TITLE PAGE

Study Title:	A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Ascending Dose Study of Subcutaneous ALXN1830 in Healthy Participants
Short Title:	Safety and Pharmacokinetic Study of Subcutaneous ALXN1830 in Healthy Adult Participants
Study Intervention:	ALXN1830
Brief Description:	This was a Phase 1, randomized, double-blind, placebo-controlled, single and multiple ascending dose study of subcutaneous ALXN1830 in healthy participants
Study Sponsor:	Alexion Pharmaceuticals, Inc. (Alexion)
Study Number:	ALXN1830-HV-105
Study Phase:	Phase 1
Study Initiation Date:	12 Nov 2019
Early Study Termination Date:	The last participant completed the last visit on 30 Mar 2020. The study was terminated on 22 Jan 2021.
Regulatory Agency Identifier Number:	EudraCT number: 2019-003496-18
Report Date:	**Document Version** Version 1 **Date** 15 Dec 2021

This trial was conducted in accordance with the ethical principles of Good Clinical Practice (GCP), according to the International Council for Harmonisation (ICH) Harmonized Tripartite Guideline.

ALEXION'S RESPONSIBLE MEDICAL OFFICER:

Manjula Dundoo, MD
Medical Director, Alexion

SYNOPSIS

Name of Sponsor/Company:

Alexion Pharmaceuticals, Inc. (Alexion)

Name of Study Intervention:

ALXN1830

Study Title:

A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Ascending Dose Study of Subcutaneous ALXN1830 in Healthy Participants

Study Number:

ALXN1830-HV-105

Study Phase:

Phase 1

Short Title:

Safety and Pharmacokinetic Study of Subcutaneous ALXN1830 in Healthy Adult Participants

Number of Study Center(s) and Countries:

This study was conducted at 1 center in the United Kingdom.

Publications (if any):

None

Study Period:

The first participant first visit (defined as when the first informed consent was signed) was on 12 Nov 2019 and the end of the study (defined as the last visit for the last participant) was on 30 Mar 2020. The study was terminated on 22 Jan 2021.

Methodology:

This was a Phase 1 study planned to evaluate the safety, PK, and PD of ALXN1830 in healthy adult participants.

Number of Participants (planned and analyzed):

Up to 56 participants were planned to be enrolled and randomized in a 6:2 ratio in up to 7 cohorts to receive either single or multiple doses of ALXN1830 subcutaneously (SC) (n = 6 per cohort) or single or multiple doses of placebo (n = 2 per cohort).

The study was terminated early due to the COVID-19 pandemic after completion of the ALXN1830 SC 750 mg dose group and partial enrollment of the ALXN1830 SC 1250 mg dose group. A total of 12 participants were treated and analyzed; 6 participants were administered a

single dose of ALXN1830 SC 750 mg, 3 participants were administered a single dose of ALXN1830 SC 1250 mg, and 3 participants received placebo.

Main Criteria for Inclusion and Exclusion:

This study enrolled healthy male and female participants aged 18 to 65 years, inclusive, who agreed to the contraception requirements of the study and were able to provide written informed consent.

Study Interventions, Dose, and Mode of Administration

Up to 7 cohorts were planned for evaluation as shown in Table 1.

Table 1 Study Drugs, Dose, and Mode of Administration

Cohort (n)	Regimen/Route of Administration	Study Drug Dose (N)
1	Single dose SC	Placebo (n = 2) or ALXN1830 750 mg (n = 6)
2	Single dose SC	Placebo (n=2) or ALXN1830 1500[b] mg (n = 6)
3	Single dose SC	Placebo (n=2) or ALXN1830 2250 mg (n = 6)
4	Multiple dose (8 doses biw) SC	Placebo (n=2) or ALXN1830 300 mg (n = 6)
5	Multiple dose (12 doses qw) SC	Placebo (n=2) or ALXN1830 750 mg (n = 6)
6	Multiple dose (4 doses qw) SC	Placebo (n=2) or ALXN1830 1500 mg (n = 6)
7[a]	Multiple dose (4 doses or 12 doses qw) SC	Placebo (n=2) or ALXN1830 2250mg (n = 6)

[a] Optional

Abbreviations: biw = twice weekly; qw = weekly; SC = subcutaneous.

Note: The study was terminated early due to the COVID-19 pandemic after completion of Cohort 1 and part of Cohort 2.

[b] The safety review committee (SRC) recommended decreasing the dose level for Cohort 2 from 1500 mg to 1250 mg due to higher (36%) than predicted (30%) decrease in IgG observed after administration of study intervention in Cohort 1.

Duration of Study Intervention:

Participants received a single dose of ALXN1830 or placebo on Day 1 and were followed until Day 64 (end of study).

Objectives, Endpoints, Statistical Methods and Results

Listed below are the objectives, endpoints, statistical methods, and results for this study.

Objectives	Endpoints	Statistical Analyses	Results
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	The frequency of TEAEs and TESAEs were tabulated by SOC, PT, and severity/intensity, as well as by SOC, PT, and relationship For clinical laboratory results, vital signs, and ECG results, summary statistics, actual values and changes from baseline were presented by treatment and by time point	Eight of 9 (88.9%) participants who were administered ALXN1830 and 3 of 3 (100%) administered placebo experienced at least 1 TEAE. All TEAEs were Grade 1 in severity. There were no deaths and no serious adverse events (SAEs) reported in the study and no participant withdrew from the study because of a TEAE. There were numerically more related TEAEs reported in participants administered ALXN1830 SC 1250 mg than in those administered ALXN1830 SC 750 mg or placebo, however due to the low number of participants it is not possible to determine whether there is a treatment or dose effect on the safety profile based on these results.
Secondary			
• To assess the PK of single and multiple doses of ALXN1830 SC	ALXN1830 PK profiles and PK parameters	Descriptive statistics for PK parameters included number of observations (n), arithmetic mean (mean), standard deviation (SD), arithmetic coefficient of variation (%CV), geometric mean, geometric coefficient of variation (%CV), median, minimum, and maximum.	The PK data collected from this study were highly variable and serum concentrations of ALXN1830 were measurable only up to 48 hours postdose. The time to peak concentrations (T_{max}) ranged from 6 – 48 hours and the terminal phase could not be characterized. In the 750 mg SC dose group, the maximal drug concentration value (Cmax) was 0.888 µg/mL and the time to C_{max} (T_{max}) was 48 h. The area under the concentration curve between the end of the SC infusion and the last measurable concentration (AUCt) was 31.8 µg·hr/mL. In the 1250 mg SC dose group, the Cmax was 2.77 µg/mL and the median Tmax was 8 h. The AUCt was 44.2 µg·hr/mL.

Objectives	Endpoints	Statistical Analyses	Results
• To explore the PD effects of single and multiple doses of ALXN1830 SC	• Change in IgG levels	PD: Absolute values as well as changes and percent changes from baseline were summarized at each timepoint by cohort.	In the ALXN1830 750 mg SC dose group, mean total IgG levels were reduced by a maximum of 36% from baseline by Day 10. By Day 29, IgG levels had recovered to 12.3% below baseline and continued to increase towards baseline throughout the follow-up period. In the ALXN1830 1250 mg SC dose group, mean total IgG levels were reduced by a maximum of 39% from baseline by Day 10. By Day 43, mean total IgG levels had recovered to 11.9% below baseline and continued to increase towards baseline throughout the follow-up period. At both dose levels explored in the present study, ALXN1830 lowered IgG 1, IgG2, and IgG3 levels significantly from baseline as compared to placebo. IgG4 levels were also lowered from baseline, however the effect is less pronounced since ALXN1830 is an IgG4 molecule and may be detected by the IgG4 assay used. There were no meaningful changes in the levels of IgA and IgM.
• To assess the immunogenicity of ALXN1830 SC	• Measurement of ADA levels and NAbs	Immunogenicity: Immunogenicity, as measured by ADA to ALXN1830 (all formulations), was listed, and summarized over time by treatment group using the Immunogenicity population.	There was no detectable pre-existing immunoreactivity in any of the participants. Overall, 6 participants were ADA positive after a single dose ALXN1830 given SC: 4 in the ALXN1830 750 mg SC dose group and 2 in the ALXN1830 1250 mg SC dose group. All 6 participants continued to have a low ADA positive titer at the end of the Study (Day 64). Of the 6 participants who developed ADA, 4 participants (44.4%, 2 each at 750 mg and 1250 mg dose groups) were also positive for NAbs. The presence of ADA was not associated with IRRs or non-acute hypersensitivity reactions.

Summary of Results and Conclusions

Demography and Baseline Characteristics:

All participants were enrolled at a single center in the UK. Most participants enrolled in this study were female (58.3%) and white (66.7%). The mean (SD) age was 24.3 (4.29) years.

Exposure:

In this study, 9 participants were administered a single dose of ALXN1830 SC, (6 participants were administered ALXN1830 750 mg SC, and 3 were administered ALXN1830 1250 mg SC). Three participants received a single dose of placebo.

Efficacy Results:

Not applicable for this study.

Safety Results:

Most participants (88.9%) who were administered ALXN1830 experienced at least 1 TEAE. The incidence of any TEAEs reported during the study was similar across dose groups and placebo. Most (88.9%) TEAEs were considered not related and all TEAEs reported were of Grade 1 severity. There were no serious adverse events (SAEs) reported in the study and no participant withdrew from the study because of a TEAE.

Parameter	ALXN1830 SC 750mg N = 6 n (%) E	ALXN1830 SC 1250mg N = 3 n (%) E	Placebo N = 3 n (%) E	Total ALXN1830 SC N = 9 n (%) E
Any TEAE	5 (83.3) 8	3 (100) 18	3 (100) 6	8 (88.9) 26
TEAE by Relationship				
Related	0	2 (66.7) 3	0	2 (22.2) 3
Not Related	5 (83.3) 8	3 (100) 15	3 (100) 6	8 (88.9) 23
TEAE by Toxicity Grade				
Grade 1	5 (83.3) 8	3 (100) 18	3 (100) 6	8 (88.9) 26
Related	0	0	0	0
Not Related	0	0	0	0

Abbreviation(s): SC - Subcutaneous, TEAE - treatment-emergent adverse event,
% = n/N*100. E=number of events.
Participants are counted once in each toxicity grade or relationship category in case of multiple events.
TEAEs are defined as those any adverse event that commences after the start of administration of study drug.
Source: Table 14.3.1.3.1.2

Pharmacokinetics

The PK data collected from this study were highly variable and serum concentrations of ALXN1830 were measurable only up to 48 hours postdose. The time to peak concentrations (T_{max}) ranged from 6 – 48 hours and the terminal phase could not be characterized. In the ALXN1830 750 mg SC dose group, the maximal drug concentration value (C_{max}) was 0.888 µg/mL and the time to C_{max} (T_{max}) was 48 hours. The area under the concentration curve between the end of the SC infusion and the last measurable concentration (AUC_t) was 31.8 µg·hr/mL. In the ALXN1830 1250 mg SC dose group, the C_{max} was 2.77 µg/mL and the median Tmax was 8

hours. The AUC_t was 44.2 µg·hr/mL. The half-life and other PK parameters should be interpreted with caution due to sparsity of the data in this study.

Pharmacodynamics

The primary PD biomarker in this study was IgG. In the ALXN1830 750 mg SC dose group, mean total IgG levels were reduced by a maximum of 36% from baseline by Day 10. By Day 29, IgG levels had recovered to 12.3% below baseline and continued to increase towards baseline throughout the follow-up period. In the ALXN1830 SC 1250 mg dose group, mean total IgG levels were reduced by a maximum of 39% from baseline by Day 10. By Day 43, mean total IgG levels had recovered to 11.9% below baseline and continued to increase towards baseline throughout the follow-up period.

At both dose levels explored in the present study, ALXN1830 lowered IgG1, IgG2, and IgG3 levels significantly from baseline as compared with placebo. IgG4 levels were also lowered from baseline, however the effect is less pronounced since ALXN1830 is an IgG4 molecule and may be detected by the IgG4 assay used. There were no meaningful changes in the levels of IgA and IgM.

Immunogenicity

Immunogenicity was assessed by detecting anti-drug antibodies (ADA) and positive ADA responses were further characterized for the presence of neutralizing antibodies (NAb) to ALXN1830.

No baseline sample from all patients was positive in the ADA assay suggesting no detectable pre-existing immunoreactivity in any of the participants. Overall, 6 participants were ADA positive after a single dose ALXN1830 given SC. Of which 4 were in the ALXN1830 750 mg SC dose group and 2 in the 1250 mg dose group. All 6 participants continued to have a low ADA positive titer at the end of the Study (Day 64). Of the 6 participants who developed ADA, 4 participants (44.4%, 2 at each dose level) were also positive in the NAb assay. A listing of ADA status for each participant is provided in Listing 16.2.6.4.1.7. The presence of ADA did not appear to be associated with IRRs or non-acute hypersensitivity reactions.

Conclusions:

- ALXN1830 was safe and well tolerated after a single dose administered SC up to 1250 mg in healthy participants. No new safety signals were identified other than those already included in the current Investigator's brochure.
- The PK data collected from this study were highly variable and serum concentrations of ALXN1830 were measurable only up to 48 hours postdose.
- Mean maximum IgG reductions of 36% and 39% were reached by Day 10 following a single SC dose of ALXN1830 750 mg and ALXN1830 1250 mg, respectively. The duration of IgG lowering was longer at a dose of 1250 mg than at 750 mg, and IgG levels increased toward baseline throughout the follow-up period.
- Six participants were ADA positive after a single dose of ALXN1830 administered SC. Of these, 4 also had positive result in the Nab assay. The presence of ADAs was not associated with IRRs or non-acute hypersensitivity reactions.

Date and Version of This Report: Final, 15-Dec-2021

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Explanation
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine transaminase
AR	adverse reaction
AUC	area under the concentration-time curve
biw	twice weekly
BMI	body mass index
BP	blood pressure
CIC	circulating immune complexes
CL	clearance
CRF	case report form
CRP	C-reactive protein
CRU	clinical research unit
CTCAE	Common Terminology Criteria for Adverse Events
D	day
ECG	electrocardiogram
eCRF	electronic case report form
EOI	end of infusion
EOS	end of study
ET	early termination
F	bioavailability
FcRn	neonatal crystallizable fragment receptor
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GLP	good laboratory practice
GMP	Good Manufacturing Practices
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
IC	immune complex
ICF	informed consent form
IEC	independent ethics committee
Ig	immunoglobulin
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IRB	institutional review board
IRR	infusion related reaction
IV	intravenous
IVIG	intravenous immunoglobulin
mAb	monoclonal antibody
MAD	multiple ascending dose
MG	myasthenia gravis
NAb	neutralizing antibody
NOAEL	no observed adverse effect level
OP	outpatient
PBO	placebo
PD	pharmacodynamics

Abbreviation	Explanation
PK	pharmacokinetics
q2w	every 2 weeks
QTcF	QT interval corrected for heart rate according to Fridericia's formula
qw	weekly
SAD	single ascending dose
SAE	serious adverse event
SC	subcutaneous
SoA	schedule of activities
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
WAIHA	warm autoimmune hemolytic anemia
WBC	white blood cell
WHO	World Health Organization

ETHICS

Independent Ethics Committee and/or Institutional Review Board

The protocol, protocol amendment, informed consent form (ICF), Investigator's Brochure, and other relevant documents (eg, advertisements) were submitted to an independent ethics committee/institutional review board (IRB/IEC) by the Investigator and reviewed and approved by the IRB/IEC before the study was initiated.

Any amendments to the protocol required IRB/IEC approval before implementation of changes made to the study design except for changes necessary to eliminate an immediate hazard to study participants.

A listing of the IRB/IEC that approved the study is provided in Appendix 16.1.3.

Ethical Conduct of the Study

This study was conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

Participant Information and Consent

The Investigator or his/her representative explained the nature of the study to the participant or his/her legally authorized representative and answered all questions regarding the study.

Participants were informed that their participation was voluntary. Participants or their legally authorized representative were required to sign a statement of informed consent that met the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record included a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent also signed the ICF.

Participants were re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) was provided to the participant or the participant's legally authorized representative.

1. INTRODUCTION

1.1. Background

ALXN1830 is a humanized, affinity-matured IgG4 kappa monoclonal antibody (mAb) that binds to the neonatal crystallizable fragment receptor (FcRn) and blocks FcRn-mediated recycling of immunoglobulin G (IgG) and IgG immune complexes (ICs), thereby lowering total IgG (including pathogenic autoantibodies) and ICs in circulation.

ALXN1830 is an mAb that specifically blocks the FcRn IgG interaction and is intended for the treatment of IgG-mediated autoimmune diseases. In order to identify optimal targets for anti FcRn therapy, Alexion has focused initially on autoimmune disorders with an accepted pathologic role for autoantibodies in which drugs such as intravenous immunoglobulin (IVIG) and/or plasmapheresis have been demonstrated to have a clinically meaningful benefit. While current treatments for certain autoimmune disorders, including chronic steroids, immunosuppressants, IVIG, plasmapheresis, and anti-CD20 mAbs (such as rituximab) can be effective, they are associated with significant adverse effects, and delayed or non-durable responses.

Due to the significant adverse effects of long-term use of high-dose corticosteroids and chronic immunosuppressants particularly in an elderly population, there remains a clear unmet medical need for the treatment of IgG mediated diseases. Administration of ALXN1830, leading to a significant decrease in total IgG, pathogenic IgG autoantibodies and the circulating immune complexes (CICs) of which these IgG are constituents, should lead to a decrease in the clinical manifestations of diseases of this type. Moreover, the ability of ALXN1830 to reduce CICs and the innate and adaptive immune responses triggered by CICs may result in sustained disease modification.

In the Phase 1 first in human study, Study SYNT-101, ALXN1830 was administered as single ascending intravenous (IV) doses in healthy adult participants at doses up to 30 mg/kg and demonstrated a good safety profile. The purpose of this Phase 1 study in healthy adult participants was to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of single ascending doses and multiple ascending doses of ALXN1830 administered subcutaneously.

Data from this study are anticipated to help design future studies in patients with IgG mediated diseases.

1.2. Study Rationale

ALXN1830 is a humanized, affinity-matured IgG4 kappa mAb that binds to the FcRn and blocks FcRn mediated recycling of IgG and IgG ICs, thereby lowering total IgG (including pathogenic autoantibodies) and ICs in circulation. While current treatments for certain autoimmune disorders, including chronic steroids, immunosuppressants, IVIG, plasmapheresis, and anti-CD20 mAbs (such as rituximab) may be effective, they are associated with significant adverse effects, and delayed or non durable responses.

Prior to the initiation of the current study, ALXN1830 had been studied in 4 clinical studies, each using the IV route of administration. It was initially tested in a single ascending dose (SAD) study in healthy participants, Study SYNT 101. The highest dose tested in the SAD study, 30

mg/kg, was well tolerated. ALXN1830 was then studied in 2 Phase 1b/2a studies in autoimmune patients: Study SYNT001 102 in patients with warm autoimmune hemolytic anemia (WAIHA), and Study SYNT001 103 in patients with pemphigus. In both studies, the participants received 5 doses of 10 mg/kg given once weekly, a dose and regimen which was well tolerated.

While these studies were ongoing, a multiple ascending dose (MAD) study in healthy participants, Study SYNT001 104, was initiated to investigate the safety, tolerability, PK, PD, and immunogenicity of ALXN1830. The dose level of the first cohort in the MAD study was 20 mg/kg, with 3 doses given once weekly (3 × qw) followed by 3 doses given every 2 weeks (3 × q2w). A second cohort was initiated using a dose level of 30 mg/kg, but the study was paused after 4 participants in Cohort 2 each received only a single dose.

All of the active clinical studies (SYNT001 102, SYNT001 103, and SYNT001 104) were paused at that time for a Good Manufacturing Practice (GMP) investigation of the study drug batches, due to the observation of acute infusion related reactions (IRRs) in the 20 mg/kg cohort of Study SYNT001 104. Although there was no conclusive clinical or safety link between the findings of the GMP investigation and the IRRs, and the drug product lots used had met all of the approved release specifications, the investigation did identify potential impurities in the drug product that could have possibly confounded the safety profile. Alexion implemented changes to the manufacturing process for future batches to enhance the control and detection of impurities.

The purpose of this Phase 1 study, ALXN1830-HV-105 in healthy adult participants was to evaluate the safety, tolerability, PK, PD, and immunogenicity of single ascending doses and multiple ascending doses of ALXN1830 administered subcutaneously. Data from this study are anticipated to help design future studies in participants with IgG mediated diseases.

Healthy participants were considered as the appropriate population for this study to enable PK and PD assessments without the potential confounding effects due to other disease activities, comorbidities, or medications. This study was designed to minimize risks to participants with strict inclusion/exclusion criteria, as well as a robust safety monitoring and a risk mitigation plan.

2. STUDY OBJECTIVES AND ENDPOINTS

The objectives and endpoints of the study are included in Table 2.

Table 2: Study Objectives and Endpoints

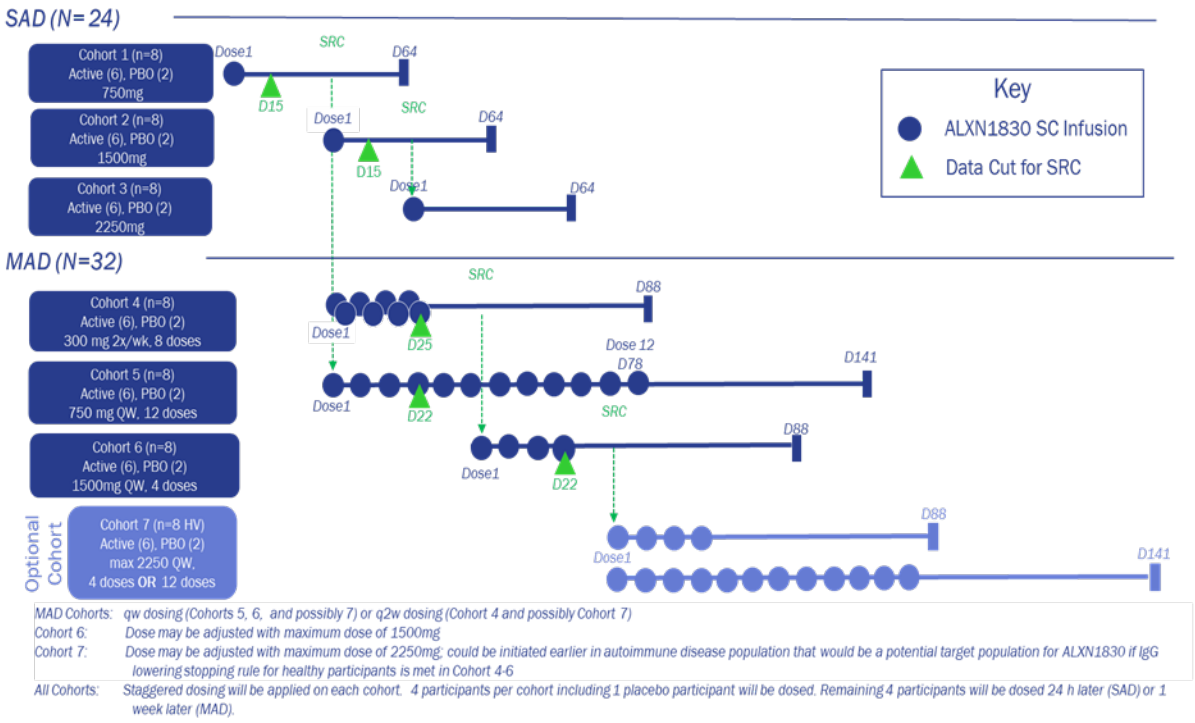
Objectives	Endpoints
Primary	
• To assess the safety and tolerability of single and multiple doses of ALXN1830 SC	• Safety assessed by the incidence and relatedness of TEAEs, SAEs, AESIs, physical examination, vital sign measurements, clinical laboratory and ECG results
Secondary	
• To assess the PK of single and multiple doses of ALXN1830 SC • To explore the PD effects of single and multiple doses of ALXN1830 SC • To assess the immunogenicity of ALXN1830 SC	• ALXN1830 PK profiles and PK parameters • Change in IgG levels • Measurement of ADA levels and NAbs

3. INVESTIGATIONAL PLAN

3.1. Overview of Study Design

This was a safety and pharmacokinetic study of ALXN1830 in healthy adult participants. The study design is depicted below in Figure 1. Additional details are available in the protocol (Appendix 16.1.1).

Figure 1: Study Schematic Diagram



Abbreviations: D = day; MAD = multiple ascending dose; max = maximum; PBO = placebo; qw = weekly; SAD = single ascending dose; SC = subcutaneous; SRC = Safety Review Committee; wk = week.

3.1.1. Discussion of Study Design

The rationale for conducting this study is described in Section 1.2. Because this was the first study of ALXN1830 administered SC, the design included SAD and MAD cohorts and enrolled a healthy participant population.

Further information on the scientific rationale for features of the study design, including chosen cohorts, doses, and endpoints, are discussed in the scientific rationale for study design section of the protocol (study protocol Sections 4.2 and 4.3; Appendix 16.1.1).

3.1.2. Changes in Study Conduct

The safety review committee (SRC) recommended decreasing the dose level for Cohort 2 from 1500 mg to 1250 mg due to a higher (36%) than predicted (30%) decrease in IgG observed after administration of study intervention in Cohort 1 (ALXN1830 750 mg SC).

The study was terminated early due to a lack of subject availability caused by the COVID-19 pandemic after completion of Cohort 1 (ALXN1830 SC 750 mg or placebo) and partial enrollment of Cohort 2 (ALXN1830 1250 mg SC or placebo). A total of 12 participants were treated and analyzed; 6 participants were administered a single dose of ALXN1830 750 mg SC, 3 participants were administered a single dose of ALXN1830 1250 mg SC, and 3 participants received placebo.

3.2. Investigators and Study Administrative Structure

The list of the Investigator and key personnel with their affiliations, their role in the study, and their qualifications is provided in Appendix 16.1.4. The signature of the Investigator is provided in Appendix 16.1.5.

An SRC, consisting of the Investigator, Safety Monitor, Medical Monitor, Study Statistician, and Clinical Pharmacologist, evaluated the study data at prespecified time points for participant safety and made recommendations on dose escalation, dose modification, or termination of the study. Relevant safety data from any other studies ongoing with ALXN1830 was made available to the SRC. At Alexion's discretion, and after consultation with the SRC, additional participants could enroll as replacement participants if a study participant discontinued within 3 weeks of the last dose for reasons other than drug-related AEs. The SRC charter is available in Appendix 16.1.13.

The clinical laboratories and contract research organizations (CROs) used for this study are listed in Appendix 16.1.4.

3.3. Selection of Study Population

3.3.1. Inclusion/Exclusion Criteria

This study enrolled healthy male and female participants aged 18 to 65 years, inclusive, who agreed to the contraception requirements of the study and were able to provide written informed consent. Participants must have had vaccination against pneumococcus (Pneumovax 23 [PPSV23]) at least 28 days, and maximally 4 years prior to Day 1. Participants must have had seasonal influenza vaccination for the current season at least 28 days prior to Day 1. The complete list of inclusion and exclusion criteria are provided in the protocol (Section 5, Appendix 16.1.1).

3.3.2. Removal of Participants from Intervention or Study

The specific criteria and procedures for early discontinuation from study intervention(s) or withdrawal from the study are described in the protocol (Section 7.3; Appendix 16.1.1).

3.4. Study Drug

3.4.1. Study Drugs Administered

The study drugs (ALXN1830 and placebo) are outlined in Table 3. The justification for the doses selected is described in the justification for dose section of the protocol (Section 4.3; Appendix 16.1.1).

Table 3: Study Drugs Administered

Drug Name	ALXN1830	Placebo
Type	Biologic	Diluent (0.9% sodium chloride)
Dose Formulation	Sterile liquid	Sterile liquid
Unit Dose Strength(s)	ALXN1830 is formulated at 150 mg/mL, and supplied as a 1500 mg/10mL vial	Placebo
Dosage Level(s)	Refer to Appendix 16.1.1	Not applicable
Route of Administration	SC injection or infusion SC push for 300 mg (2 ml) and SC infusion for 750 mg and above	SC injection or infusion
Use	Investigational Product	Placebo
IMP and NIMP	IMP	IMP
Sourcing	Provided by Alexion	Provided by trial site
Packaging and Labeling	Study Drug was provided in a 10mL Vial. Each vial will be labeled as required per country requirement	Placebo was provided in country-specific commercially available form

Abbreviations: IMP = investigational medicinal product; SC = subcutaneous

A listing of batch numbers is available upon request.

3.4.2. Measures to Minimize Bias

The method used for blinding/masking is described in the measures to minimize bias section of the protocol (Section 6.3; Appendix 16.1.1).

3.4.3. Study Drug Compliance

Participants were administered study drug in a controlled setting under the supervision of the Investigator, thereby ensuring compliance with study drug administration (Section 6.4; Appendix 16.1.1).

3.4.4. Prior, Concomitant, and Post-dosing therapy

The medications/treatments/vaccinations allowed or disallowed before, during, and after study drug dosing, including any exceptions to these requirements, are described in the concomitant therapy section of the protocol (Section 6.5; Appendix 16.1.1).

3.5. Study Assessments and Procedures

3.5.1. Planned Measurements and Timing of Assessments

The schedule and measurement/collection methods for specific PK, PD, safety, immunogenicity, and other assessments, are provided in the schedule of activities (Protocol Section 1.3; Appendix 16.1.1) and described in the study assessments and procedures section of the protocol (Protocol Section 8; Appendix 16.1.1). The collection and assessment of safety information during the study (evaluation, definitions, recording, and reporting of AEs, SAEs, and other reportable safety events) is detailed in the AE reporting section of the protocol (Protocol Section 8.3; Appendix 16.1.1).

3.5.2. Appropriateness of Measures

The PK/PD, and safety endpoints used in this study were standard, generally reliable, and relevant to the objectives set forth in the protocol (Appendix 16.1.1).

3.6. Data Quality Assurance

An audit was not conducted for this study.

3.6.1. Study Monitoring

The study center was monitored by Alexion Pharmaceuticals, Inc. The center was visited at regular intervals and a Visit Log was maintained. Monitors were responsible for reviewing adherence to the protocol; compliance with GCP; and the completeness, accuracy, and consistency of the data. Direct access to participant medical and laboratory records was permitted to verify entries on the study-specific CRFs.

3.6.2. Investigator Meetings and Staff Training

Investigator staff training was provided by the Alexion during site initiation visits and routine monitoring visits. Alexion organized investigator and monitor meetings before study start and during the study to provide information on the investigational product, the study rationale and design, responsibilities under GCP and training on the detailed study requirements.

3.6.3. Standardization of Laboratory Procedures

There was no central laboratory used in this study. Information regarding each local laboratory used is provided in Appendix 16.1.10.

3.6.4. Investigator Responsibilities

The Investigator was responsible for all data entered in the CRFs and documented their review and approval of the data by signing a form verifying the validity and completeness of the data. The Investigator was responsible for appropriate retention of essential study documents.

3.6.5. Clinical Data Management

Case report form data were captured via data entry by study center personnel. Data quality checks were applied using electronic verification methods. An audit trail to support data query resolution and any modification to the data was maintained.

3.6.6. Clinical Quality Assurance Audits

No audits were performed for this study.

3.7. Statistical Analysis

3.7.1. Statistical Analysis Plan

The planned analyses and determination of sample size are described in the final version of the SAP (Appendix 16.1.9) and included in the protocol (Appendix 16.1.1)

3.7.2. Changes in Planned Analyses Prior to Unblinding or Database Lock

All changes in the planned analyses for the study were implemented by protocol amendments as described in Appendix 16.1.1, Study Protocol and amendments to the SAP, Appendix 16.1.9, Statistical Methods.

4. STUDY PARTICIPANTS

4.1. Disposition of Participants

Twelve participants were enrolled and dosed; 11 (91.7%) participants completed the study. One participant in the placebo group who was administered placebo was lost to follow-up. The disposition of participants is provided in Table 4.

Eight participants (6 randomized to ALXN1830 750 mg SC and 2 randomized to placebo) were enrolled and dosed in Cohort 1 and 4 participants (3 randomized to ALXN1830 1250 mg SC and 1 to placebo) were enrolled and dosed in Cohort 2. A listing of participants by study intervention is provided in Listing 16.2.1.1.6.

Table 4: Participant Disposition -All Randomized Participants

	ALXN1830 SC 750mg N = 6 n (%)	**ALXN1830 SC 1250mg N = 3 n (%)**	**Placebo N = 3 n (%)**	**Total N = 12 n (%)**
Dosed	6 (100)	3 (100)	3 (100)	12 (100)
Completed	6 (100)	3 (100)	2 (66.7)	11 (91.7)
Discontinued Study:	0	0	1 (33.3)	1 (8.3)
Adverse Event	0	0	0	0
Death	0	0	0	0
Withdrawal by Participant	0	0	0	0
Lost to Follow-up	0	0	1 (33.3)	1 (8.3)

Abbreviation(s): SC - Subcutaneous.
% = n/N*100; Percentages are calculated based on the total number of participants in each group
Source: Table 14.1.1.2.6

4.2. Protocol Deviations

At least 1 protocol deviation was reported for all 12 participants. The most common deviation was missed study procedures/tests, which was reported for 100% of participants. Deviations related to laboratory assessments were reported for 3 participants (50.0%) who received ALXN1830 SC 750 mg, 1 participant (33.3%) administered ALXN1830 SC 1250 mg, and 2 participants (66.7%) who received placebo.

Eligibility and entry criteria deviations were reported for 2 participants in the ALXN1830 SC 1250 mg dose group and 2 participants who were administered placebo. Of these 4 participants, 3 participants (2 in the ALXN1830 SC 1250 dosing group and 1 in the placebo group) had IgM levels higher than the upper limit of normal; in each case the higher IgM levels were considered related to receiving the vaccinations required for study entry. Two participants who were administered ALXN1830 SC 1250 mg and one participant who was administered placebo had taken paracetamol less than 14 days predose. The participants were allowed to enter the study because this was a premedication drug per protocol.

Protocol deviations are summarized in Table 5. All deviations were considered minor and not to have impacted the integrity of data or participant safety.

A by-participant listing of all protocol deviations is provided in Listing 16.2.2.3.6.

Table 5 Protocol Deviations

	ALXN1830 SC 750mg N = 6 n (%)	ALXN1830 SC 1250mg N = 3 n (%)	Placebo N = 3 n (%)	Total N = 12 n (%)
Type of Deviation: ALL				
At least one Deviation				
Eligibility and Entry Criteria	0	2 (66.7)	2 (66.7)	4 (33.3)
Laboratory Assessment	3 (50.0)	1 (33.3)	2 (66.7)	6 (50.0)
Study Procedures/Tests	6 (100)	3 (100)	3 (100)	12 (100)
Other	4 (66.7)	0	2 (66.7)	6 (50.0)
Type of Deviation: Minor				
At least one Deviation				
Eligibility and Entry Criteria	0	2 (66.7)	2 (66.7)	4 (33.3)
Laboratory Assessment	3 (50.0)	1 (33.3)	2 (66.7)	6 (50.0)
Study Procedures/Tests	6 (100)	3 (100)	3 (100)	12 (100)
Other	4 (66.7)	0	2 (66.7)	6 (50.0)

Abbreviation(s): SC - Subcutaneous.
Percentages are based on the number of participants in the respective group and may add to more than 100% since a participant may have more than one protocol deviation.
Source: Table 14.1.1.4.6

4.3. Populations Analyzed

The number of participants included in each analysis population is provided in Table 6.

No participants were excluded from the analyses. A by-participant listing of participants in each analysis population is provided in Listing 16.2.1.1.6.

Table 6 Summary of Analysis Populations – All Participants

	ALXN1830 SC 750mg n	ALXN1830 SC 1250mg n	Placebo n	Total n
Randomized	6	3	3	12
Safety Set	6	3	3	12
Pharmacokinetic Set	6	3	3	12
Pharmacodynamic Set	6	3	3	12
Immunogenicity Set	6	3	3	12

Abbreviation(s): SC - Subcutaneous.
Source: Table 14.1.1.1.6

4.4. Demographics and Other Baseline Characteristics

Most participants enrolled in this study were female (58.3%) and white (66.7%) The mean (SD) age was 24.3 (4.29) years (Table 7).

A by-participant listing of demographic data is provided in Listing 16.2.4.1.

Table 7 Demographic and Other Baseline Characteristics – Safety Population

Demographic	ALXN1830 SC 750mg N = 6	ALXN1830 SC 1250mg N = 3	Placebo N = 3	Total N = 12
Sex, n (%)				
Male	3 (50.0)	0	2 (66.7)	5 (41.7)
Female	3 (50.0)	3 (100)	1 (33.3)	7 (58.3)
Race, n (%)				
White	3 (50.0)	3 (100)	2 (66.7)	8 (66.7)
Chinese	0	0	1 (33.3)	1 (8.3)
Other Asian	1 (16.7)	0	0	1 (8.3)
Other	2 (33.3)	0	0	2 (16.7)
Ethnicity, n (%)				
Not of Hispanic, Latino/a, or Spanish Origin	6 (100)	3 (100)	2 (66.7)	11 (91.7)
Another Hispanic, Latino/a, or Spanish Origin	0	0	1 (33.3)	1 (8.3)
Age (years)				
n	6	3	3	12
Mean (SD)	22.8 (2.93)	23.0 (3.46)	28.3 (5.86)	24.3 (4.29)
Min, Max	20, 27	21, 27	24, 35	20, 35
Median	21.5	21.0	26.0	23.0
Height (cm)				
n	6	3	3	12
Mean (SD)	174.7 (8.02)	165.7 (2.52)	171.3 (7.57)	171.6 (7.45)
Min, Max	163, 187	163, 168	166, 180	163, 187
Median	173.5	166.0	168.0	170.0
Weight (kg)				
n	6	3	3	12
Mean (SD)	73.00 (7.146)	60.10 (5.597)	62.53 (7.718)	67.16 (8.819)
Min, Max	63.3, 84.9	55.2, 66.2	56.4, 71.2	55.2, 84.9
Median	72.25	58.90	60.00	68.05
BMI (kg/m^2)				
n	6	3	3	12
Mean (SD)	23.88 (0.943)	21.93 (2.608)	21.27 (0.751)	22.74 (1.796)
Min, Max	22.2, 24.8	20.0, 24.9	20.5, 22.0	20.0, 24.9
Median	24.05	20.90	21.30	22.90
Any Positive Serum Pregnancy Test Result, n (%)				
Yes	0	0	0	0
No	6 (100)	3 (100)	3 (100)	12 (100)
Any Positive Alcohol Breath Test Result, n (%)				
Yes	0	0	0	0
No	6 (100)	3 (100)	3 (100)	12 (100)
Any Positive Urine Drug Screen Result, n (%)				
Yes	0	0	0	0
No	6 (100)	3 (100)	3 (100)	12 (100)

Abbreviation(s): SC - Subcutaneous.
Percentages are based on number of participants with non-missing values in each group
Source: Table 14.1.2.1.2

4.5. Prior Medication

All participants in the study reported use of prior medications. Medications reported by all participants included ranitidine, paracetamol, and chlorpheniramine; these were all recommended premedication per protocol. Vaccinations reported included influenza vaccine (100%), Pneumovax 23 (100%), haemophilus influenzae B (91.7%), measles, mumps, and rubella (MMR) (91.7%), and tetanus (91.7%) (Table 14.1.3.1.1.2 and Listing 16.2.4.5.6.).

4.5.1. Exposure

A by-participant listings of study drug administration is provided in Listing 16.2.5.1.6. Six participants were administered a single dose of ALXN1830 750 mg SC, 3 were administered a single dose of ALXN1830 1250 mg SC, and 3 were administered a single dose SC of placebo.

4.5.2. Dose Modification

There were no dose modifications for individual participants (Listing 16.2.5.1.6).

Refer to Section 3.1.2 for more information on the change in planned dose of ALXN1830 for Cohort 2 from 1500 mg to 1250 mg.

4.5.3. Measurement of Compliance

All participants received their planned dose (Listing 16.2.5.1.6).

5. EVALUATION OF RESPONSE TO STUDY INTERVENTION

5.1. Efficacy

Efficacy was not evaluated in this study.

5.2. Safety

5.2.1. Adverse Events

The following sections focus on treatment emergent adverse events (TEAEs), ie, an AE with a start date or time on or after the first dose of the study drug. A by-participant listing of TEAEs is provided in Listing 16.6.2.7.1.6. A by-participant listing of AEs that occurred before the first dose of study drug was administered is provided in Listing 16.2.7.2.6.

5.2.1.1. Brief Summary of Adverse Events

An overview of AEs is provided in Table 8 . Most participants (88.9%) who were administered ALXN1830 experienced at least 1 TEAE. All TEAEs were Grade 1 in severity. There were no serious adverse events (SAEs) reported in the study and no participant withdrew from the study because of a TEAE.

Table 8: Overview of Adverse Events

Parameter	ALXN1830 SC 750mg N = 6 n (%) E	ALXN1830 SC 1250mg 2 N = 3 n (%) E	Placebo N = 3 n (%) E	Total ALXN1830 SC N = 9 n (%) E
Any TEAE	5 (83.3) 8	3 (100) 18	3 (100) 6	8 (88.9) 26
Any AESI	0	0	0	0
Any Serious TEAE	0	0	0	0
TEAE Leading to Withdrawal	0	0	0	0
Serious TEAE Leading to Withdrawal	0	0	0	0
TEAE by Relationship				
Related	0	2 (66.7) 3	0	2 (22.2) 3
Not Related	5 (83.3) 8	3 (100) 15	3 (100) 6	8 (88.9) 23
Serious TEAE by Relationship				
Related	0	0	0	0
Not Related	0	0	0	0
TEAE by Toxicity Grade				
Grade 1	5 (83.3) 8	3 (100) 18	3 (100) 6	8 (88.9) 26
Grade 2	0	0	0	0
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0

Abbreviation(s): SC - Subcutaneous, TEAE - treatment-emergent adverse event, AESI - adverse event of special interest.
% = n/N*100. E=number of events.
Participants are counted once in each toxicity grade or relationship category in case of multiple events.
TEAEs are defined as those any adverse event that commences after the start of administration of study drug.
Source: Table 14.3.1.3.1.2

5.2.1.2. Analyses of All Adverse Events

5.2.1.2.1. Frequency of Adverse Events by System Organ Class and Preferred Term

Treatment-emergent adverse events are summarized by System Organ Class (SOC) and Preferred Term in Table 9.

TEAEs were reported for 5 participants (83.3%) in the ALXN1830 750 mg SC dose group and for all 3 participants administered ALXN1830 1250 mg SC. Three participants who were administered placebo experienced a total of 6 TEAEs.

The most frequently reported TEAE was viral upper respiratory infection, reported for 5 participants (83.3%) who were administered ALXN1830 SC 750 mg SC, 3 participants (100%) administered ALXN1830 SC 1250 mg, and 2 participants (66.7%) administered placebo. None of these events were deemed related to COVID.

Two participants experienced a total of 3 TEAEs (2 reports of injection site discomfort and 1 report of pruritus) that were considered by the investigator as related to treatment, all after a single dose of ALXN1830 SC 1250 mg.

There were numerically more related TEAEs reported in in participants who were administered ALXN1830 SC 1250 mg as compared with those who were administered ALXN1830 SC 750 mg and placebo, however due to the low number of participants it is not possible to determine whether there was a treatment or dose effect on the safety profile based on these results.

Table 9 Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Population)

System Organ Class (SOC) Preferred Term (PT)	ALXN1830 SC 750mg N = 6 n (%) E	ALXN1830 SC 1250mg N = 3 n (%) E	Placebo N = 3 n (%) E	Total ALXN1830 SC N = 9 n (%) E
Any TEAE	5 (83.3) 8	3 (100) 18	3 (100) 6	8 (88.9) 26
Infections and infestations	5 (83.3) 5	3 (100) 3	2 (66.7) 3	8 (88.9) 8
Viral upper respiratory tract infection	5 (83.3) 5	3 (100) 3	2 (66.7) 3	8 (88.9) 8
Gastrointestinal disorders	2 (33.3) 2	2 (66.7) 2	0	4 (44.4) 4
Diarrhoea	0	1 (33.3) 1	0	1 (11.1) 1
Dyspepsia	1 (16.7) 1	0	0	1 (11.1) 1
Food poisoning	0	1 (33.3) 1	0	1 (11.1) 1
Nausea	1 (16.7) 1	0	0	1 (11.1) 1
Nervous system disorders	0	2 (66.7) 4	1 (33.3) 2	2 (22.2) 4
Headache	0	2 (66.7) 3	1 (33.3) 2	2 (22.2) 3
Dizziness	0	1 (33.3) 1	0	1 (11.1) 1
Skin and subcutaneous tissue disorders	0	3 (100) 4	0	3 (33.3) 4
Pruritus	0	2 (66.7) 2	0	2 (22.2) 2
Dry skin	0	1 (33.3) 1	0	1 (11.1) 1
Rash pruritic	0	1 (33.3) 1	0	1 (11.1) 1
General disorders and administration site conditions	0	2 (66.7) 2	1 (33.3) 1	2 (22.2) 2
Injection site discomfort	0	2 (66.7) 2	0	2 (22.2) 2
Chest pain	0	0	1 (33.3) 1	0

Abbreviation(s): SC - Subcutaneous, TEAE - treatment-emergent adverse event, SOC - system organ class, PT - preferred term.
% = n/N*100. E=number of events.
In summarizing n(%), if a participant had multiple events for a particular SOC or PT, he/she is counted only once for that SOC or PT.
TEAEs are defined as those any adverse event that commences after the start of administration of study drug.
Note(s): System Organ Class and Preferred Term according to MedDRA dictionary version 23.0 or higher.
Source: Table 14.3.1.3.2.2

5.2.1.3. Deaths

No deaths were reported during the study.

5.2.1.4. Serious Adverse Events

No serious adverse events were reported during the study.

5.2.1.5. Discontinuations and/or Dose Modifications Due to Adverse Events

There were no discontinuations or dose modifications due to AEs.

5.2.1.6. Adverse Events of Special Interest

Adverse events of special interest (AESI) were pre-defined per protocol as IRRs and non-acute hypersensitivity reactions (study protocol Section 8.3.6; Appendix 16.1.1).

No AESIs occurred during this study (Table 14.3.1.3.1.2).

5.2.2. Clinical Laboratory Evaluation

In general, the mean values for urinalysis, serum chemistry and hematology were within the reference ranges and there were no apparent trends identified for the mean changes from baseline.

By-participant listings of hematology, coagulation, and urinalysis are provided in Listing 16.2.8.2.6, Listing 16.2.8.3.6, Listing 16.2.8.4.6, respectively.

By-participant listings of blood chemistry are provided in Listing 16.2.8.1.6.

A by-participant listing of serology is provided in Listing 16.2.8.9.6.

By-participant listings of laboratory results outside the normal range are provided in Listing 16.2.8.5.6.

5.2.3. Other Safety Evaluations

5.2.3.1. Vital Signs

There were neither any observable changes from baseline in vital sign measurements nor any clinically significant abnormalities in vital signs consistently observed for individual participants.

Descriptive statistics and change from baseline for vital signs measurements are summarized for each timepoint by treatment in Table 14.3.5.1.2**.** A by-participant listing of vital signs measurements is provided in Listing 16.2.9.2.1.6.

5.2.3.2. Electrocardiograms (ECGs)

Descriptive statistics and change from baseline in ECG results are summarized by treatment in Table 14.3.6.1.1.2. A by-participant listing of ECG results is provided in Listing 16.2.9.1.1.6 Telemetry monitoring results are provided by participant in Listing 16.2.9.1.3.6.

A by participant listing of abnormal QT and QT interval corrected using the Fridericia's formula (QTcF) values is provided in Listing 16.2.9.1.2.6.

No notable changes from baseline in the mean QT and QTcF interval were observed during the study. No mean QTcF intervals > 450 msec (Table 14.3.6.1.4.2.2) or interval increases from baseline of > 30 msec (Table 14.3.6.1.4.2.2) were observed. A summary of the changes from baseline in the mean QT interval outlier categories for each timepoint by treatment is provided in Table 14.3.6.1.4.1.2. A summary of the mean QT interval increases from baseline outlier categories is provided in Table 14.3.6.1.4.1.2.

5.2.3.3. Physical Examination Findings

A by-participant listing of physical exam findings is provided in Listing 16.2.4.4.6.

5.3. Pharmacokinetics

Serum samples for PK analysis were collected on Days 1 – 8, 10, 12, 15, 22, 29, 36, 43, 50, 57, and 64. On Day 1, samples were collected predose, at the end of the SC infusion, and postdose at 0.5, 2, 4, 8, 12 hours. Serum drug concentrations were measured using a validated liquid

chromatography/mass spectrometry (LC/MS) assay which detected a signature peptide sequence unique to ALXN1830. Serum samples were treated with a tryptic digest, analyzed via LC/MS, and concentration values are extrapolated from a calibration curve. The dynamic range of the assay was 325 – 10^6 ng/mL and the lower limit of quantitation was 375 ng/mL.

The PK data collected from this study were highly variable **(**Figure 2 and Figure 3**)** and serum concentrations of ALXN1830 were measurable only up to 48 hours postdose. The time to peak concentrations (Tmax) ranged from 6 – 48 hours and the terminal phase could not be characterized. In the ALXN1830 750 mg SC dose group, only 1 of 6 (16.7%) participants treated had serum drug concentrations above the lower limit of quantitation (LLQ), 3 of 6 (50%) participants had detectable serum concentrations below the limit of quantitation (BLQ), and 2 of 6 (33.3%) participants had no detectable serum concentrations. In the ALXN1830 SC 1250 mg dose group, all participants had detectable serum concentrations, however 1 of 3 (33.3%) participants had detectable serum drug concentrations at only a single timepoint. Two of the participants in the ALXN1830 SC 1250 mg dose group had serum concentrations with peaks detected approximately 12 hours after the end of infusion.

Figure 2 Overlaid Mean (+/-SD) Serum Concentration of ALXN1830 [µg/mL] versus Nominal Time by Treatment Group – Linear Scale – PK Population

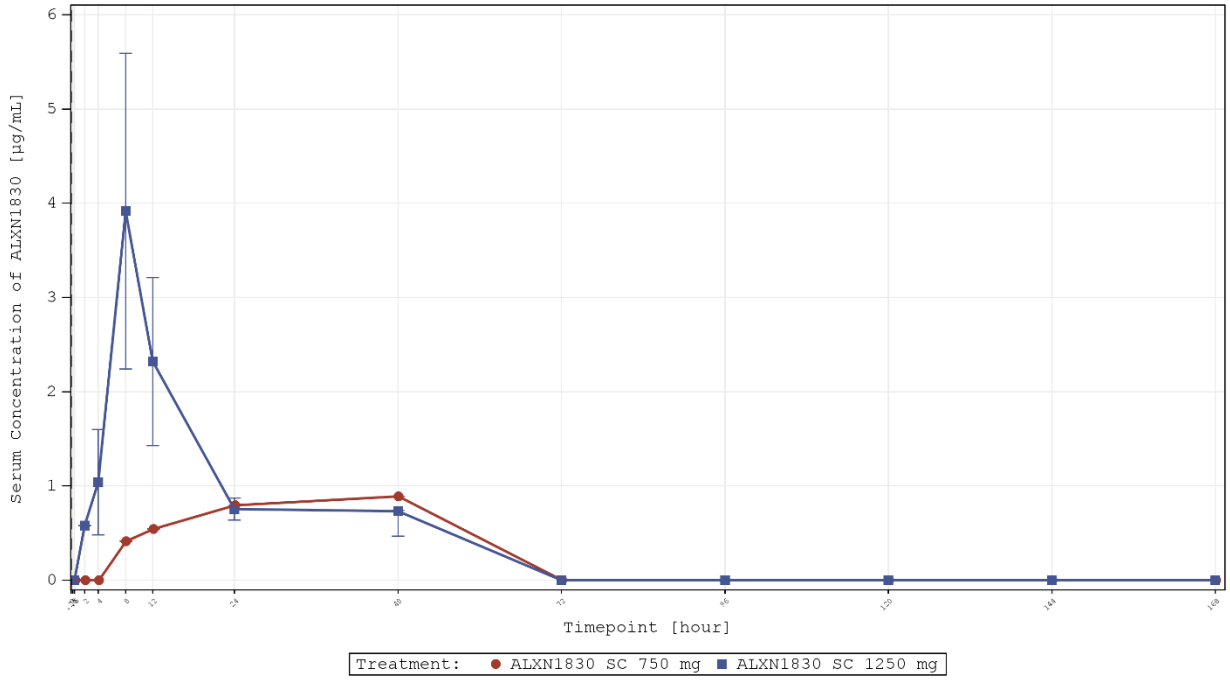
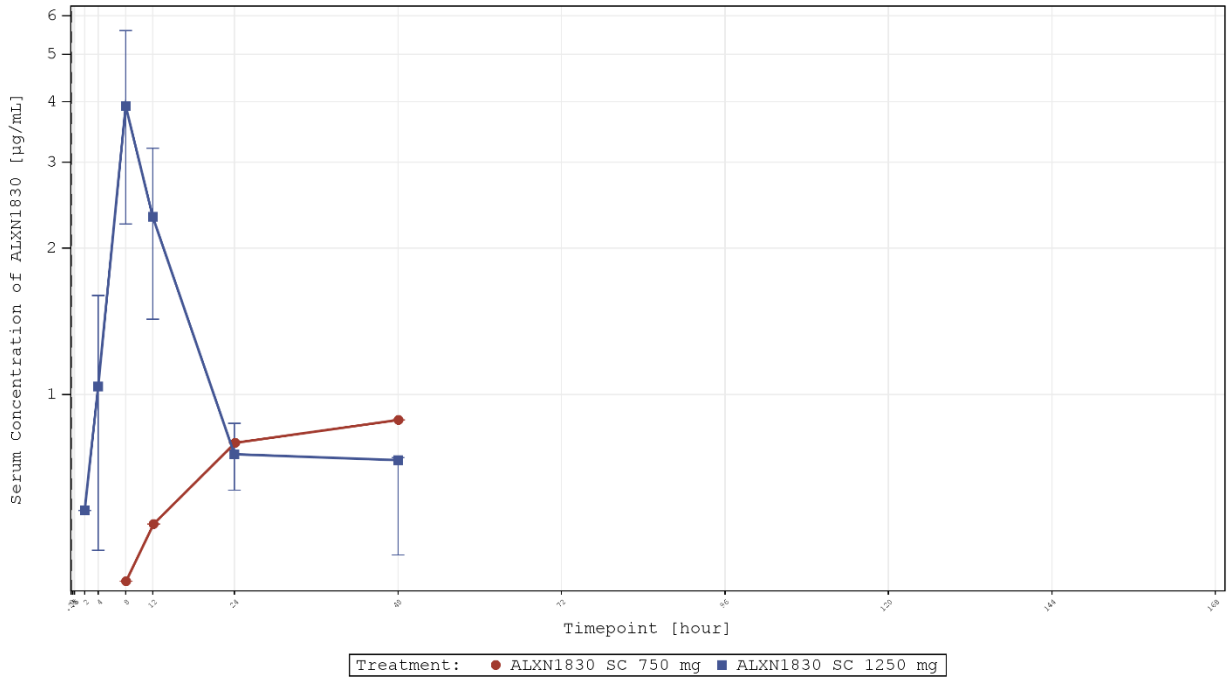


Figure 3 Mean (+/-SD) Serum Concentration of ALXN1830 [µg/mL] versus Nominal Time by Treatment Group – Semi-log Scale – PK Population



A non-compartmental analysis (NCA) was performed using the measurable serum drug concentrations in both cohorts, however, the only data eligible for inclusion were from one participant in the ALXN1830 SC 750 mg dose group and 2 participants in the ALXN1830 SC 1250 mg dose group and PK parameters are shown Table 10. In the ALXN1830 750 mg SC dose group, the maximal drug concentration value (C_{max}) was 0.888 µg/mL and the time to C_{max} (T_{max}) was 48 hours. The area under the concentration curve between the end of the SC infusion and the last measurable concentration (AUC_t) was 31.8 µg·hr/mL. In the ALXN1830 1250 mg SC dose group, the C_{max} was 2.77 µg/mL and the median T_{max} was 8 hours. The AUC_t was 44.2 µg·hr/mL. The half-life and other PK parameters should be interpreted with caution due to sparsity of the data in this study.

Table 10 Pharmacokinetic Parameters of Serum ALXN1830 – PK Population

Treatment Group	Statistic	C_{max} [µg/mL]	T_{max} [h]	AUC_t [h*µg/mL]	AUC_{inf} [h*µg/mL]	Lambda_z [1/h]	t_half [h]	CL or CL/F [L/h]	Vd or Vd/F [L]
ALXN1830 SC 750 mg	n	1	1	1	0	0	0	0	0
	Mean (SD)	0.888 (NC)	48 (NC)	31.8 (NC)	NA	NA	NA	NA	NA
	Median	0.888	48	31.8	NA	NA	NA	NA	NA
	Min, Max	0.888, 0.888	48, 48	31.8, 31.8	NA	NA	NA	NA	NA
	CV%	NA	NA	NA	NA	NA	NA	NA	NA
	Geom. Mean	0.888	48	31.8	NA	NA	NA	NA	NA
	Geom. CV%	NA	NA	NA	NA	NA	NA	NA	NA
ALXN1830 SC 1250 mg	n	3	3	3	2	2	2	2	2
	Mean (SD)	2.77 (2.6)	21.3 (23.1)	44.2 (33.7)	95.4 (5.65)	0.0254 (0.0147)	32.7 (18.9)	13.1 (0.777)	630 (395)
	Median	2.24	8	42.6	95.4	0.0254	32.7	13.1	630
	Min, Max	0.469, 5.59	8, 48	11.3, 78.6	91.4, 99.4	0.015, 0.0358	19.4, 46.1	12.6, 13.7	351, 910
	CV%	94	108	76.4	5.92	57.8	57.8	5.92	62.6
	Geom. Mean	1.8	14.5	33.5	95.3	0.0232	29.9	13.1	565
	Geom. CV%	194.2	137.4	129.8	5.9	67.7	67.7	5.9	75.7

Abbreviation(s): SC – Subcutaneous, CV% - Coefficient of Variation, Geom - Geometric, SD - Standard Deviation, AUCt - Area Under The Serum Concentration Versus Time Curve From Time Zero (Dosing) To The Last Quantifiable Concentration, AUCinf - Area Under The Serum Concentration Versus Time Curve From Time Zero (Dosing) Extrapolated To Infinity, Lambda_z - Apparent Terminal-Phase Elimination Rate Constant, t_half - Terminal Elimination Half-life, CL/F - Apparent Total Clearance, Vd/F - Apparent Volume Of Distribution During Terminal Phase.
Pharmacokinetic Parameters calculated using WinNonLin v8.0 using actual Sampling Time.
Source listing(s): Listing 16.2.6.2.1.4

5.4. Pharmacodynamics

5.4.1. Immunoglobulin G

The PD effects of ALXN1830 were determined by measuring serum concentrations of immunoglobulin (Ig) G, IgG subclasses 1 – 4, IgA, IgM, circulating immune complexes (CIC), and albumin. Serum samples for PD analysis were collected on Days 1-8, 10, 12, 15, 22, 29, 36, 43, 50, 57, and 64. On Day 1, samples were collected predose, at the end of the SC infusion, and at 0.5, 2, 4, 8, 12 hours. Serum concentration of all Ig classes and subclasses were measured using validated nephelometric assays.

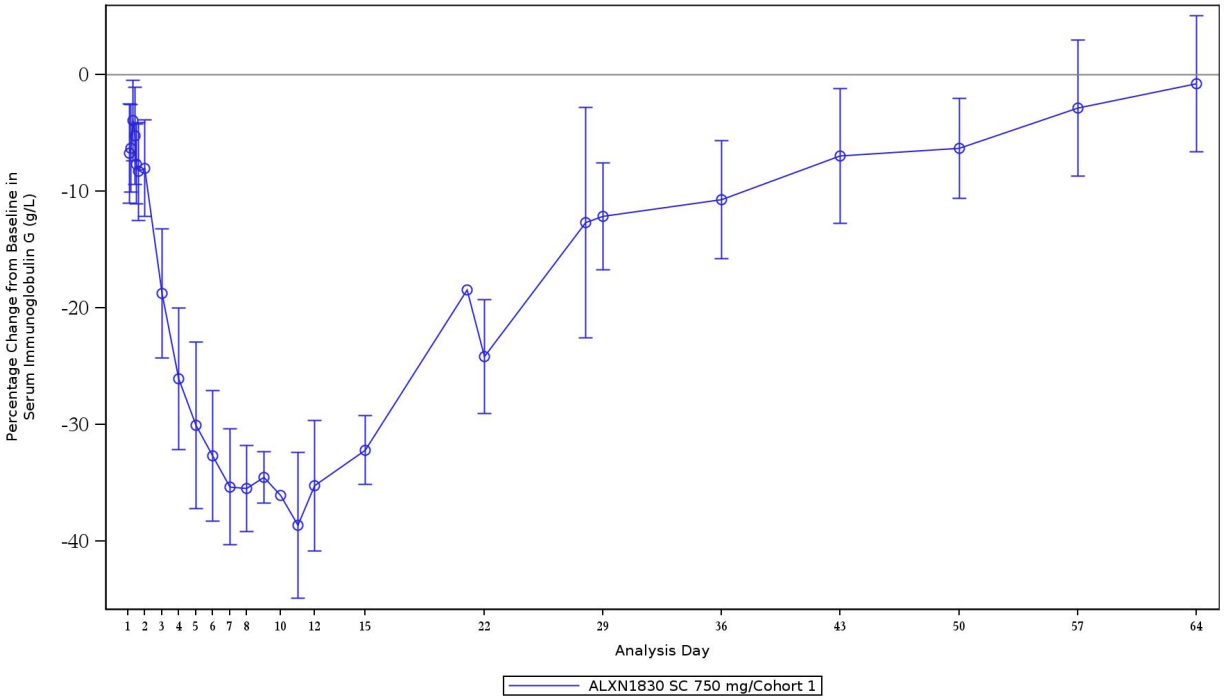
The primary PD biomarker in this study was IgG. In the ALXN1830 750 mg SC dose group, mean total IgG levels were reduced by a maximum of 36% from baseline by Day 10. By Day 29, IgG levels had recovered to 12.3% below baseline and continued to increase towards baseline throughout the follow-up period. In the ALXN1830 SC 1250 mg dose group, mean total IgG

levels were reduced by a maximum of 39% from baseline by Day 10. By Day 43, mean total IgG levels had recovered to 11.9% below baseline and continued to increase towards baseline throughout the follow-up period. IgG reductions relative to individual IgG baseline values are shown in Figure 4.

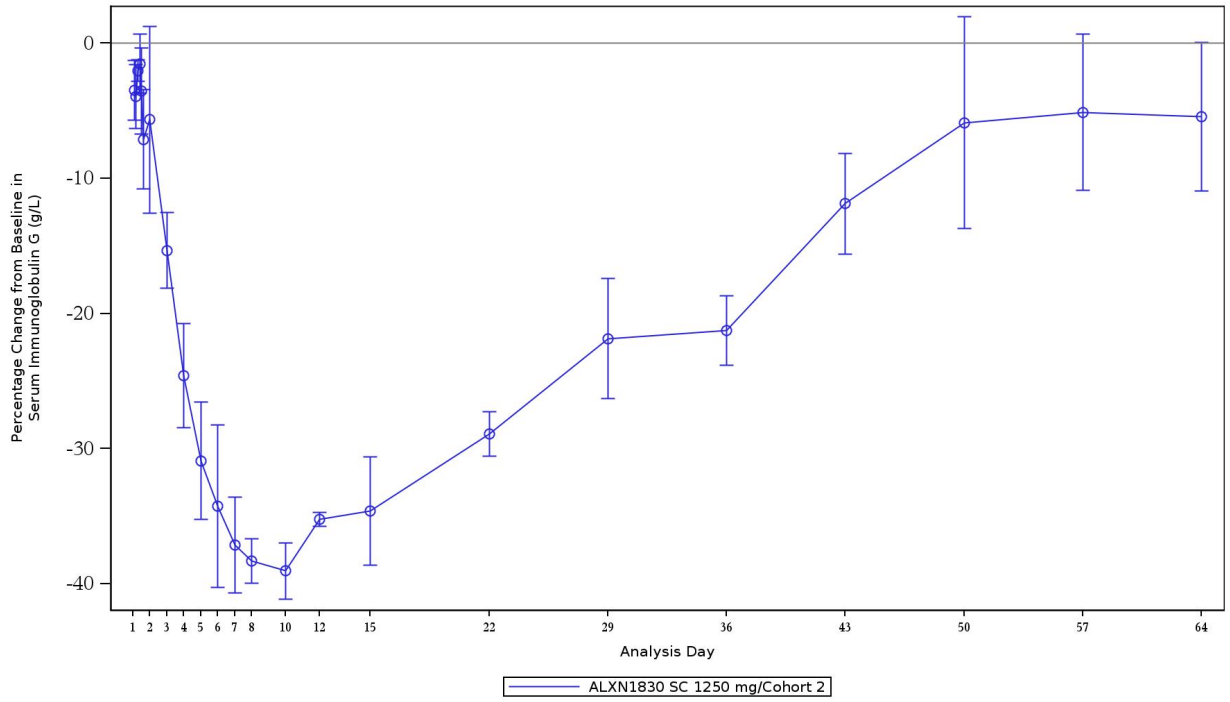
At both dose levels explored in the present study, ALXN1830 lowered IgG1, IgG2, and IgG3 levels significantly from baseline as compared to placebo IgG4 levels were also lowered from baseline, however the effect is less pronounced since ALXN1830 is an IgG4 molecule and may be detected by the IgG4 assay used.

Figure 4 Plot of Percent Change (+/- SD) from Baseline - IgG by Treatment Group - PD Population

ALXN1830 SC 750mg



ALXN1830 SC 1250 mg



5.4.2. Other PD Biomarkers

There were no meaningful changes in the levels of IgA, IgM, or albumin. The lack of impact on IgA, IgM, and albumin is consistent with findings from previous studies of ALXN1830 in healthy participants and patients.

5.4.3. Circulating Immune Complexes

Circulating immune complexes (CICs) were measured using a validated C1q binding activity assay. However, the assay used in this study was unable to detect CIC levels in any participant and no conclusions can be drawn regarding circulating immune complexes due to sparsity of the data.

5.4.4. Immunogenicity

Immunogenicity was assessed as ADA incidence and titer to ALXN1830.

There was no detectable pre-existing immunoreactivity in any of the participants. Overall, 6 participants were ADA positive after a single dose of ALXN1830 given SC: 4 in the ALXN1830 SC 750 mg dose group and 2 in the ALXN1830 SC 1250 mg dose group (Table 11). All 6 participants continued to have a low ADA positive titer until the end of the Study (Day 64). Of the 6 participants who developed ADA, 4 participants (44.4%, 2 each in ALXN1830 SC 750 mg and ALXN1830 SC 1250 mg dose groups) were also positive in the NAb assay. The presence of ADA was not associated with IRRs or non-acute hypersensitivity reactions. A listing of ADA status for each participant is provided in Listing 16.2.6.4.1.7.

Table 11: Immunogenicity Antidrug Antibodies Results – Frequency Table by Treatment (Immunogenicity Population)

		Participants Developing Anti-Drug Antibodies			
Scheduled Study Day	**Result**	**ALXN1830 SC 750 mg N = 6 n (%)**	**ALXN1830 SC 1250 mg N = 3 n (%)**	**Placebo N = 3 n (%)**	**Total ALXN1830 SC N = 9 n (%)**
Day 1	ADA - Negative	6 (100)	3 (100)	3 (100)	9 (100)
	ADA - Positive	0	0	0	0
	NAB - Negative	0	0	0	0
	NAB - Positive	0	0	0	0
Day 15	ADA - Negative	4 (66.7)	3 (100)	3 (100)	7 (77.8)
	ADA - Positive	1 (16.7)	0	0	1 (11.1)
	NAB - Negative	0	0	0	0
	NAB - Positive	1 (16.7)	0	0	1 (11.1)
Day 29	ADA - Negative	5 (83.3)	2 (66.7)	3 (100)	7 (77.8)
	ADA - Positive	1 (16.7)	1 (33.3)	0	2 (22.2)
	NAB - Negative	0	0	0	0
	NAB - Positive	1 (16.7)	1 (33.3)	0	2 (22.2)
Day 43	ADA - Negative	3 (50.0)	1 (33.3)	3 (100)	4 (44.4)
	ADA - Positive	3 (50.0)	2 (66.7)	0	5 (55.6)
	NAB - Negative	3 (50.0)	0	0	3 (33.3)
	NAB - Positive	0	2 (66.7)	0	2 (22.2)
Day 64/ET	ADA - Negative	2 (33.3)	1 (33.3)	2 (66.7)	3 (33.3)
	ADA - Positive	4 (66.7)	2 (66.7)	0	6 (66.7)
	NAB - Negative	2 (33.3)	0	0	2 (22.2)
	NAB - Positive	2 (33.3)	2 (66.7)	0	4 (44.4)
Overall	ADA - Always negative	2 (33.3)	1 (33.3)	3 (100)	3 (33.3)
	ADA - At least once positive	4 (66.7)	2 (66.7)	0	6 (66.7)
	NAB - Always negative	2 (33.3)	0	0	2 (22.2)
	NAB - At least once positive	2 (33.3)	2 (66.7)	0	4 (44.4)

Note: Percentages are calculated based on the number of participants randomized in each treatment group.
Abbreviations: ADA = antidrug antibody; ET = early termination; NAB = neutralizing antibody; SC = subcutaneous
Source: Table 14.2.4.1.7 and Listing 16.2.6.4.1.7

6. CONCLUSIONS

- ALXN1830 was safe and well tolerated after a single dose administered SC up to 1250 mg in healthy participants. No new safety signals were identified, and safety results are aligned with what is included in the current Investigator's brochure.
- The PK data collected from this study were highly variable and serum concentrations of ALXN1830 were measurable only up to 48 hours postdose. In the ALXN1830 750 mg SC dose group, the maximal drug concentration value (C_{max}) was 0.888 µg/mL and the time to Cmax (T_{max}) was 48 hours. In the 1250 mg SC dose group, the C_{max} was 2.77 µg/mL and the median T_{max} was 8 hours.
- The mean maximum IgG reductions of 36% and 39% were reached by Day 10 following a single SC dose of ALXN1830 750 mg and 1250 mg, respectively. The duration of IgG lowering was somewhat longer for the 1250 mg dose than at 750 mg and the IgG levels increased toward baseline throughout the follow-up period.
- Six participants were ADA positive after a single dose of ALXN1830 administered SC. Of these, 4 also had positive result in the Nab assay. The presence of ADAs was not associated with IRRs or non-acute hypersensitivity reactions.

7. REFERENCES

No references cited in the report.

14 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

Note: This section is intentionally numbered as Section 14 to align with ICH E3.

14.1 Demographic Data Summary Figures and Tables

Table 14.1.1.2.6 Patient Disposition (All Randomized Subjects)

Table 14.1.1.3.6 Inclusion And Exclusion Criteria (All Randomized Subjects)

Table 14.1.1.4.6 Protocol Deviations (All Randomized Subjects)

Table 14.1.2.1.2 Demographics/Baseline Characteristics (Safety Population)

Table 14.1.3.1.1.2 Prior Medication (Safety Population)

Table 14.1.3.2.1.2 Concomitant Medication (Safety Population)

Table 14.1.1.1.6 Analysis Sets (All Randomized Subjects)

14. 2 Efficacy Data Summary Figures and Tables

Not applicable.

14.3 Safety Data Summary Figures and Tables

Table 14.3.1.3.1.2 Overview Of Treatment-Emergent Adverse Events (Safety Population)

Table 14.3.1.3.2.2 Treatment-Emergent Adverse Events By MedDRA System Organ Class And Preferred Term (Safety Population)

Table 14.3.1.3.3.2 Serious Treatment-Emergent Adverse Events By MedDRA System Organ Class And Preferred Term (Safety Population)

Table 14.3.1.3.4.2 Adverse Events Of Special Interest By MedDRA System Organ Class And Preferred Term (Safety Population)

Table 14.3.1.3.5.2 Treatment-Emergent Adverse Events By MedDRA System Organ Class And Preferred Term By Toxicity Grade (Safety Population)

Table 14.3.1.3.1.2 Overview Of Treatment-Emergent Adverse Events (Safety Population)

Table 14.3.1.3.2.2 Treatment-Emergent Adverse Events By MedDRA System Organ Class And Preferred Term (Safety Population)

Table 14.3.1.3.3.2 Serious Treatment-Emergent Adverse Events By MedDRA System Organ Class And Preferred Term (Safety Population)

Table 14.3.1.3.4.2 Adverse Events Of Special Interest By MedDRA System Organ Class And Preferred Term (Safety Population)

Table 14.3.1.3.5.2 Treatment-Emergent Adverse Events By MedDRA System Organ Class And Preferred Term By Toxicity Grade (Safety Population)

14.3.1 Displays of Adverse Events

14.3.2 Clinical Pharmacology and Immunogenicity

14.3.3 Abnormal Laboratory Value Listing

16 APPENDICES

Note: This section is intentionally numbered as Section 16 to align with ICH E3.

16.1 Study Information

16.1.1 Protocol or Amendment

16.1.2 Sample Case Report Form

16.1.3 IEC-IRB Consent Form List

16.1.4 List Description Investigator Site

16.1.5 Signatures Investigators

16.1.6 List Patients with Batches

16.1.7 Randomization Scheme

16.1.8 Audit Certificates Report

16.1.9 Statistical Methods Interim Analysis Plan

16.1.10 Documentation of Inter-laboratory Standardization Methods and Quality Assurance Procedures

16.1.11 Publications Based on Study

16.1.12 Publications Referenced in Report

16.1.13 DMC and Bioanalytical Reports

16.2 Participant Data Listings

16.2.1 Discontinued Participants

16.2.2 Protocol Deviations

16.2.3 Participants Excluded From Efficacy Analysis

16.2.4 Demographic Data

16.2.5 Compliance and Drug Concentration Data

16.2.6 Individual Pharmacokinetics and Pharmacodynamics Response Data

16.2.7 Adverse Event Listings

16.2.8 Listing of Individual Laboratory Measurements by Participant

16.3 Case Report Forms

16.3.1 CRFs for Deaths, Other Serious Adverse Events, and Withdrawals for Adverse Events

16.3.2 Other CRFs Submitted