# 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<br>ALXN1830 750 mg (n = 6) |
| 2 | Single dose SC | Placebo (n=2) or<br>ALXN1830 1500[b] mg (n = 6) |
| 3 | Single dose SC | Placebo (n=2) or<br>ALXN1830 2250 mg (n = 6) |
| 4 | Multiple dose (8 doses biw) SC | Placebo (n=2) or<br>ALXN1830 300 mg (n = 6) |
| 5 | Multiple dose (12 doses qw) SC | Placebo (n=2) or<br>ALXN1830 750 mg (n = 6) |
| 6 | Multiple dose (4 doses qw) SC | Placebo (n=2) or<br>ALXN1830 1500 mg (n = 6) |
| 7[a] | Multiple dose (4 doses or 12 doses qw) SC | Placebo (n=2) or<br>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<br><br>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.<br><br>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:<br>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.<br>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:<br>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