Statistical Analysis Plan for Interventional Studies

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Sponsor Name: Alexion Pharmaceuticals, Inc.

Protocol Number: ALXN1830-HV-108
Protocol Title: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Ascending Dose Study of Subcutaneous ALXN1830 in Healthy Participants

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Syneos Health Project Code: 7019592

Authors: [redacted]

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I confirm that I have reviewed this document and agree with the content.

Approvals

Syneos Health Approval

[redacted]	[redacted] Signature	Electronically signed by: [redacted] Reason: I am the author Date: Feb 28, 2022 09:38 GMT+1 Date (DD-Mmm-YYYY)
[redacted]	[redacted] Signature	Electronically signed by: [redacted] Reason: I am the reviewer Date: Mar 1, 2022 07:45 GMT Date (DD-Mmm-YYYY)
[redacted]	[redacted] Signature	Electronically signed by: [redacted] Reason: I am the reviewer Date: Mar 1, 2022 08:06 EST Date (DD-Mmm-YYYY)

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[redacted] Alexion Pharmaceuticals	DocuSigned by: [redacted] Signature Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 24-Feb-2022 | 12:20:46 EST 824F31850412435780 6497AD68F0186D	24-Feb-2022 | 12:21:15 EST Date (DD-Mmm-YYYY)
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1. Glossary of Abbreviations

Abbreviation	Description
AUC_{extrap}	AUC extrapolated from time t to infinity as a percentage of total AUC_{∞}
λ_z	Apparent terminal phase elimination rate constant
ADA	Anti-drug antibodies
AE	Adverse Event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate aminotransferase
AUC	Area under the serum concentration versus time curve
AUC_t	Area under the serum concentration versus time curve from time 0 to the last quantifiable concentration
AUC_{tau}	Area under the concentration-time curve during the dosing interval
AUC_{∞}	Area under the serum concentration versus time curve from zero to infinity
BLQ	Below Lower Limit of Quantitation
BMI	Body Mass index
BUN	Blood urea nitrogen
CI	Confidence Interval
CIC	Circulating immune complexes
CL/F	Apparent oral clearance
C_{max}	Maximum observed concentration
Ctrough	Concentration at predose times on Day 8, 15 and 22. Observed directly from Data
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
CV	Coefficient of Variation
ECG	Electrocardiogram
eDISH	Evaluation of drug-induced serious hepatotoxicity
EMA	European Medicines Agency
EOS	End of Study

FcRn	Neonatal crystallizable fragment receptor
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GMR	Geometric mean ratio
HbA1c	Glycated Hemoglobin
HBC	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV	Human Immunodeficiency Virus
HTD	Highest tolerated dose
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
Ig	immunoglobulin
IGS	Immunogenicity Set
IMP	Investigational medicinal product
IQR	Interquartile range
IRR	Infusion related reaction
IV	Intravenous
LDL	Low-density lipoprotein
MAD	Multiple ascending dose
Max	Maximum
MD	Multiple dose
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
NAb	Neutralizing Antibodies
NIMP	non-IMP
PBO	Placebo
PD	Pharmacodynamic(s)

PDS	PD Analysis Set
PK	Pharmacokinetic(s)
PKS	PK Analysis Set
PT	Preferred Term
Q1	First quartile, 25th percentile of the data
Q3	Third quartile, 75th percentile of the data
QTcF	QT interval corrected for heart rate using Fridericia's formula
qw	Weekly
R_{ac}	Accumulation ratio
RBC	Red blood cells
RNA	Ribonucleic acid
SAD	Singlel ascending dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation / Single dose
SI	Standard International System of Units
SoA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
SS	Safety Set
$t_{½}$	Terminal elimination half-life
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
T_{max}	Time to maximum concentration
ULN	Upper limit of normal
V_d/F	Apparent volume of distribution
WHO	World Health Organization

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies which will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. Responsibilities

Syneos Health will perform the statistical analyses and is responsible for the production and quality control of all tables, figures and listings

2.2. Timings of Analyses

The primary analysis of safety, pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity is planned after all participants complete the final study visit or terminate early from the study.

3. Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of single and multiple doses of ALXN1830 SC	• Safety assessed by the incidence and relatedness of TEAEs, SAEs, AESIs, physical examination, vital sign measurements, clinical laboratory, and ECG results
Secondary	
• To assess the PK of single and multiple doses of ALXN1830 SC	• Serum ALXN1830 concentration profiles and single- and multiple-dose PK parameters
• To explore the PD effects of single and multiple doses of ALXN1830 SC	• Change in serum IgG levels over time; FcRn saturation as measured by receptor occupancy
• To assess the immunogenicity of ALXN1830 SC	• Incidence of anti-drug antibodies and neutralizing antibodies to ALXN1830
• To compare safety and tolerability, PK, PD, and immunogenicity of ALXN1830 SC between Japanese and non-Japanese healthy participants*	• Quantitative assessment of safety, PK parameters, PD parameters, and immunogenicity between Japanese and non-Japanese healthy participants*

Abbreviations: AESI = adverse events of special interest; ECG = electrocardiogram; FcRn = neonatal crystallizable fragment receptor; IgG = immunoglobulin G; PD = pharmacodynamics; PK = pharmacokinetics; SAE = serious adverse event; SC = subcutaneous; TEAE = treatment-emergent adverse event.

*: These objectives/endpoints were not achieved due to early termination of the study.

4. Study Details/Design

4.1. Brief Description

This is a Phase 1 study in up to 48 healthy adult participants (36 on active treatment, 12 on placebo [PBO]). The study will consist of 2 SAD (Cohorts 1 and 2) and 4 MAD cohorts (Cohorts 3 to 6). Cohort 6 will enroll only Japanese participants). Eight participants will be randomly assigned in a 6:2 ratio to each of the 6 cohorts to receive either single or multiple doses of ALXN1830 SC (n = 6 per cohort) or single or multiple doses of PBO (n = 2 per cohort). The study was terminated early, therefore cohort 2 has only 2 participants and cohort 6 has none.

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

Progression to the next dosing cohort will be gated by review of initial dosing data by a Safety Review Committee (SRC). At Alexion's discretion, and after consultation with the SRC, additional participants may be enrolled as replacement participants only if a participant discontinues within 3 weeks of the last dose for reasons other than drug-related adverse events.

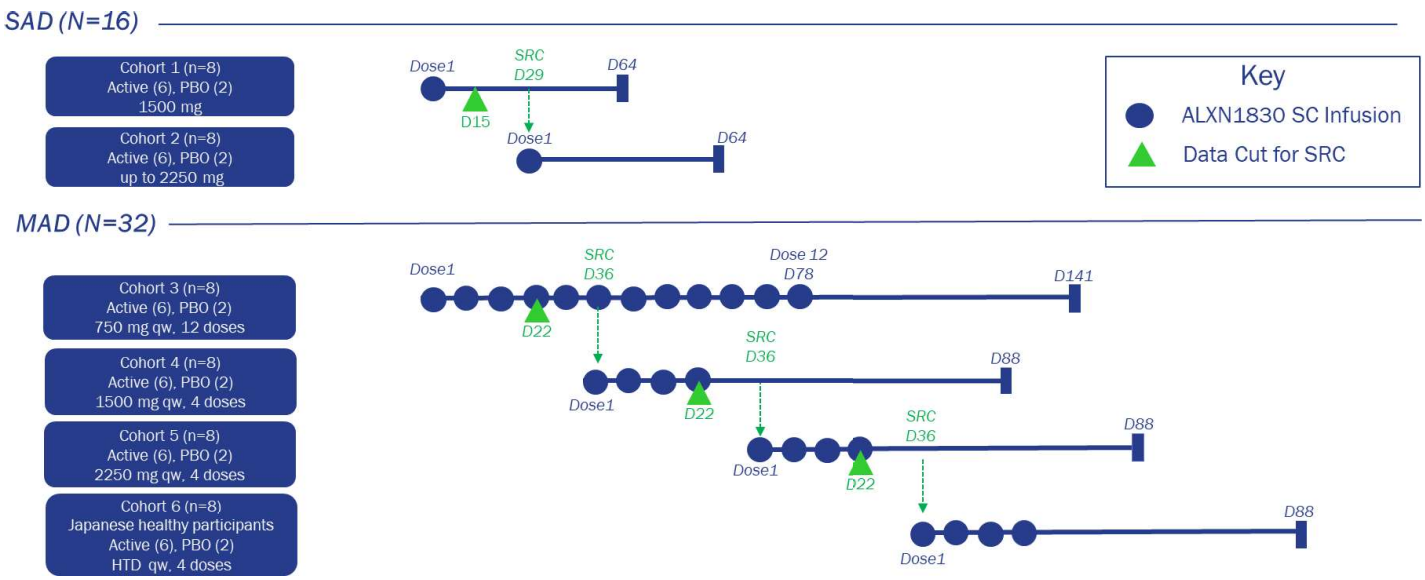
Participants will be randomly assigned in a 6:2 ratio to each of the 6 cohorts to receive either single or multiple doses of ALXN1830 SC (n = 6 per cohort) or single or multiple doses of PBO (n = 2 per cohort). The planned dose and dose regimens are shown in Table 1. The planned study duration is approximately 124 days for Cohorts 1 and 2: up to 60 days for screening and approximately 64 days for dosing and follow-up; 201 days for Cohort 3: up to 60 days for screening and approximately 141 days for dosing and follow-up; and 148 days for Cohorts 4 to 6: 60 days for screening and approximately 88 days for dosing and follow-up. Participants will be admitted to an inpatient facility during the dosing and follow-up period as shown in the schedule of activities (SoA) in Protocol Section 1.3 . The study design is presented in Figure 1.

Table 1: Planned Dose and Dose Regimens in Healthy Participants

Cohort No.	Regimen/Route of Administration	Study Drug (N)
1	Single dose SC	Placebo (n = 2) or ALXN1830 1500 mg (n = 6)
2	Single dose SC	Placebo (n = 2) or ALXN1830 2250 mg (n = 6)
3	Multiple dose (12 doses qw) SC	Placebo (n = 2) or ALXN1830 750 mg (n = 6)
4	Multiple dose (4 doses qw) SC	Placebo (n = 2) or ALXN1830 1500 mg (n = 6)
5	Multiple dose (4 doses qw) SC	Placebo (n = 2) or ALXN1830 2250 mg (n = 6)
6[a]	Multiple dose (4 doses qw) SC Japanese healthy participants	Placebo (n = 2) or ALXN1830 HTD (n = 6)

[a] Healthy, Japanese participants enrolled in Cohort 6 will be dosed according to the HTD established in the non-Japanese cohorts. This cohort was not achieved due to early termination of the study. Abbreviations: qw = weekly; SC = subcutaneous; HTD = highest tolerated dose.

Figure 1: Study Design Schematic



Abbreviations: D = day; HTD = highest tolerated dose; MAD = multiple ascending dose; PBO = placebo; qw = weekly; SAD = single ascending dose; SC = subcutaneous; SRC = Safety Review Committee.

Progression to the next dosing cohort will be gated by review of initial dosing data by an SRC consisting of the Investigator, and Alexion Safety Physician, Medical Monitor, Study Statistician, and Clinical Pharmacologist.

4.2. Participant Selection

Inclusion- and exclusion criteria are described in detail in Protocol Sections 5.1 and 5.2.

Lifestyle Considerations are described in Protocol Section 5.3.

4.3. Determination of Sample Size

Up to 48 participants will be enrolled. Participants will be randomly assigned in a 6:2 ratio to up to 6 planned cohorts to receive either single or multiple doses of ALXN1830 SC (n = 6 per cohort) or single or multiple doses of PBO (n = 2 per cohort). Progression to the next dosing cohort will be gated by review of initial dosing data by an SRC.

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

4.4. Treatment Assignment and Blinding

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

On Day 1 participants will be assigned a unique number (randomization number) in ascending numerical order. The randomization number encodes the participant's assignment to one of the 6 cohorts of the study, according to the randomization schedule generated prior to the study by Syneos Health Biostatistics.

Participants will be randomly assigned in a 6:2 ratio to receive either single or multiple doses of ALXN1830 or PBO (Table 1). The Investigator will remain blinded to each participant's assigned study drug throughout the course of the study. In order to maintain this blind, site's pharmacy staff will be responsible for the reconstitution and dispensation of all study drug.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study drug records at the site(s) to verify that randomization/dispensing has been done accurately.

In the event of an emergency, an envelope for each participant containing his/her study drug assignment will be available in the pharmacy at the clinical study site. Unblinding should only be considered for the safety of the participant. If unblinding is deemed necessary by the Investigator, the Investigator can unblind the participant's treatment allocation using the envelope available from the pharmacy staff. The Investigator must note the date, time, and reason for unblinding. The Investigator should inform the Medical Monitor that the participant was unblinded; however, the Investigator should not reveal to the Medical Monitor the participant's treatment allocation. The blind will be maintained for persons responsible for the ongoing conduct of the study (such as the management, monitors, Investigator) and those responsible for data analysis and interpretation of results at the conclusion of the study, such as biometrics personnel. Unblinded information will only be accessible to those who need to be involved in the safety reporting to health authorities, independent ethics committees (IECs), or persons performing ongoing safety evaluations during the study. The Investigator will receive only blinded information unless unblinded information is judged necessary for safety reasons.

4.5. Administration of Study Medication

The doses to be administered in the study and study drug dose formulation are provided in Table 2.

The SAD and MAD cohorts will use study drug that has been manufactured with different composition. Analytical and characterization data provide assurance that the formulations can be considered comparable. Placebo will be commercially available normal saline.

Table 2: Study Drug

Drug name	ALXN1830	Placebo
Type	Biologic	Diluent
Dose formulation	Sterile liquid	Sterile liquid
Unit dose strength(s)	ALXN1830 is formulated at 150 mg/mL, and supplied as a 1500 mg/10 mL vial	Placebo
Dosage level(s)	Refer to Table 1	Not applicable
Route of administration	SC infusion	SC infusion
Use	Investigational Product	Placebo
IMP and NIMP	IMP	IMP
Sourcing	Provided by Alexion	Provided by study site
Packaging and labeling	Study drug will be provided in a 10 mL vial. Each vial will be labeled as required per country requirement	Placebo (normal saline) will be provided in country-specific commercially available form

Abbreviations: IMP = investigational medicinal product; NIMP = non-IMP; SC = subcutaneous.

4.6. Study Procedures and Flowchart

Schedules of activities are in Protocol Section 1.3.

5. Endpoints

5.1. Primary Endpoints

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

5.2. Secondary Endpoints

- Serum ALXN1830 concentration profiles and single- and multiple-dose PK parameters
- Change in serum IgG levels over time; FcRn saturation as measured by receptor occupancy
- Incidence of anti-drug antibodies and neutralizing antibodies to ALXN1830
- Quantitative assessment of safety, PK parameters, PD parameters, and immunogenicity between Japanese and non-Japanese healthy participants

6. Analysis Sets

6.1. Enrolled Set

The Enrolled Set will include all participants who sign the informed consent form (ICF) and pass inclusion/exclusion criteria and are randomized. Unless specified otherwise, this set will be used for participant listings and summaries of participant disposition.

6.2. Safety Set

The Safety Set (SS) will include all participants who receive at least 1 dose of study drug. Participants will be analyzed according to the study drug they actually received. The SS will be used for all analyses of safety endpoints.

6.3. Pharmacokinetic Set

The Pharmacokinetic Set (PKS) will include all participants who received at least 1 dose of study drug (only active) and have at least one post-dose serum ALXN1830 concentration measured. Participants will be analyzed according to the study drug they actually received. Serum concentrations will be summarized for all participants in the PKS. The exclusions from summary statistics for serum concentrations and/or PK parameters will be defined based on review of protocol deviations (if any) prior to database lock by PK scientist and study statistician at the discretion of the sponsor. Pharmacokinetic analyses will be performed using the PKS.

6.4. Pharmacodynamic Set

The Pharmacodynamic Set (PDS) will include all participants who received at least 1 dose of study drug (active and placebo) who have evaluable serum Immunoglobulin data (IgG, IgG subtypes, Ig subtypes, and CIC) or FcRn data. Participants will be analyzed according to the study drug they actually received. Pharmacodynamic analyses will be performed using the PDS.

6.5. Immunogenicity Set

The Immunogenicity Set (IGS) will include all participants who have a predose (baseline) and at least 1 postdose ADA sample collected. Immunogenicity analyses will be performed using the IGS.

7. General Aspects for Statistical Analysis

7.1. General Methods

- In general, descriptive statistics for continuous variables will include number of non-missing values, arithmetic mean, SD, median,interquartile range (IQR), Q1, Q3, minimum, and maximum. Categorical variables will be summarized using percentages and frequency counts. Descriptive statistics and percentages and frequency counts will be summarized by treatment, and period, where appropriate.

- For the summary statistics of all continuous variables unless otherwise specified, 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, and SD will be presented to two more decimal places than the raw data.

- All statistical analyses will be conducted using SAS® for Windows® Version 9.4 or higher.

- All relevant participant data will be included in listings. All participants entered into the database will be included in participant data listings.

In general, tables will be split over multiple pages, with the following columns:

- Cohort 1: SAD ALXN1830 1500 mg
- Cohort 2: SAD ALXN1830 2250 mg
- Cohort 3: MAD ALXN1830 750 mg QW x 12
- Cohort 4: MAD ALXN1830 1500 mg QW x 4
- Cohort 5: MAD ALXN1830 2250 mg QW x 4
- All Cohorts Placebo
- All Cohorts Total

7.2. Key Definitions

End of Study (EOS)
The EOS for each participant is defined as the date the last participant completes the last visit as shown in the Schedule of Activities in Section 1.3 of the Protocol.

Trial day
If the event date ≥ date of first dose of IP, trial day = event date – date of first dose of IP + 1.
If the event date < date of first dose of IP, trial day = event date – date of first dose of IP.

Nominal Time
Nominal time is the scheduled measurement time relative to time 0. Time 0 is the time of start of study drug dosing on Day 1.

Baseline Value
Baseline value will be defined as the last non-missing value recorded prior to first intake of study treatment.

Change from Baseline (CFB)

CFB = Post-baseline value – Value at baseline

7.3. Missing Data

For participants who are withdrawn from the study prior to the end of the study, all data collected up to the point of discontinuation will be used for analysis. There will be no imputation for missing data, unless otherwise specified.

7.4. Visit Windows

If there are multiple planned assessments for any study procedure at a given time point the latest non-missing value will be used for summarization. Unscheduled assessments will be listed and will be used to flag baseline visit if this is the last non-missing assessment before the first dose of study drug, but unscheduled assessments will not be included in the summarization.

7.5. Pooling of Centers

Not Applicable.

7.6. Subgroups

Not Applicable.

8. Participant Disposition, Demographic, Other Baseline Characteristics and Medication

8.1. Participant Disposition and Withdrawals

Listings of treatment assignments, including the participant's identification, date of randomization, and assignment to treatment, will be presented.

The following frequencies (number and percent) will be displayed for all participants in the Enrolled Set: participants enrolled, participants randomized, screen failures, and reasons for screen failure.

The analysis sets will be summarized with counts and percentages by treatment. This table will include the following: number of participants in Enrolled Set, participants in Safety Set, reasons for exclusion from the Safety Set, participants in PK set, reasons for exclusion from the PK set, number of participants in PD Set, reasons for exclusion from the PD Set.

The following frequencies (number and percent) will be displayed for all participants in the Enrolled Set: randomized participants, participants in the Safety Set, participants in the PK Set and participants in the PD Set, participants who completed the study (including follow-up), participants who discontinued early, participants who completed study treatment, participants who discontinued study treatment early also presented by reason for early discontinuation and study duration in days. The denominators will be the number of enrolled participants.

Completion/discontinuation status, inclusion/exclusion criteria definitions and Inclusion/exclusion criteria violations will be listed by participant.

A listing of participants excluded from the analysis populations will also be generated.

8.2. Protocol Deviations

Protocol deviation management at Syneos Health is detailed in Protocol Deviation and Non-compliance Management). For details on the process for defining analysis datasets refer to (Blind) Data Review and Definition of Analysis Sets SOP.

All protocol deviations recorded in Clinical Trial Management System (CTMS) will be listed. The Protocol deviation criteria are graded as not important or important. Protocol deviations will be summarized by the number and percentage of participants for the Safety Set.

8.3. Demographic and Baseline Characteristics

Demographic and baseline characteristics, including age, sex, race, ethnicity, child-bearing potential, evidence of vaccination, height, body weight, and BMI will be summarized using standard descriptive statistics. No formal statistical comparisons between populations will be performed. Demographics will be listed for all participants in the Enrolled Set.

8.4. Medical and Surgical History

Medical and surgical history will be coded using MedDRA 23.1 and summarized for the Safety Set presenting the number and percentages of participants within each preferred term (PT) grouped by the system organ class (SOC). A participant with multiple occurrences of an event in a PT is counted only once. Medical and surgical history will be listed by participant.

8.5. Medication

The WHO Drug, September 2020, B3 will be used to classify prior and concomitant medications by therapeutic class and drug name.

Prior medication is defined as any medication taken before the date of the first dose of study treatment. Concomitant medication is defined as any medication taken on or after the date of the first dose of study treatment.

The use of prior and concomitant medications will be summarized by the number and percentage of participants for the Safety Set. If a participant takes a specific medication multiple times or takes multiple medications within a specific therapeutic class, that participant would be counted only once for the coded drug name or therapeutic class.

8.6. Non-Medication Therapies or Procedures

The WHO Drug, September 2020, B3 will be used to classify non-medication therapies by therapeutic class. Prior non-medication therapy is defined as any non-medication therapy taken before the date of the first dose of study treatment. Concomitant non-medication therapy is defined as any non-medication therapy taken on or after the date of the first dose of study treatment.

Non-medication procedure data will be listed but not summarized.

8.7. Extent of Exposure

Exposure data will be summarized by total dose administered (mg), total volume administerd (mL) and the number of interruptions (SC Infusion). Study drug administration data will be listed.

8.8. Treatment Compliance

Not Applicable.

9. Pharmacokinetics

Pharmacokinetic analyses will be performed using the PKS. Note that placebo are not required.

PK parameters will be calculated for ALXN1830 using noncompartmental methods with Phoenix® WinNonlin® (Certara USA Inc., Princeton, New Jersey) Version 8.0 or higher. Calculations of individual PK parameters will be based on ALXN1830 concentrations and the actual sampling times elapsed from the actual reference dosing time data recorded during the study.

9.1. PK Sampling Schedule

Whole blood samples will be collected for measurement of serum concentrations of ALXN1830 as specified in the SoA (Protocol Section 1.3). All efforts should be made to obtain the PK samples at the exact nominal time relative to dosing within the specified window. Additional samples may be collected during the study.

9.2. Serum PK Endpoint

Following PK parameters will be derived from the serum ALXN1830 concentrations when feasible and supported by the available data.

For the single dose cohorts 1-2, PK parameters will be derived on Day 1.

For the multiple dose cohort 3, PK parameters will be derived on Days 1, 22, and 78.

For the multiple dose cohort 4 to 5, PK parameters will be derived on Days 1, and 22.

Parameters	Dosing	Definition
C_{max}	SD, MD	Maximum observed serum concentration
T_{max}	SD, MD	Time to maximum observed serum concentration
AUC_t	SD, MD	Area under the serum concentration versus time curve from time 0 to the last quantifiable concentration
AUC_{tau}	MD	Area under the concentration-time curve during the dosing interval
$AUC_{0-\infty}$	SD, MD	Area under the concentration-time curve from time 0 (dosing) to time infinity
C_{trough}	MD	Concentration at predose times on Day 8, 15 and 22. Observed directly from Data
$t_{½}$	SD, MD	Terminal elimination half-life
λ_z	SD, MD	Terminal-phase elimination rate constant
CL or CL/F	SD, MD	Total body clearance or apparent clearance
V_d or V_d/F	SD, MD	Volume of distribution or apparent volume of distribution
R_{ac}	MD	Accumulation ratio

Abbreviations: MD = Multiple-dose; SD = Single dose

Note: tau is the dosing interval for steady-state data, i.e., the time between doses (tau = 1 week).

The primary PK parameters will be summarized by overall treatment and the sub treatment category ADA status (at least one positive/negative). Boxplots will present PK parameters by ADA status and by healthy non-Japanese participants. Some PK parameters may not be calculated for all or some subjects, at the

discretion of the pharmacokineticist, 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 report.

Additional serum PK parameters may be calculated if deemed appropriate.

9.3. Presentation of Concentration Data

9.3.1. Handling of Missing Data

Missing concentration data for all participants who are administered scheduled study treatments will be considered as non-informative missing and will not be imputed. No concentration estimates will be provided for missing sample values.

For the derivation of AUC and for the individual serum concentration versus time curves, the following rules will apply:

- Concentration values below the assay's lower limit of quantification (BLQ) in pre-dose Day 1 samples will be treated as zero;
- The sampling time of pre-dose samples relative to dosing will also be treated as zero;
- BLQ's between two quantifiable samples will be set to missing;
- The first BLQ after the last measurable sample will be set to zero; any subsequent BLQ's will be set to zero;

For serum concentration summary the following rules will apply:

- All BLQ values will be set to zero;
- No further imputation will be applied to any missing values.

9.3.2. Listing and Presentation of Individual PK Data

The actual and nominal sampling times of PK blood sample collection will be listed for each participant and will include the deviation in time from the protocol scheduled time (i.e., nominal time), if applicable.

All measured concentrations will be presented in original precisions (i.e., significant figures) and units as reported by Bioanalytical lab – eg ng/mL.

Serum concentrations and time deviation data will be presented in a data listing by participant.

9.3.3. Summary of PK Concentrations by Matrix

Serum concentration data will be summarized separately by time point for each cohort/actual treatment using the following descriptive statistics: number of participants, arithmetic mean, SD, CV, geometric mean, geometric CV, median, minimum, and maximum.

Mean serum concentration versus scheduled time profiles will be presented in figures on both linear and semilogarithmic scales. Individual serum concentration versus nominal time profiles will be presented similarly.

9.4. Derivation of Pharmacokinetic Parameters

- The apparent C_{max} and the corresponding T_{max} will be read directly from the concentration-time plot (observed data).

- AUC_t will be calculated using the log-linear trapezoidal interpolation rule for extravascular model.
- The terminal elimination rate constant (λ_z) will be determined by log linear regression obtained on at least the 3 last quantifiable concentrations and will not include C_{max}; $t_{1/2}$ is calculated by the program as $\ln 2/\lambda_z$;
- AUC_∞ will be calculated by the program as: $AUC_\infty = AUC_t + AUC_{extrap}$ where last is the sampling time point of the last measurable concentration (tlast). AUC_{extrap} will be calculated by the program as: C_{last}/λ_z, where Clast is the observed concentration at time t_{last} and λ_z is the elimination rate constant during the apparent terminal elimination phase. AUC_∞ will only be presented for participants with a reliable λ_z;
- CL/F will be calculated by program as dose amount/AUC_∞;
- V_z/F will be calculated by the program as (dose amount/AUC_∞)/λ_z;

The following PK acceptance criteria will be applied to assess the reliability of elimination parameters:

- Number of points to calculate λ_z is greater than or equal to 3 excluding C_{max} point;
- The adjusted square of the correlation coefficient or coefficient of determination (R_{square} adjusted) for the goodness of fit of the regression line through the data points must be ≥0.80;
- AUC_{extrap} ≤20%.

Unreliable PK parameters will be listed but flagged and excluded from summary.

9.4.1. PK Parameters Summarization

Pharmacokinetic parameters derived from serum concentrations will be presented in data listings and summarized separately using the following descriptive statistics: number of participants, arithmetic mean, SD, arithmetic CV, geometric mean, geometric CV, median, minimum, and maximum.

9.5. Planned Statistical Models for PK Parameters and Concentrations

The primary analysis will be based on the PKS.

Dose proportionality of Multiple-Dose (Cohort 3 to 5)

The power model will be used and will include the PK parameter as the response variable and dose (mg) as the explanatory variable. For this model, the variable dose will be treated as a continuous variable.

The form of the model is as follows:

PK Parameter = $e^{\alpha} \times \text{Dose}^{\beta} \times e^{\epsilon}$, where Dose ≥ 0, and e^{ϵ} represents the associated error.
Thus, perfect dose proportionality is met when β=1 (ignoring error). This becomes a linear relationship following a natural-log transformation, to which a linear regression will be fit by ordinary least squares (OLS):
ln(PK Parameter) = α + β × ln(Dose) + ϵ, where Dose > 0, α is the intecept, β is the slope and ϵ represents the associated error.
The estimate of β together with a 90% confidence interval (CI) will be provided (for each PK parameter model), and this will be used to quantify dose proportionality. According to Hummel et al. (2009), the following criterion may be used for exploratory dose proportionality evaluations: If the (two-sided) 90% CI for β is wholly contained within the interval, [1+ln(0.5)/ln(ρ), 1+ln(2)/ln(ρ)], then dose proportionality is suggested across the investigated dose range. Here, ρ is defined as the ratio of the highest to lowest dose. This interval criterion will be reported along with the corresponding 90% CI estimate for β (presented to three decimal places).

ln(PK Parameter) = mu + β *ln(Dose)

- *where β = 1 indicates perfect dose proportionality. Estimation of beta, along with its 90% CI, will be provided.

Assessment of Steady State (MAD)

For the MAD study portion, a visual assessment of C_{trough} concentrations will be undertaken. The geometric mean of C_{trough} values obtained from Days 8 through 22 will be plotted (y-axis) agains visit number (x-axis). The data points will be connected, and a box plot of individual values (for that visit) will juxtaposed to each geometric mean.

9.6. Deviation from Analyses Planned in Protocol

The study was terminated early, therefore cohort 2 has only 2 participants and cohort 6 has none. Therefore the secondary objective, to compare safety and tolerability, PK, PD, and immunogenicity of ALXN1830 SC between Japanese and non-Japanese healthy participants cannot be met and the secondary endpoint the quantitative assessment of safety, PK parameters, PD parameters, and immunogenicity between Japanese and non-Japanese healthy participants cannot be analyzed.

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10. Pharmacodynamics

Venous blood samples will be collected for measurement of IgA, IgM, IgG, and IgG subtypes (1 - 4), FcRn receptor occupancy, and CIC at timepoints described in the SoA (Protocol Section 1.3).

As data become available during the study, the timing of PD sampling may be altered in order to ensure appropriate monitoring of participants.

Whole blood for assessment of exploratory biomarkers will be collected as per the SoA (Protocol Section 1.3). Residual PK/PD samples may also be used for exploratory analyses.

10.1. Endpoints and Analysis

10.1.1. Endpoints

- Change in serum levels of IgA, IgM, IgG, and IgG subtypes (1 to 4)) over time
- FcRn saturation as measured by receptor occupancy
- Quantitative assessment of PD parameters between Japanese and non-Japanese healthy participants

10.1.2. Analysis of the Endpoints

Pharmacodynamic analyses will be performed using the PD Set.

The endpoint regarding the quantitative assessment of PD parameters between Japanese and non-Japanese healthy participants cannot be analyzed due to early termination of the study.

Missing concentration data for all participants who are administered scheduled study treatments will be considered as non-informative missing and will not be imputed. No concentration estimates will be provided for missing sample values.

For the PD/biomarker levels, actual values, changes from baseline and percentage change from baseline will be summarized by time point for each treatment using the following descriptive statistics: number of participants, arithmetic mean, SD, CV, geometric mean, geometric CV, median, minimum, and maximum.

Mean PD/biomarker levels (change from baseline and percentage change from baseline) versus scheduled time profiles will be presented in figures.

Individual PD/biomarker levels (change from baseline and percentage change from baseline) versus scheduled time profiles will be presented similarly.

PD/biomarker levels, change from baseline and percentage change from baseline will be presented in a data listing by participant.

11. Immunogenicity

The population used for immunogencity analyses will be the Immunogenicity Set (IGS).

Samples for immunogenicity should be collected at times specified in the SoA (Protocol Section 1.3).

The immunogenicity analyses will include an analysis of anti-drug antibodies (ADA) using descriptive statistics.

The actual date and time (24-hour clock time) of each sample will be recorded.

All samples that are positive in a screening assay will be confirmed for antibody specificity and further characterized for titer. All samples that are confirmed positive for ADA will be evaluated for the presence of neutralizing antibodies.

Participants found to have anti-ALXN1830 antibodies still present at the end of the study will be requested to return to the clinic for up to 1 year (from the first drug administration) or until ADA titers return to baseline levels (whichever occurs first). The follow-up visits are to be scheduled at 90-day intervals for blood collection to assess ADA.

11.1.1. Immunogenicity Endpoints

- Incidence of anti-drug antibodies and neutralizing antibodies (NAb) to ALXN1830
- Quantitative assessment of immunogenicity between Japanese and non-Japanese healthy participants

11.1.2. Analysis of the Endpoints

The endpoint regarding the quantitative assessment of immunogenicity between Japanese and non-Japanese healthy participants cannot be analyzed due to early termination of the study.

ADA and NAb data reporting

- Incidence, titer, duration, time to detection, pre-existing ADA
- PK concentration or parameter by immunogenicity response
- PD response by immunogenicity response
- Individual PK data listing or spaghetti plots with ADA category overlaid.
- For ADA categories and participants, summary of individual plots of PK, PD, ADA titer, and NAb time course to better understand the clinical impact of immunogenicity at a subject level.

12. Safety

The population used for safety analyses will be the Safety Set.

Safety analyses will include an analysis of all treatment-emergent adverse events (TEAEs), SAEs, AESIs, ECGs, clinical laboratory data, physical examinations, and vital sign measurements using descriptive statistics.

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

12.1. Adverse Events / Adverse Drug Reactions

AEs for all participants in the Safety Set will be included in the AE summaries.

Adverse events will be summarized by system organ class (SOC) and preferred term (PT) for each treatment and overall, based on the MedDRA dictionary version 23.1.

If the relationship to study drug is missing for TEAEs, then the relationship will be counted as related to study product for the summary tables. Missing severity for TEAEs will be counted as Grade 3.

Pretreatment AEs are defined as AEs that were reported or worsened after signing the ICF up to the start of study drug dosing. Treatment-emergent AEs are defined as AEs that were reported or worsened on or after the start of study drug dosing through the safety follow-up visit.

If the start date of an AE is partially or completely missing, the date will be compared as far as possible with the date of the start of administration of study drug. The AE will be assumed to be treatment-emergent if it cannot be definitively shown that the AE did not occur or increase in severity during the treatment period (worst case approach). The following general rules will be used:

- If the start day is missing but the start month and year are complete, an AE will not be considered as being treatment-emergent only if the start month/year is before the month/year of the first study drug administration.
- If the start day and month are missing but the start year is complete, an AE will not be considered as being treatment-emergent only if the start year is before the year of the first study drug administration.
- If the start date is completely missing, an AE will be considered treatment-emergent unless the stop date is before the first study drug administration.

Duration will be calculated for AEs that resolve as the difference between the resolution date and onset date plus 1 and expressed in days. Should an AE have a short duration (*i.e.* < 24 hours), the duration will be calculated as the difference between the resolution time and the onset time.

Adverse events of special interest are defined as any IRR equal to or higher than Grade 3; or any IRR that may jeopardize the participant and requires immediate intervention to prevent it from leading to severe outcomes. Potential cases of any delayed hypersensitivity reactions, equal to or higher than Grade 2.

The summary tables will include the number of participants and the number of events. Percentages will be based on the number of participants and on the number of events. For summaries by SOC and PT, a participant will be counted once at the SOC level and once at each PT within the SOC level.

For summaries by SOC, PT, and maximum severity, a participant will be counted once at the highest severity level for which the event occurred at the SOC level and the highest severity level for each unique PT within that SOC level. Therefore, participants may only contribute once to each PT and once to each SOC level.

The summaries presenting frequency of AEs by SOC and PT will be ordered by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT.

The following tables will be provided:

- An overall summary of the number and percentage of participants reporting TEAEs, serious TEAEs (TESAEs), TEAEs resulting in death, TEAEs of special interest, TEAEs leading to study drug discontinuation, TESAEs leading study drug discontinuation, TEAEs by relationship and TEAEs by toxicity grade;
- TEAEs overall by system organ class and preferred term;
- TEAEs by maximum toxicity grade, overall and by system organ class and preferred term;
- TEAEs by toxicity grade, overall and by system organ class and preferred term;
- TEAEs by maximum relationship to study medication, overall and by system organ class and preferred term;
- TEAEs by relationship to study medication, overall and by system organ class and preferred term;
- TEAEs by system organ class sorted by decreasing frequency;TEAEs by preferred term sorted by decreasing frequency;
- Related TEAEs by preferred term sorted by decreasing frequency;
- TESAEs, overall and by system organ class and preferred term;
- TESAEs by maximum relationship to study medication, overall and by system organ class and preferred term;
- TESAEs by relationship to study medication, overall and by system organ class and preferred term;
- Non-serious TEAEs overall and by system organ class and preferred term;
- TEAEs leading to study drug discontinuation, overall and by system organ class and preferred term;
- TEAEs leading to death, overall and by system organ class and preferred term;
- TEAEs of special interest, overall and by system organ class and preferred term;

Only TEAEs will be included in the summary tables, however separate listings for treatment-emergent and non-treatment-emergent AEs will be generated. Additional listings will be provided for deaths, AESIs, serious AEs and Adverse Events Leading to Study Drug Discontinuation.

12.2. Laboratory Evaluations

Safety laboratory samples for chemistry, hematology, urinalysis and coagulation will be collected at various different timepoints for different cohorts.

Refer to Section 1.3 of the Protocol for the schedule of activities indicating when the respective samples are taken for each cohort.

The following parameters will be included:

Clinical chemistry: BUN, chloride, potassium, bicarbonate, sodium, glucose, AST, ALT, alkaline phosphatase, gamma glutamyltransferase, HbA1C (Screening only), urea, total and direct bilirubin, total protein, albumin, cholesterol (total), LDL, HDL, triglycerides, creatinine, creatine phosphokinase.

Hematology: Platelet count, RBC count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, % reticulocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils.

Urinalysis: Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase. Microscopic examination (if any leucocytes, more than a trace protein, nitrites, and blood [if not menstruating] are abnormal).

Coagulation: International normalized ratio, partial thromboplastin time, prothrombin time.

Serology: HIV-1 and HIV-2 antibodies, HBsAg, anti-HBC IgG + IgM (if IgG positive), and anti-HCV with confirmation by HCV RNA.

Serum hCG pregnancy test (as needed for women of childbearing potential), FSH (postmenopausal females only)

Alcohol breath and **urine drug screen:** Amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, methamphetamine, 3,4-methylenedioxy-methamphetamine, methadone, and tetrahydrocannabinol [cannabinoids]) at minimum.

IRR*:* In the event of an IRR, it is recommended to collect a blood sample for assessment of tryptase, histamine, C-reactive protein, complement C3, complement C5a, complement C5, Interleukin 1 Beta, Interleukin 2, Interleukin 4, Interleukin 5, Interleukin 6, Interleukin 8, Interferon Gamma, Interleukin 10, Interleukin 12 and Tumor Necrosis Factor as soon as the IRR is observed (prior to administering any IRR medication), and 2 hours, 24 hours and 7 days (prior to the next dose of study drug) after onset of the IRR.

Signs of infection: If a participant shows signs of infection, the following investigations should be included:

- Blood cultures (taken prior to start of antibiotics)
- Routine profile

Laboratory parameter values will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE).

All summaries will be based on results in SI (standard international system of units) units and will be

output in the order listed above.

Toxicity grading following the NCI CTCAE grades version 5.0 will also be derived for laboratory variables where applicable (see list below). Note, where gradings require investigator/clinical input, this will not be considered and only the numeric criteria will be used for the assignments. If this results in the criteria for more than one grade being met, the highest (worst) CTCAE grade will be assigned. For creatinine only, the criteria based on the upper limit of normal (ULN) will be used (changes compared to the baseline value will not be used), eg, CTCAE defines Grade 1 as > ULN - 1.5 x ULN or > 1 - 1.5 x baseline. Only the ULN – 1.5 x ULN criterion will be used (and not the baseline criterion).

The following parameters are CTCAE gradable:

• **Clincal Chemistry**: Alanine aminotransferase albumin, alkaline phosphatase, aspartate aminotransferase, total bilirubin, creatinine, gamma-glutamyl transferase , glucose (only do the grading the hypoglycemia, no grading for hyperglycemia), creatine kinase.

• **Hematology**: Absolute neutrophil count (neutrophil) , total leukocytes (Leukocytes) , hemoglobin (only do the grading for anemia, no grading for hemoglobin increased), platelet count , lymphocyte.

• **Coagulation**:International normalized ratio.

Actual values and changes from baseline in clinical chemistry, hematology and coagulation, will be summarized by treatment.

Shift tables for clinical chemistry, hematology, and coagulation from baseline CTCAE toxicity for each visit and to the maximum grade on treatment for each parameter will be provided. Participants with both a non-missing baseline and at least one non-missing post-baseline grade will be included in the shift tables. Unscheduled data will be included in the worst case across all scheduled and unscheduled visits after the first dose of study treatment. This means that if there are CTCAE grades derived from both unscheduled and scheduled visits data per test per participant then the highest grade will be summarized.

For non-CTCAE gradable tests, a shift table will be provided showing shifts relative to the normal ranges. This summary of normal range category changes illustrates the number and percentage of participants who fall into specified categories (Decrease to Low, Change to Normal or No Change, Increase to High) by comparing the baseline normal range category to the overall worst-case normal range category. The worst-case post-baseline row will be used to summarize the participants' overall worst-case normal range category change. The determination of the worst-case takes into account both planned and unscheduled assessments. Only laboratory tests which cannot be graded per CTCAE v. 5.0 specified criteria will be included.

Participants with missing baseline value are to be assumed to have normal baseline value. Worst-case can be either High or Low. If a participant has a Decrease to Low and an Increase to High during the same time interval, then the participant is counted in both the 'Decrease to Low' and 'Increase to High' categories. If a participant was high at baseline and decreases to Low during the time interval, then the participant is counted in the 'Decrease to Low' category. Likewise, if a participant was Low at baseline and increases to High during the time interval, then the participant is counted in the 'Increase to High' category. Participants are only counted in the 'Change to Normal or No Change' category if they are:

- Normal at baseline and have no normal range High and no normal range Low values during the time interval
- High at baseline and do not change to Low during the time interval
- Low at baseline and do not change to High during the time interval

Shift tables by treatment will be produced for these laboratory parameters. These tables will summarize the number of participants with each baseline grade relative to the reference ranges and changes to the worst highest grade assessed post-dose during the study.

All events of ALT ≥ 3 × upper limit of normal (ULN) and bilirubin ≥ 2 ×ULN (> 35% direct bilirubin) or ALT ≥ 3 × ULN and international normalized ratio (INR) > 1.5, if INR measured which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE. Liver function results will be presented in a summary table and eDISH (evaluation of drug-induced serious hepatotoxicity) plots.

All laboratory results, as well as CTCAE grades will be included in data listings. Abnormal results for clinical chemistry, hematology, urinalysis and coagulation will be listed separately. Laboratory results for serology, pregnancy tests, FSH, urine drug screen, alcohol breath test, IRR lab data and signs of infection lab data will be listed only.

12.3. Vital Signs

Systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (bpm), respiratory rate (breaths per minute), pulse oximetry (%) and temperature (degree Celsius) will be measured at different timepoints as per the SoA in Protocol Section 1.3.

Actual values and changes from baseline in vital sign measurements will be summarized by treatment.

All vital signs will be provided in data listings.

12.4. ECG

The ECG parameters include heart rate, PR, RR, QRS, QT, and corrected QTcF intervals.

12-lead ECGs in triplicate will be taken at at different timepoints as per the SoA in Protocol Section 1.3. 12-lead ECGs should be measured after a minimum of 5 minutes in supine position. The average of the triplicate ECG readings at the time points collected will be calculated and used in the analyses.

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

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

Actual values and change from baseline of these average ECGs will be summarized by treatment.

All ECG parameters, including all single ECG measurements, but also the mean value and overall ECG evaluation will be provided in data listings.

12.5. Physical Examination

A full physical examination will be performed at different timepoints as per the SoA (Section 1.3) in the Protocol. A symptom-driven physical examination of relevant body systems may be performed at other times, at the Investigator's discretion.

Physical examination data will be listed.

13. Interim Analyses

No interim analyses are planned.

14. Changes from Analysis Planned in Protocol

The study was terminated early, therefore cohort 2 has only 2 participants and cohort 6 has none. Therefore the secondary objective, to compare safety and tolerability, PK, PD, and immunogenicity of ALXN1830 SC between Japanese and non-Japanese healthy participants cannot be met and the secondary endpoint the quantitative assessment of safety, PK parameters, PD parameters, and immunogenicity between Japanese and non-Japanese healthy participants cannot be analyzed.

Analysis sets definitions as specified in Protocol Section 9.3 were updated as follows:

For the Enrolled Set participants also need to be randomized.

For the Pharmacokinetic Set participants need to receive at least 1 dose of study drug (only active) and have at least one post-dose serum ALXN1830 concentration measured. Participants will be analyzed according to the study drug they actually received. Serum concentrations will be summarized for all participants in the PKS. The exclusions from summary statistics for serum concentrations and/or PK parameters will be defined based on review of protocol deviations (if any) prior to database lock by PK scientist and study statistician at the discretion of the sponsor.

For the Pharmacodynamic Set participants need to receive at least 1 dose of study drug (active and placebo) and have evaluable serum Immunoglobulin data (IgG, IgG subtypes, Ig subtypes, CIC) or FcRn.

Immunogenicity Set was not define in the protocol, but added to the SAP as follows: The Immunogenicity Set (IGS) will include all participants who have a predose and at least 1 postdose ADA sample collected. Immunogenicity analyses will be performed using the IGS.

15. Reference List

FDA. Guidance for Industry, Clinical/Medical, Guidance for Industry: Immunogenicity assessment for therapeutic protein product. 2014.

Hunley TE, Corzo D, Dudek M, et al. Nephrotic syndrome complicating alpha-glucosidase replacement therapy for Pompe disease. Pediatrics. 2004;114(4): e532 535.

Smith BP, Vandenhende FR, DeSante KA, et al. Confidence interval criteria for assessment of dose proportionality. Pharm Res. 2000;17(10):1278-1283.

16. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in Syneos Health Developing Statistical Programs SOP (3907) .

Syneos Health Developing Statistical Programs SOP (3907), Conducting the Transfer of Biostatistical Deliverables SOP (3908) and the SAS Programming and Vaidation Plan describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

Syneos Health SOP Pharmacokinetic and Related Data Analysis (3913) describes the process for the interaction between the Biostatistics and Pharmacokinetics departments for the analysis of pharmacokinetic and pharmacodynamic data.

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[redacted] [redacted] [redacted] Alexion Pharmaceuticals Inc. Security Level: Email, Account Authentication (Required), Digital Certificate **Signature Provider Details:** Signature Type: Alexion Pharmaceuticals, Inc. (Regulated) (Client ID: [redacted]) Signature Issuer: Alexion Pharmaceuticals Issue 2 CA **Electronic Record and Signature Disclosure:** Not Offered via DocuSign	[redacted] Signature Adoption: Pre-selected Style Signature ID: [redacted] Using IP Address: [redacted] Signature Provider Location: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 24-Feb-2022 | 12:20 Viewed: 24-Feb-2022 | 12:20 Signed: 24-Feb-2022 | 12:21

In Person Signer Events	Signature	Timestamp

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Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	24-Feb-2022 | 12:20
Certified Delivered	Security Checked	24-Feb-2022 | 12:20
Signing Complete	Security Checked	24-Feb-2022 | 12:21
Completed	Security Checked	24-Feb-2022 | 15:08

Payment Events	Status	Timestamps

ALXN1830-HV-108_SAP_v2.0_24Feb2022

Final Audit Report 2022-03-01

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