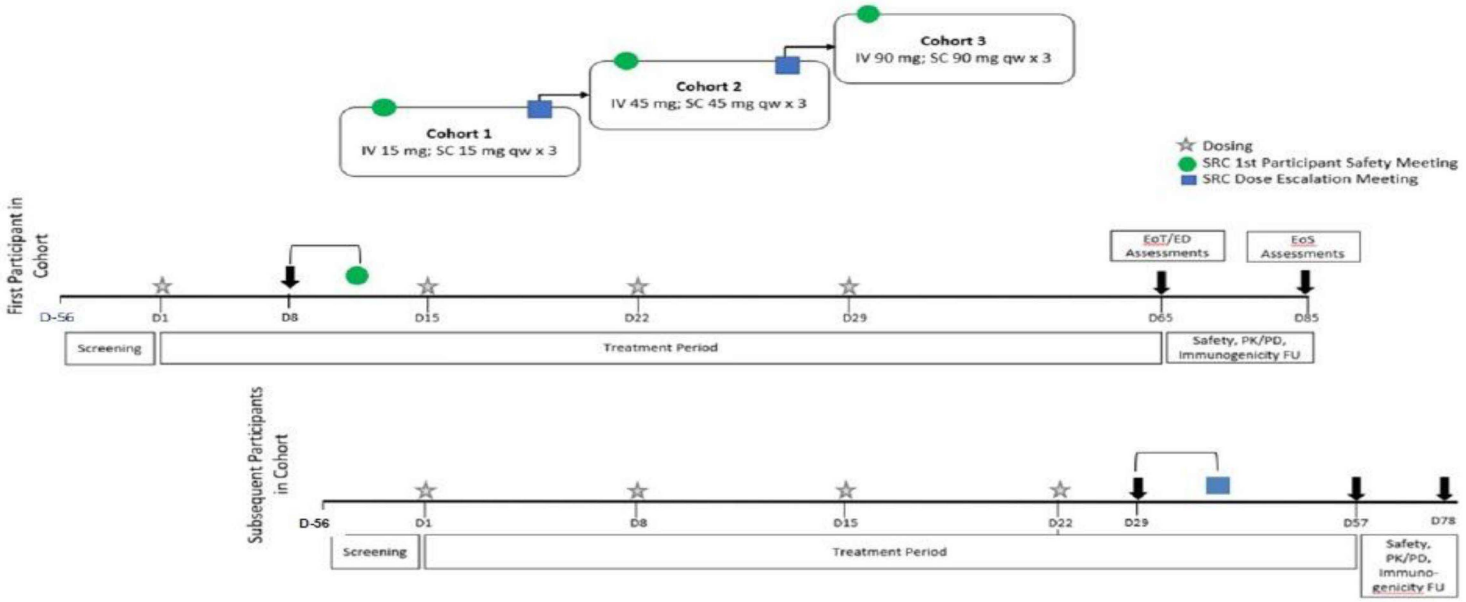
Any changes from this SAP will be documented in the CSR for this study.

15. References

Not applicable.

16. Schema

Figure 1: Study Schema



Notes: Further details of SRC meeting requirements and timelines are provided in the SRC charter.
Completion of EoT assessments (Day 65 [1st participant in each cohort]/ Day 57 [subsequent participants in each cohort] Visit) is the end of the Treatment Period, while completion of EoS assessments (Day 85 [first participant in each cohort]/ Day 78 [subsequent participants in each cohort] Visit) is end-of-study.
For the timing of each visit during the study, whether it should be an Outpatient or Inpatient Visit (or either at the Investigator's discretion), its permitted time window, and the assessments to be performed, see Table 1, Table 2, and Table 3.
Telemedicine visits may be performed by study site staff for safety reasons/AE FU.
Abbreviations: D = day; ED = early discontinuation; EoS = end-of-study; EoT = end-of-treatment; FU = follow-up; IV = intravenous; PD =pharmacodynamics; PK = pharmacokinetics; qw = weekly; SC = subcutaneous; SRC = Safety Review Committee

Notes: Further details of SRC meeting requirements and timelines are provided in the SRC charter (Protocol Section 9.6).

Statistical Analysis Plan (SAP) Client Approval Form

Client:	**Alexion Pharmaceuticals, Inc**
Protocol Number:	**ALXN1850-HPP-101**

Document Description:	Statistical Analysis Plan
SAP Title:	A Phase 1, Open-label, Dose-escalating Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ALXN1850 in Adults with Hypophosphatasia
SAP Version Number:	2.0
Effective Date:	05/03/2022

Author(s):

For PPD: [redacted]

[redacted]

Approved by:

[redacted]

03-May-2022 | 11:48:23 EDT

Date *(DD-MMM-YYYY)*

[redacted]

03-May-2022 | 12:07:33 EDT

Date *(DD-MMM-YYYY)*

[redacted]

04-May-2022 | 07:31:00 EDT

Date *(DD-MMM-YYYY)*

[redacted]

03-May-2022 | 11:53:34 EDT

Date *(DD-MMM-YYYY)*

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Subject: Please DocuSign: ALXN1850-HPP-101_SAP.docx, Statistical Analysis Plan (SAP) Client Approval For...
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Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

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Signing Complete	Security Checked	03-May-2022 | 12:07
Completed	Security Checked	04-May-2022 | 07:31

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

Alexion affirms that an e-signature, affixed using an Alexion Digital Identity, is equivalent to a handwritten signature when applied to electronic records and documents of any kind and in any format that are part of the Alexion system of record.

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Memorandum

Date: October 11, 2022

To: Memo to File

From: [redacted]

Regarding: Alexion 1850-HPP-101 SAP Versioning Error

The statistical analysis plan (SAP) dated 04/26/2022 and versioned 1.0 should have been version 2.0.

This Memo-to-File serves to document this versioning error of SAP

X [redacted]