TITLE PAGE

Protocol Title:

A Phase 1, Randomized, Double-blind, Placebo-controlled, Single Ascending Dose Study of Subcutaneously and Intravenously Administered ALXN1910 in Healthy Adult Participants

Protocol Number: ALXN1910-HV-101

Amendment Number: 3**Compound:** ALXN1910

Study Phase: Phase 1

Short Title: Safety and Tolerability, Pharmacokinetic, and Pharmacodynamic Study of ALXN1910 in Healthy Participants

Sponsor Name: Alexion Pharmaceuticals, Inc.

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Regulatory Agency Identifier Number(s):

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Approval Date:

Protocol Amendment 3	27 Jul 2022
Protocol Amendment 2	20 Apr 2022
Protocol Amendment 1	27 Jan 2022
Original protocol	06 Dec 2021

Sponsor Signatory:

PPD

Medical Monitor Name and Contact Information can be found in the Study Contact List.

INVESTIGATOR'S AGREEMENT

I have read the Study ALXN1910-HV-101 protocol amendment 3 and agree to conduct the study in accordance with this protocol, all applicable government regulations, the principles of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Guideline for Good Clinical Practice, and the principles of the World Medical Association Declaration of Helsinki. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol.

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 3 (27 Jul 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and any applicable local regulations.

Overall Rationale for the Amendment

The main reason for this amendment is to have all participants return on Day 75 for the EOS visit (instead of Day 43), regardless of ADA results, to maintain blinding of Alexion staff, the Investigator, and site staff. Changes implemented in Administrative Change Letter No.2 (14 Jun 2022), as well as some clarifications to wording and minor administrative changes, have also been made.

Changes to the protocol are detailed below:

Section Number and Name	Description of Change	Brief Rationale and/or Clarification
1.1 Synopsis	Text in the "Study Cohort and Duration" subsection was updated to reflect the Dosing and Follow-up Period as a total of 74 days for all participants.	To ensure consistency with the changes made to Schedule of Activities for EOS visit.
1.2 Schema, Figure 1	Number of days for Follow-up period was updated from 42 days to 74 days.	Number of days for the Follow-up period was updated to align with the EOS visit.
1.3 Schedule of Activities	Text was updated to reflect the change in Schedule of Activities from "Day 6 through Day 43" to "Day 6 through Day 75".	To ensure consistency with Table 3 in Schedule of Activities.
1.3 Schedule of Activities, Table 3 Footnote b	Title of Table 3 was changed from "Schedule of Activities – Single Ascending Dose Cohorts (Day 6 through Day 43 [or Day 75 if Positive for ADAs])" to "Schedule of Activities – Single Ascending Dose Cohorts (Day 6 through Day 75)" Footnote b text changed to reflect End of Study procedures will be performed on Day 75.	To maintain blinding of Alexion staff, the Investigator, and site staff, all participants are required to return on Day 75 for the EOS visit (instead of Day 43), regardless of ADA results.
2.4.1.1 Coronavirus Disease 2019	Removed text saying that Day 75 is only necessary for positive ADAs.	To ensure consistency with study timeline specified in Schedule of Activities.
4.5 Duration of Treatment and End of Study Duration	Text updated to specify that End of Study activities will occur on Day 75.	To clarify End of Study timeline for all participants.
4.5 Duration of Treatment and End of Study Duration, Figure 2	Figure 2 was updated to reflect Day 75 as the EOS, and text regarding EOS for ADA positive participants was removed.	To indicate Day 75 as EOS visit for all participants, regardless of ADA results.

Section Number and Name	Description of Change	Brief Rationale and/or Clarification
6.3 Measures to Minimize Bias: Randomization and Blinding	Text related to ALP data blinding was added.	To maintain blinding of Alexion staff, the Investigator, and site staff.
8.3.1 Time Period and Frequency for Collecting AE and SAE Information	Edited text to specify AEs and SAEs will be collected until Day 75.	To ensure AE and SAE collection procedures reflect the Schedule of Activities including Day 75 for all participants
8.9.1 ADA Variables	Added text that includes "Treatment-boosted ADA Responses" as part of ADA positive categorizations.	This ADA response category was missing in the previous version of the protocol.
10.1.1 Regulatory and Ethical Considerations	Removed repeated mention of European regulation 536/2014.	This regulation was erroneously mentioned twice in a sentence.
10.2 Clinical Laboratory Tests, Table 10	Removed repeated mention of "urea" as a parameter of "clinical chemistry" assessments. Added "Serum or urine pregnancy test" as a parameter of "other screening tests" laboratory assessments.	This parameter was erroneously mentioned twice. To ensure consistency with the Schedule of Activities.
Overall	Minor administrative changes.	For clarity.

Abbreviations: ADA = antidrug antibodies; AE = adverse event; ALP = alkaline phosphatase; SAE = serious adverse event

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 1, Randomized, Double-blind, Placebo-controlled, Single Ascending Dose Study of Subcutaneously and Intravenously Administered ALXN1910 in Healthy Adult Participants

Short Title: Safety and Tolerability, Pharmacokinetic, and Pharmacodynamic Study of ALXN1910 in Healthy Participants

Rationale:

To gain an understanding of the safety, tolerability, PK, PD, and immunogenicity of ALXN1910, an FIH SAD study in healthy adult participants is proposed. Cohorts of Japanese and non-Japanese participants will also be evaluated to enable comparison between these 2 populations.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of ALXN1910	• Incidence of TEAEs and TESAEs
Secondary	
• To assess the PK of single ascending doses of ALXN1910	• Serum ALXN1910 PK (activity) and PK parameters
• To explore the PD effects of single ascending doses of ALXN1910	• Plasma concentrations of PPi, PLP, PL, and PA versus time profiles
• To assess the immunogenicity of ALXN1910	• Incidence and titers of treatment-emergent ADAs
• To assess the absolute bioavailability of ALXN1910 SC	• GMR of AUC values of SC versus IV from serum concentrations of ALXN1910
• To compare the safety, tolerability, PK, and PD of ALXN1910 SC between Japanese and non-Japanese healthy participants	• Quantitative assessment of safety/tolerability and PK/PD parameters between Japanese and non-Japanese participants

Abbreviations: ADA = antidrug antibody; AUC = area under the serum concentration-time curve; GMR = geometric mean ratio; IV = intravenous; PA = pyridoxic acid; PD = pharmacodynamics(s); PK = pharmacokinetic(s); PL = pyridoxal; PLP = pyridoxal-5′-phosphate; PPi = inorganic pyrophosphate; SC = subcutaneous; TEAE = treatment emergent adverse event; TESAE = treatment emergent serious adverse event

Overall Design

This is a Phase 1, randomized, double-blind, placebo-controlled study designed to evaluate the safety, tolerability, PK, PD, and immunogenicity of SADs of ALXN1910 SC and a SAD of ALXN1910 IV in up to approximately 48 healthy adult participants across treatment cohorts (up to approximately 36 participants to receive ALXN1910 and up to approximately 12 participants to receive placebo). Of the 48 participants, 8 will be of Japanese descent, defined as those participants whose parents and grandparents are both Japanese and who have spent less than 10 years outside of Japan.

For this FIH study, 8 participants will be randomly assigned in a 3:1 ratio to treatment and placebo in each of the 6 cohorts with escalating doses of 5 mg IV (Cohort 1), 15 mg SC

(Cohort 2), 15 mg IV (Cohort 3) in parallel with 15 mg SC in Japanese participants (Cohort 4) and 45 mg SC (Cohort 5), followed by 135 mg SC (Cohort 6). The first 2 participants randomized to each cohort will be dosed as a sentinel pair, with 1 participant on active treatment and 1 participant on placebo. This dosing strategy is justified given the large exposure margins (approximately 15-fold at the highest planned single dose of 135 mg SC). At the discretion of the Investigator, up to 3 more participants will be dosed at least 48 hours (as anticipated t_{max} occurs prior to 48 hours postdose) after the dosing of the sentinel pair, followed by dosing of the remaining participants in the cohort no earlier than 72 hours after sentinel pair dosing, as long as no suspension/stopping criteria have been met. At no time will more than 4 participants per cohort be dosed in a given day.

Participants who meet the qualifications for the study based on screening will be admitted to the CRU the day prior to dosing (Day -1) to undergo Check-in assessments per the applicable SoA. Final determination of eligibility will be determined based on Check-in and predose procedures, and eligible participants will be randomized to ALXN1910 or placebo on Day 1 prior to dosing. There will be extensive PK/PD sampling during the first 24 hours after dosing. Safety assessments will be performed per the SoA.

Safety Review Committee: The blinded SRC, consisting of the Investigator, Medical Monitor, Drug Safety Physician, Study Statistician, and Clinical Pharmacologist will evaluate the available study data at prespecified time points for participant safety and make recommendations on dose escalation, dose modification, or termination of the study. Decisions to continue, modify (explore the dose cohort further), or escalate dosing will be made by the Investigator and/or SRC.

Number of Participants:

Up to approximately 48 participants will be randomized according to a randomization schedule generated prior to the start of the study.

Study Cohort and Duration:

The participants in each dose cohort will be randomized in a 3:1 ratio to receive ALXN1910 or placebo. Following a Screening Period of up to 28 days, there will be a Dosing and Follow up Period (single dose on Day 1 through the EOS Visit) of approximately 74 days.

Table 1: Planned ALXN1910-HV-101 Dosing Cohorts

Cohort[a]	Number of Participants (ALXN1910:Placebo)	Route of Administration	Dose	Number of Doses/Dose Interval
1	8 (3:1)	IV[b]	5 mg	Single dose
2	8 (3:1)	SC	15 mg	Single dose
3	8 (3:1)	IV[b]	15 mg	Single dose
4	8 (3:1) (Japanese participants)	SC	15 mg	Single dose
5	8 (3:1)	SC	45 mg	Single dose
6	8 (3:1)	SC	135 mg	Single dose

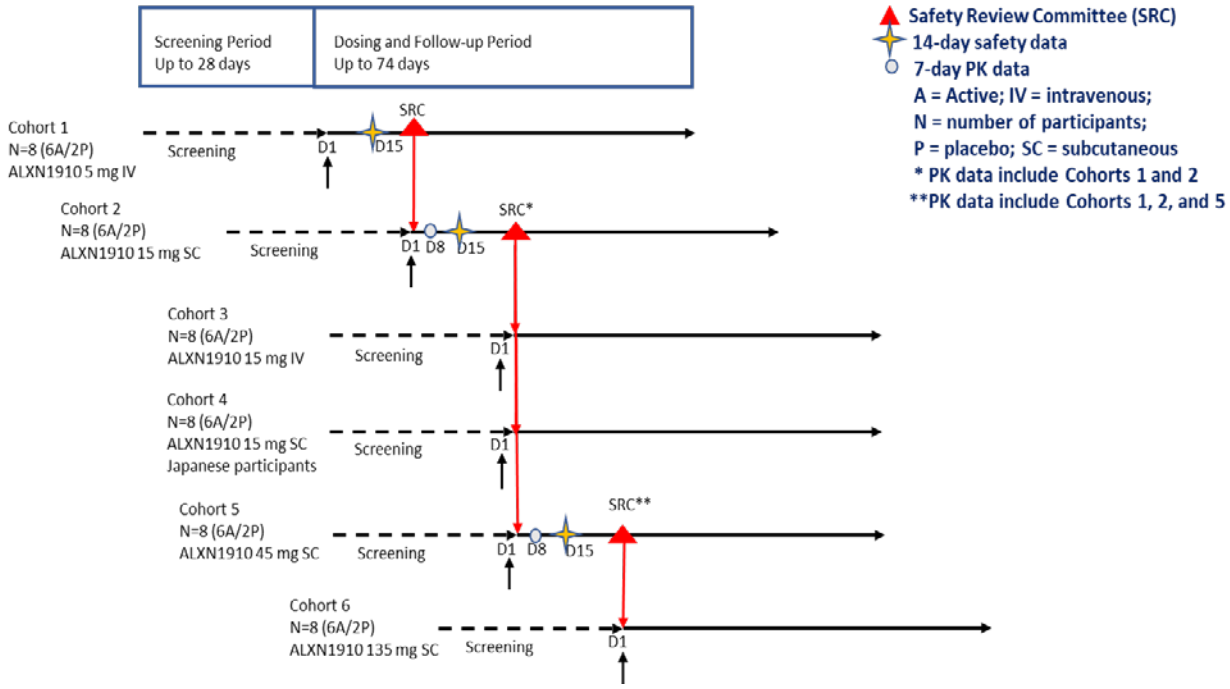
[a] Cohort 3, Cohort 4, and Cohort 5 can be initiated in parallel after dose escalation decision following SRC review of Cohort 2 safety and PK data.

[b] Slow IV infusions (rate of infusion = 6 mL/h) using a controllable infusion pump. The pharmacy manual will include details regarding infusion rate and duration.

Abbreviations: IV = intravenous; PK =pharmacokinetic; SC = subcutaneous; SRC = Safety Review Committee

1.2. Schema

Figure 1: Study Design Schematic



1.3. Schedule of Activities

The SoAs for all cohorts from Screening through Day 5 and from Day 6 through Day 75 are presented in Table 2 and Table 3, respectively.

Table 2: Schedule of Activities – Single Ascending Dose Cohorts (Screening through Day 5)

Study Day[a]	**Screen-ing**	**Day -1**	**Day 1**							**Day 2**		**Day 3**		**Day 4**		**Day 5**
Assessments	**D -29 to D-2**	**Admit**	**Pre-dose**	**0 h I/ SOI**	**30 min post I/SOI**	**2 h post I/SOI**	**4 h post I/SOI**	**8 h post I/SOI**	**12 h post I/SOI**	**24 h post I/ SOI**	**36 h post I/ SOI**	**48 h post I/ SOI**	**60 h post I/ SOI**	**72 h post I/ SOI**	**84 h post I/ SOI**	**96 h post I/SOI**
Status (OP or CRU)	**OP**	**CRU**														
Admission		X														
Discharge																X[b]
Informed consent[c]	X															
Inclusion/exclusion[d]	X	X														
Medical history[e]	X															
Demographics	X															
Height, weight, and BMI[f]	X	X														
Hepatitis B and C screen	X															
HIV (Types 1 and 2) screen	X															
Follicle-stimulating hormone[g]	X															
Urine alcohol test	X	X														
Urine drug screen	X	X														
Serum pregnancy test[h]	X															
Urine pregnancy test[h]		X														
Randomization[i]			X													
Study intervention administration (ALXN1910 or placebo)				X												
Injection/infusion site evaluation[j]				X			X			X		X		X		X
Physical examination	X	X														

Table 2: Schedule of Activities – Single Ascending Dose Cohorts (Screening through Day 5)

Study Day[a]	**Screen -ing**	**Day -1**	**Day 1**							**Day 2**		**Day 3**		**Day 4**		**Day 5**
Assessments	**D -29 to D-2**	**Admit**	**Pre-dose**	**0 h I/ SOI**	**30 min post I/SOI**	**2 h post I/SOI**	**4 h post I/SOI**	**8 h post I/SOI**	**12 h post I/SOI**	**24 h post I/ SOI**	**36 h post I/ SOI**	**48 h post I/ SOI**	**60 h post I/ SOI**	**72 h post I/ SOI**	**84 h post I/ SOI**	**96 h post I/SOI**
Status (OP or CRU)	**OP**	**CRU**														
Brief physical examination[k]										X		X				X
Vital sign measurements[l]	X		X		X	X	X	X	X	X		X		X		X
ECG[m]	X		X		X	X	X	X	X	X	X	X		X		X
Chemistry[n]	X	X								X						X
Hematology[n]	X	X								X						X
Coagulation[n]	X	X								X						X
Urinalysis[n]	X	X								X						X
PK[o]			X		X	X	X	X	X	X		X		X		X
PD (PPi, PLP, PL, and PA)			X							X		X				X
Urine for calcium, phosphorus, and creatinine[p]			X							X		X				X
Immunogenicity samples[q]			X													
Hypersensitivity reactions[r]				←Monitor continuously after dose→												
Hypersensitivity reaction laboratory tests (tryptase & complement C5b-9)[s]			X	←See footnote[r]→												
Concomitant medications	←Monitor continuously (after ICF is signed at Screening)→															
Adverse events review and evaluation	←Monitor continuously (after ICF is signed at Screening)→															

Note: When scheduled at the same timepoint, the triplicate ECG should be performed first, followed by vital sign measurements, and then PK/PD sampling.

[a] Permissible windows for study assessments are described in the Windows Allowance Document.
[b] Participants will be discharged from the CRU after completing all Day 5 assessments. Due to the time needed for turnaround of laboratory test results, discharge will actually occur on Day 6.
[c] A signed and dated IEC-approved ICF must be obtained before any study-specific screening procedures are performed.
[d] Recheck clinical status before randomization and/or dose of study intervention.
[e] Including substance usage (drugs, alcohol, tobacco, and caffeine) and past/current medical conditions.
[f] Height and BMI only at Screening.
[g] Only female participants claiming postmenopausal status will have a follicle-stimulating hormone test to confirm postmenopausal status.
[h] All female participants will have a pregnancy test (serum at Screening and urine on Day -1) to confirm the participant is not pregnant. Any female participant who becomes pregnant while participating in the study will be withdrawn.
[i] Randomization will occur predose on Day 1.
[j] Injection/infusion site evaluations will be performed within 15 minutes after I/SOI and ± 15 minutes at 4 and 24 hours post I/SOI. See Section 10.5 for additional details.
[k] Brief physical examination to be conducted on Day 5 prior to discharge from the CRU.
[l] At Screening, supine and standing (orthostatic) blood pressures will be performed according to the CRU's typical procedure to exclude participants who are prone to orthostatic hypotension.
[m] Each ECG timepoint during the study will be 12-lead and performed in triplicate sequentially within 5 minutes, at least 1 minute apart after 10 minutes of bedrest in supine position (note, no bedrest is required post ECG), at Screening and 90, 75, and 60 minutes before dosing. ECGs should not be performed within 1 hour after any major meal or major meals should be withheld until after ECG assessments.
[n] Investigators should review Day 5 laboratory results to ensure each participant is suitable for discharge.
[o] The IV dose cohorts will also have an end-of-infusion PK time point.
[p] Spot urine collection.
[q] Sample for ADA assessments will be collected prior to administration of the drug. In the event of suspected SAE like hypersensitivity or anaphylaxis, additional samples may be collected for ADA assessments at or near the event.
[r] See Section 10.4 for details.
[s] Collect 3 lab samples after a suspected hypersensitivity reaction: as soon as possible and at 2 and 8 hours after the suspected reaction (+ 1 hour window for each sample). If the suspected hypersensitivity reaction persists beyond 8 hours, the CRU should contact the Medical Monitor for guidance. Predose samples will only be analyzed for participants with a reported suspected hypersensitivity reaction.

Abbreviations: ADA = antidrug antibody; BMI = body mass index; C5b-9 = terminal complement complex; CRU = clinical research unit; ECG = electrocardiogram; h = hours; HIV = human immune deficiency virus; I = injection; ICF = informed consent form; IEC = Independent Ethics Committee; OP = outpatient; min = minutes; PA = pyridoxic acid; PD = pharmacodynamic; PK = pharmacokinetic; PL = pyridoxal; PLP = pyridoxal 5′-phosphate; PPi = inorganic pyrophosphate; SOI = start of infusion; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event

Table 3: Schedule of Activities – Single Ascending Dose Cohorts (Day 6 through Day 75)

Study Day[a]	**Day 6 post I/SOI**	**Day 7 post I/SOI**	**Day 8 post I/SOI**	**Day 15 post I/SOI**	**Day 22 post I/SOI**	**Day 29 post I/SOI**	**Day 36 post I/SOI**	**Day 43 post I/SOI**	**Day 75 post I/SOI (EOS/ED**[b]**)**
Status (OP or CRU)	**OP**								
Full physical examination								X	
Brief physical examination			X	X		X			
Vital sign measurements[c]			X	X		X		X	
12-lead ECG (triplicate)[d]	X	X	X	X				X	
Chemistry			X	X	X	X	X	X	X
Hematology			X	X	X	X	X	X	X
Coagulation			X	X	X	X	X	X	X
Urinalysis (via dipstick)			X	X	X	X	X	X	X
Urine pregnancy test[e]						X			
Serum pregnancy test[e]								X	X
PK	X	X	X	X	X	X	X	X	X
PD (PPi, PLP, PL, and PA)			X	X	X	X	X	X	X
Immunogenicity samples[f]						X		X	X
Urine for calcium, phosphorus, and creatinine[g]			X	X		X		X	X
Hypersensitivity reactions[h]	←Monitor continuously after dose→								
Hypersensitivity reaction laboratory tests (tryptase and complement C5b-9)[i]	←See footnote[h]→								
Concomitant medications	←Monitor continuously (after ICF is signed at Screening)→								
Adverse event review and evaluation	←Monitor continuously (after ICF is signed at Screening)→								

Note: When scheduled at the same timepoint, the triplicate ECG should be performed first, followed by vital sign measurements, and then PK/PD sampling.

[a] Permitted windows for study assessments are described in the Windows Allowance Document.

[b] EoS procedures will be performed on Day 75. If possible, participants who withdraw/are withdrawn from the study should have an ED visit conducted at the time of discontinuation that includes the EoS assessments. All efforts will be made to contact participants who discontinued early from the study via phone for a safety follow-up call approximately 30 days (4.5 half-lives) after their last dose to assess AEs.

[c] Vital signs taken postdose will be performed before the coinciding blood collection, whenever possible.

[d] Each ECG will be 12-lead and performed in triplicate sequentially within 5 minutes, at least 1 minute apart after 10 minutes of bedrest in supine position (note, no bedrest is required post ECG). ECGs should not be assessed within 1 hour after any major meal or major meals should be withheld until after ECG assessments.

[e] Only female participants of childbearing potential will have a pregnancy testing to confirm the participant is not pregnant.

[f] Sample for ADA assessments will be collected prior to administration of the drug. In the event of suspected SAE like hypersensitivity or anaphylaxis, additional samples may be collected for ADA assessments at or near the event.

[g] Spot urine collection.

[h] See Section 10.4 for details.

[i] If the participant is in the clinic, collect the first sample as soon as possible (preferred) or within 1 hour of the suspected hypersensitivity reaction, and 2 additional samples at 2 and 8 hours after the suspected hypersensitivity reaction (+ 1 hour window for each sample). If the participant is not in the clinic, these samples do not need to be collected and suspected hypersensitivity reactions will be reported as TEAEs/TESAEs only. If the suspected hypersensitivity reaction persists beyond 8 hours, the CRU should contact the Medical Monitor for guidance.

Abbreviations: ADA = anti-drug antibody; C5b-9 = terminal complement complex; CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; EOS = end of study; h = hours; I = injection; ICF = informed consent form; OP = outpatient; PA = pyridoxic acid; PD = pharmacodynamic; PK = pharmacokinetic; PL = pyridoxal; PLP = pyridoxal 5′-phosphate; PPi = inorganic pyrophosphate; SOI = start of infusion; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event

2. INTRODUCTION

Similar to asfotase alfa (STRENSIQ®, Alexion Pharmaceuticals, Inc.), ALXN1910 is intended to replace or enhance TNSALP activity in deficient tissues, resulting in improved mineralization of the skeleton that is important for normal bone development, homeostasis, and repair. This mechanism of action is anticipated to be useful in conditions associated with poor bone mineralization due to elevated PPi and/or impaired TNSALP activity, such as HPP where supplementation with a bone-directed TNSALP ERT may result in conditions more favorable for proper bone mineralization. ERT may also be beneficial in conditions of poor bone healing (eg, after fractures or surgical interventions), including AFFs and NF1.

2.1. Study Rationale

To gain an understanding of the safety, tolerability, PK, PD, and immunogenicity of ALXN1910, an FIH SAD study in healthy adult participants is proposed.

This study is also being conducted to meet regulatory requirements of the ICH Guidance E5(R1), which provides a general framework for evaluating the potential impact of ethnic factors on the acceptability of foreign clinical data. Therefore, cohorts of Japanese and non-Japanese participants will also be evaluated to enable comparison between these 2 populations.

2.2. Background

ALXN1910 is a fusion protein comprised of a human TNSALP catalytic domain, a human Ig Fc domain, and a C-terminal poly-aspartate (n = 7) peptide.

In humans, there are 4 ALP isoenzymes, each encoded by a separate gene. Three of these isoenzymes are primarily expressed in specific tissues: intestine, placenta, and germ cells. The fourth isoenzyme is expressed throughout the body, but primarily in the liver, kidney, and bone; and hence, it is referred to as TNSALP and is encoded by the *ALPL* gene.

The physiological role of TNSALP has not been fully elucidated, but its function in bone is best understood. In bone, TNSALP enables mineralization by locally cleaving PPi, thereby removing this inhibitor of mineralization, while increasing the local concentration of Pi. Pi then precipitates with calcium to form calcium phosphate, which is transformed into the hydroxyapatite crystal that gives bone its strength and rigidity. ALXN1910 has been rationally engineered to confer greater enzymatic activity than asfotase alfa, with the intention to improve mineralization of the skeleton in conditions associated with poor bone mineralization due to elevated PPi and/or impaired TNSALP activity.

Compared with asfotase alfa, the human TNSALP catalytic domain in ALXN1910 has been rationally altered in a single position to confer greater enzymatic activity, remaining 99.8% identical to the catalytic domain in asfotase alfa. Additionally, the IgG Fc domain isotype in ALXN1910 is IgG2/4 instead of the IgG1 Fc domain present in asfotase alfa. This alteration was designed to improve ALXN1910's PK profile relative to asfotase alfa, including improved systemic exposure/bioavailability and terminal half-life (approximately 7 days for ALXN1910 versus approximately 5 days for asfotase alfa). These improvements are anticipated to support lower doses and longer dosing intervals.

Moreover, unlike the C-terminal deca-aspartate of asfotase alfa, ALXN1910 utilizes an affinity optimized hepta-aspartate C-terminal peptide to direct the molecule to sites of bone mineralization.

ALXN1910 is a next-generation ERT developed with the intent to deliver a molecule with equivalent potency and improved activity compared with asfotase alfa, providing higher exposure, longer half-life, and better bioavailability. These improvements may support lower doses and longer dosing intervals, which may mitigate the risk of injection site reactions.

A detailed description of the chemistry, pharmacology, and toxicology data available for ALXN1910 is provided in the IB.

Alexion is planning to initiate a Phase 1, randomized, double-blind, placebo-controlled, SAD study of SC and IV administered ALXN1910 in healthy adult participants (Study ALXN1910-HV-101). The proposed study is designed to evaluate the safety and tolerability, PK, immunogenicity, and absolute and relative bioavailability of SADs of ALXN1910 administered SC and compared with a single dose of IV ALXN1910.

2.3. Target Indications

Similar to asfotase alfa (STRENSIQ®), ALXN1910 is intended to replace TNSALP activity in deficient tissues, resulting in improved mineralization of the skeleton that is important for normal bone development, homeostasis, and repair. This mechanism of action is anticipated to be useful in conditions associated with poor bone mineralization due to elevated PPi and/or impaired TNSALP activity, such as HPP where supplementation with a bone-directed TNSALP ERT may result in conditions more favorable for proper bone mineralization. ERT may also be beneficial in conditions of poor bone healing (eg, after fractures or surgical interventions), including AFFs and NF1.

2.3.1. Hypophosphatasia

HPP is a rare, serious, genetic disorder caused by loss of function mutation(s) in the *ALPL* gene, which encodes TNSALP.

As a direct result of deficient TNSALP, progressive damage to vital organs along with other clinical sequelae may occur, including deformity and softness of bones (rickets-like bone deformities and osteomalacia), fractures and pseudofractures, pain, profound muscle weakness, respiratory failure (primarily in infants), seizures (mainly in infants), impaired renal function, impaired mobility, and dental abnormalities. HPP is associated with a high fracture and orthopedic/dental surgical burden, pain, need for assistive walking devices (due to impaired mobility), and impairments in activities of daily living in children and adults. Rachitic changes in the chest often lead to diminished respiratory function (due to lack of rib cage support) and risk of ventilator dependence and premature death (mainly in infants). The deficiency of PLP, (vitamin B6) in the central nervous system in patients with HPP can result in seizures (Whyte, 1994; Baumgartner-Sigl, 2007).

2.3.2. Atypical Femoral Fracture

TNSALP plays a significant role in fracture healing and mineralization. Significant elevation of serum ALP is a normal physiological response in the first few weeks after bone fracture

(Hosking, 1978). A normal response to femoral fracture is a 2- to 3-fold elevation of serum ALP within the first 5 weeks of the fracture. A lack of this response has been shown to lead to greater rates of delayed fracture healing or non-union after 9 months (Singh, 2013). Delayed healing and non-union occur in many fractures, but certain fracture types, such as AFFs, are particularly prone to complications.

AFFs are transverse fractures in the shaft of the femur associated with minimal or no trauma, such as a fall from a standing height. AFFs can be complete, breaking through both femoral cortices, or incomplete. AFFs are a common complication of HPP, but are also seen in other subpopulations, including patients taking long-term bisphosphonate treatment. Chronic bisphosphonate treatment for osteoporosis is a known risk factor for development of AFF (and has been implicated in chronic lowering of serum ALP activity in some patients; Bhattacharyya, 2016).

As the effect of bisphosphonates is to cause a reduction of bone turnover, long-term bisphosphonate use is associated with an altered bone structure and biomechanics that can predispose some patients to the occurrence of an AFF. AFFs can be slow to heal and have relatively high rates of delayed union and non-union, even after surgery and intermedullary nailing. Clinical studies have shown that a significant number of patients suffering from an AFF have low serum ALP, which is a risk factor for delayed fracture healing or nonunion (Nakagawa, 2006; Singh, 2013; Sipani, 2020).

2.3.3. Neurofibromatosis Type 1

NF1 is caused by pathogenic variants in the *NF1* gene resulting in the loss of production or reduced function of the protein neurofibromin, which belongs to a family of GTPase-activating proteins and is an inhibitor of the Ras-MAPK signaling pathway. Therefore, in patients with NF1, the MAPK/extracellular signal-regulated kinase signaling pathway is constitutively activated. NF1 occurs in approximately 1:3000 people worldwide and is inherited in an autosomal dominant fashion (Lammert, 2005; Evans, 2010). Almost half of all affected individuals have the disorder as the result of de novo mutation. The mutation rate for NF1 (approximately 1:10000) is among the highest known for any gene in humans. The cause of the unusually high mutation rate is unknown (Friedman, 1999).

NF1 is a multisystemic disease, affecting the skin, nervous system, eyes, and bones. Typical symptoms include neurofibromas, café-au-lait macules, Lisch nodules, and optic gliomas among others. Approximately 30% to 70% of patients with NF1 have significant musculoskeletal manifestations that can be generalized (eg, low bone mineral density that affects about 50% of patients) or focal (eg, tibial dysplasia/pseudoarthrosis or dystrophic scoliosis that affects up to 10% of patients) (Stevenson, 2007; Lodish, 2012). Bone mineral density deficits are more pronounced in children with localized skeletal abnormalities. The presence of these bone abnormalities is usually coupled with poor bone mineralization, which compromises their strength and makes them prone to fracture. Patients with NF1 with known long bone dysplasia have a very high rate of fracture of the dysplastic bone (70%) and a higher rate of multiple fractures compared with controls (George-Abraham, 2013). Surgery is often required to repair these fractures, which, due to low bone TNSALP activity and/or high PPi concentrations, may be very slow to heal and require repeated surgical interventions, including lower limb amputation (Kolanczyk, 2007; Brunetti-Pierri, 2008; Stevenson, 2009; Seitz, 2010).

ALXN1910 treatment increases the TNSALP activity on the bone tissue and is anticipated to improve the defective bone mineralization in patients with NF1. In agreement with this hypothesis, a preclinical study evaluated the efficacy of asfotase alfa using a mouse model of postnatal osteoprogenitor cell NF1 ablation. Mice treated with asfotase alfa, using a dose and dose frequency that had demonstrated efficacy in the Akp2-/- mouse model of HPP, showed a 73% reduction in osteoid volume per bone volume, indicating substantial improvement of bone mineralization in NF1 ablated mice compared with untreated control mice (de la Croix Ndong, 2014).

In 2020, a case study was published in which a patient with NF1 suffering from severe dystrophic lumbar scoliosis and 3 prior surgical interventions was treated with STRENSIQ® after corrective spinal surgery. In this case, the patient received recombinant human bone morphogenetic protein-2 intraoperatively, followed by a bisphosphonate at 3 months after surgery, then STRENSIQ® starting at 7 months after surgery to achieve solid arthrodesis after spinal surgery, a successful outcome for the patient. The authors of this study suggest that the inclusion of asfotase alfa in the treatment regimen of the NF1 patient after surgery likely improved bone mineralization and healing of bone fractures after surgery in this patient (Harindhanavudhi, 2020).

2.4. Benefit/Risk Assessment

Identified potential risks are described below. More detailed information may be found in the IB.

2.4.1. Risk Assessment

This study is the first human exposure to ALXN1910, and as there is no clinical experience to date.

A detailed assessment of potential risks is provided in Table 4.

Table 4: Risk Assessment for ALXN1910

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
ISRs and IARs (including hypersensitivity)	ISRs are a potential risk with any agent administered SC or IV.	Monitoring for ISRs and IARs will be conducted as part of routine safety assessments for this study, including signs and symptoms of anaphylaxis for the FIH study. ALXN1910 treatment will be discontinued in case a severe hypersensitivity reaction occurs. See Section 10.4 for the management of potential AEs, including injection/infusion-related reactions, during study intervention administration.
Immunogenicity	Treatment with any therapeutic protein may induce an immune response, so ALXN1910 has the potential to elicit an ADA response.	Immunogenicity monitoring for ALXN1910 is in place for this study, as specified in the SoA (Section 1.3) and Section 10.4, including ADA and PK/PD monitoring, an algorithm for hypersensitivity reaction management, stopping rules, and staggered dosing.

Abbreviations: ADA = antidrug antibody; AE = adverse event; FIH = first-in-human; IAR = injection/infusion-associated reaction; ISR = injection/infusion site reaction; IV = intravenous; PD = pharmacodynamic; PK =pharmacokinetic; SC = subcutaneous; SoA = schedule of activities

2.4.1.1. Coronavirus Disease 2019

Alexion is carefully considering the potential impact of COVID-19 on the proposed FIH study, including Investigators, other site staff, and study participants. The protocol will include provisions to mitigate risks so that participant/site personnel safety and study integrity are ensured considering the COVID-19 pandemic status at time of Clinical Trial Applications submission. At this time, provisions are being considered, including housing participants in the CRU facility during the study observation period (i.e., Day -1 to Day 75), as well as testing for COVID-19 infection at Screening and prior to admission to the CRU. The mitigations will be finalized based on the conditions in the future and conditions in the local area of the CRU. Alexion notes that, based on its mechanism of action, ALXN1910 is not expected to act as an immunosuppressant. Further, safety data collected in the clinical studies for the related ERT, asfotase alfa, indicate that it did not reduce the immune response in study participants or increase the risk of viral infections.

See Section 10.10 and Section 10.11 for more detailed information on COVID-19 and COVID-19 vaccine risk assessments, respectively.

2.4.2. Benefit Assessment

This is a healthy participant study, and there is no direct benefit to participants.

Data obtained from this clinical study may inform future clinical studies in participants with HPP, NF1, and/or AFFs.

2.4.3. Overall Benefit: Risk Conclusion

This is the first time that ALXN1910 will be administered to humans. Healthy participants are the appropriate population for this study as they will enable PK and PD assessments without the potential of confounding effects due to other disease activity, comorbidities, or concomitant medications.

ALXN1910 is a next-generation ERT of asfotase alfa. In 2015, a healthy participant study has been completed for asfotase alfa (Study AA-HV-104), which tested a single 2 mg/kg dose by SC injection. Asfotase alfa was generally well tolerated with an acceptable safety profile. No NAb response to asfotase alfa was observed in any of the treated healthy participants at 42 days post dose, suggesting a very low risk to healthy participants with short term dosing of asfotase alfa. As the catalytic domains of ALXN1910 and asfotase alfa are structurally 99.8% identical, it is anticipated that ALXN1910 and asfotase alfa will possess pharmacologic and immunological similarities and share the same safety profile. Additional results for this study are provided in the ALXN1910 IB.

This study has been designed to minimize the identified potential risks to participants; there are strict inclusion/exclusion criteria with a robust safety monitoring and risk mitigation plan in place.

As described in Section 4.1, a sentinel group will be implemented for each cohort. The first 2 participants randomized to each cohort will be dosed as a sentinel pair with 1 participant on active treatment and 1 participant on placebo. This dosing strategy is justified given the large safety margin (approximately 15-fold [based on predicted $AUC_{0\text{-}168h}$ value] at the highest

planned single dose of 135 mg SC). A sentinel safety report will be produced and reviewed before dosing the remaining participants in each cohort.

At the discretion of the Investigator, up to 3 more participants will be dosed at least 48 hours after dosing of the sentinel pair, followed by dosing of the remaining participants in the cohort no earlier than 72 hours after sentinel pair dosing, as long as no suspension/stopping criteria have been met. At no time will more than 4 participants per cohort be dosed in a given day.

A blinded SRC, consisting of the Investigator, Medical Monitor, Drug Safety Physician, Study Statistician, and Clinical Pharmacologist will evaluate the available study data at prespecified time points for participant safety and make recommendations on dose escalation, dose modification, or termination of the study. Decisions to continue, modify (explore the dose cohort further), or escalate dosing will be made by the Investigator and/or SRC as described in Section 4.1 and Section 7.

The SC and IV doses to be studied in healthy participants in this study are predicted to be within the PK/safety exposure margins established from a 28-day toxicology study in monkeys.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of ALXN1910	• Incidence of TEAEs and TESAEs
Secondary	
• To assess the PK of single ascending doses of ALXN1910	• Serum ALXN1910 PK (activity) and PK parameters
• To explore the PD effects of single ascending doses of ALXN1910	• Plasma concentrations of PPi, PLP, PL, and PA versus time profiles
• To assess the immunogenicity of ALXN1910	• Incidence and titers of treatment-emergent ADAs
• To assess the absolute bioavailability of ALXN1910 SC	• GMR of AUC values of SC versus IV from serum concentrations of ALXN1910
• To compare the safety, tolerability, PK, and PD of ALXN1910 SC between Japanese and non-Japanese healthy participants	• Quantitative assessment of safety/tolerability and PK/PD parameters between Japanese and non-Japanese participants

Abbreviations: ADA = antidrug antibody; AUC = area under the serum concentration-time curve; GMR = geometric mean ratio; IV = intravenous; PA = pyridoxic acid; PD = pharmacodynamics(s); PK = pharmacokinetic(s); PL = pyridoxal; PLP = pyridoxal-5′-phosphate; PPi = inorganic pyrophosphate; SC = subcutaneous; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, randomized, double-blind, placebo-controlled study designed to evaluate the safety, tolerability, PK, PD, and immunogenicity of SADs of ALXN1910 SC and a SAD of ALXN1910 IV in up to approximately 48 healthy adult participants across treatment cohorts (up to approximately 36 participants to receive ALXN1910 and up to approximately 12 participants to receive placebo) (Table 5).

Of the 48 participants, 8 will be of Japanese descent, defined as those participants whose parents and grandparents are both Japanese and who have spent less than 10 years outside of Japan. The inclusion of Japanese participants aims to meet the regulatory requirements of the ICH Guidance E5(R1), which provides a general framework for evaluating the potential impact of ethnic factors on the acceptability of foreign clinical data.

For this FIH study, 8 participants will be randomly assigned in a 3:1 ratio to treatment and placebo in each of the 6 cohorts with escalating doses of 5 mg IV (Cohort 1), 15 mg SC (Cohort 2), 15 mg IV (Cohort 3) in parallel with 15 mg SC in Japanese participants (Cohort 4) and 45 mg SC (Cohort 5), followed by 135 mg SC (Cohort 6). The first 2 participants randomized to each cohort will be dosed as a sentinel pair, with 1 participant on active treatment and 1 participant on placebo. This dosing strategy is justified given the large exposure margins (approximately 15-fold at the highest planned single dose of 135 mg SC).

At the discretion of the Investigator, up to 3 more participants will be dosed at least 48 hours (as anticipated t_{max} occurs prior to 48 hours postdose) after the dosing of the sentinel pair, followed by dosing of the remaining participants in the cohort no earlier than 72 hours after sentinel pair dosing, as long as no suspension/stopping criteria have been met. At no time will more than 4 participants per cohort be dosed in a given day.

Participants who meet the qualifications for the study based on screening will be admitted to the CRU the day prior to dosing (Day -1) to undergo Check-in assessments per the applicable SoA (Section 1.3).

Final determination of eligibility will be determined based on Check-in and predose procedures, and eligible participants will be randomized to ALXN1910 or placebo on Day 1 prior to dosing. There will be extensive PK/PD sampling during the first 24 hours after dosing. Safety assessments will be performed per the SoA. The study schematic is presented in Figure 1.

Table 5: Planned ALXN1910-HV-101 Dosing Cohorts

Cohort[a]	Number of Participants (ALXN1910:placebo)	Route of Administration	Dose	Number of Doses/Dose Interval
1	8 (3:1)	IV[b]	5 mg	Single dose
2	8 (3:1)	SC	15 mg	Single dose
3	8 (3:1)	IV[b]	15 mg	Single dose
4	8 (3:1) (Japanese Participants)	SC	15 mg	Single dose
5	8 (3:1)	SC	45 mg	Single dose
6	8 (3:1)	SC	135 mg	Single dose

[a] Cohort 3, Cohort 4, and Cohort 5 can be initiated in parallel after dose escalation decision following SRC review of Cohort 2 safety and PK data.

[b] Slow IV infusions (rate of infusion = 6 mL/h) using a controllable infusion pump. The pharmacy manual will include details regarding infusion rate and duration.
Abbreviations: IV = intravenous; PK =pharmacokinetic; SC = subcutaneous; SRC = Safety Review Committee

4.2. Scientific Rationale for Study Design

To gain an understanding of the safety, tolerability, PK, PD, and immunogenicity of ALXN1910, an FIH SAD study in healthy adult participants is proposed. Cohorts of Japanese and non-Japanese participants will also be evaluated to enable comparison between these 2 populations.

4.3. Dose Escalation

Prior to initiating the next higher dose cohort, safety from the preceding dose cohort will be reviewed. After dosing 8 participants in Cohort 1, Cohort 2, and Cohort 5, the SRC will review 14-day safety data (equivalent to 2 half-lives), including TEAEs, safety laboratory results, 12-lead ECG findings, and vital sign measurements. PK data will be reviewed by SRC prior to dose escalation decision from Cohort 2 to Cohort 5, and from Cohort 5 to Cohort 6. For detailed cohort dose escalation requirements, please refer to Table 8.

4.4. Justification for Dose

The FIH dose selection is based on PK data collected from rat and monkey dose-range finding studies, 28-day GLP toxicology studies in rats and monkeys, and efficacy data from 2 Akp2GW (-/-) mouse efficacy studies.

Two methods have been evaluated to determine a starting dose, with the first method based on the NOAEL and a second method based on the MABEL (EMA, 2017b). After comparing expected safety and feasibility factors for each method's proposed starting dose, a NOAEL-based approach was selected to determine the final starting dose. The NOAEL-based starting dose at 5 mg is considered as the maximum recommended starting dose and is justified by the FIH starting dose decision tree, low concern of the risk factors (not an agonist, not a novel target, relevant, and translatable model) (Leach, 2021) and experience from asfotase alfa study AA-HV-104. In addition, this approach can avoid logistical challenges with dosing small volumes associated with the MABEL approach. The starting dose was selected based on NOAEL from the 28-day GLP toxicology study in monkeys dosed SC once weekly, which was determined to be 50 mg/kg. Monkey was selected because it has relevant biology with humans. Assumptions of 1) no allometric scaling for a molecule with molecule weight > 100 kDa (FDA, 2005), 2) applying safety factor of 750, 3) SC bioavailability (90%), and 4) adult body weight of 70 kg were factored into the calculation of the starting dose. Based on Pop-PK simulation results, the observed exposure of the NOAEL at 50 mg/kg/dose from the GLP toxicology study in monkeys is approximately 230-fold of projected human exposure from the 5 mg IV starting dose (Table 6). Moreover, a single dose of 5 mg is not expected to be pharmacologically active with respect to bone mineralization.

Single dose will be escalated by 3-fold from 5 mg IV (Cohort 1) to 15 mg SC (Cohort 2), by 3-fold from 15 mg SC (Cohort 2) to 45 mg SC (Cohort 5), and by 3-fold from 45 mg SC (Cohort 5) to 135 mg SC (Cohort 6). A single dose of 15 mg IV (Cohort 3) and a single dose of

15 mg SC in Japanese participants (Cohort 4) will be administered after dose escalation decision following SRC review of Cohort 2 safety and PK data.

At 15 mg SC, ALXN1910 is predicted to achieve clinical meaningful response in 85% of a treated population at steady state and is considered as the target effective dose. Based on the established extrapolation of asfotase alfa dose-response relationship with respect to improvements of bone mineralization in Akp2GW (-/-) mouse model of HPP, the dose producing normal bone mineralization in ED85 is considered as the target effective dose. Mouse ED85 was calculated using a dose response model developed using ALXN1910 preclinical efficacy studies in Akp2GW (-/-) mouse model of HPP and allometrically scaled to a weekly flat dose of 15 mg/week in humans. A 135 mg SC dose is projected to achieve normalized bone mineralization in 98% of a treated population at steady state and is expected to cover the therapeutic range in humans. Predicted human exposure at 135 mg SC is around 1/15 of the 28-day monkey NOAEL exposure with the NOAEL dose at the highest dose of 50 mg/kg. Three-fold dose escalation is supported by results of a single dose range finding study in monkeys and rats where the high dose was well tolerated, and there were no ALXN1910 treatment-related mortalities and noteworthy biologically meaningful veterinary observations.

The Pop-PK model uses standard body weight-based allometric principles and approach to account for body weight differences between species to simulate human exposure. Safety (including PK) exposure margins were estimated using simulated human exposure based on the Pop-PK model and observed 28-day monkey NOAEL exposure. Table 6 shows the FIH SAD study design and a summary of the predicted exposure and safety exposure margin for ALXN1910. The forecasted human exposure for the single SC and IV doses to be studied in healthy participants are predicted not to exceed exposure of the NOAEL dose (50 mg/kg) of the 28-day monkey GLP toxicology study. The proposed maximum SC single dose (135 mg) is expected to maintain a large safety exposure margin of at least 15-fold in human.

Table 6: Simulated ALXN1910 PK Exposure and Safety Exposure Margins in Humans

Cohort	Dose	Predicted AUC_{168h} (hour × µg /mL)	Predicted C_{max} (µg/mL)	Expected Safety Exposure Margin for $AUC_{0\text{-}168h}$	Expected Safety Exposure Margin for C_{max}
1	5 mg IV	78.2	1.2	230	232
2	15 mg SC	136.0	1.2	132	231
3	15 mg IV	225.1	3.4	80	79
4	15 mg SC (Japanese participants)	153.6	1.3	117	205
5	45 mg SC	398.2	3.3	45	81
6	135 mg SC	1208.8	10.2	15	26

Abbreviations: AUC_{168h} = area under the serum concentration-time curve from time 0 to 168 hours; C_{max} = maximum observed serum concentration; IV = intravenous; PK = pharmacokinetics; SC = subcutaneous

4.5. Duration of Treatment and End of Study Definition

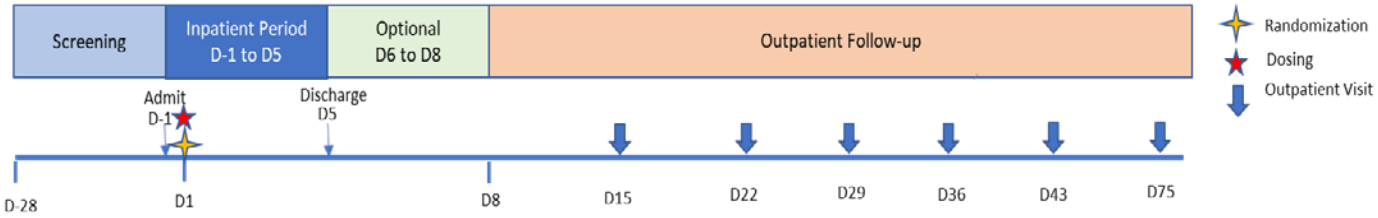
Following a Screening Period of up to 28 days, there will be a Dosing and Follow up Period (single dose on Day 1 through the EOS Visit) of approximately 74 days.

Based on data from preclinical models, the half-life of ALXN1910 is expected to be approximately 7 days in healthy adult participants; therefore, the end of study visit is planned on Day 75, representing approximately 10 half-lives after initial study intervention administration. The total study duration per participant is approximately 103 days. An overview of the study visits is present in Figure 2.

A participant is considered to have completed the study if they complete all visits of the study including the last scheduled visit specified in the SoA (Section 1.3).

The end of the study is defined as the date the last participant completes the last visit (as specified in the SoA [Section 1.3]).

Figure 2: Overview of Study Visits



Abbreviation: D = day

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participants must be between 18 and 55 years of age (Japanese participants must be between 20 and 55 years of age), inclusive, at the time of signing the ICF.

Sex

2. Male or female, and willing to follow protocol-specified contraception guidance as specified in Section 10.7.

Type of Participant

3. Participants who are healthy as determined by satisfactory medical assessment with no clinically significant or relevant abnormalities as determined by medical history, physical examination, vital signs, 12-lead ECG, and clinical laboratory evaluation (hematology, chemistry, coagulation, and urinalysis) that is reasonably likely to interfere with the participant's participation in or ability to complete the study, or to potentially confound interpretation of study results, as assessed by the Investigator.
4. Female participants must have a negative serum pregnancy test at Screening and negative urine pregnancy test on Day -1.
5. Participants of Japanese descent are defined as:
    - First generation (born to 2 Japanese parents and 4 Japanese grandparents).
    - Participant must have been born in Japan, and not have lived outside Japan for more than 10 years.
    - Lifestyle, including diet, must not have significantly changed since leaving Japan.

Weight

6. Body weight within 50 to 100 kg, inclusive, and body mass index within the range 18 to 29.9 kg/m^2, inclusive.

Informed Consent

7. Capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Current or recurrent disease (eg, cardiovascular, hematological, neurological, endocrine, immunological, rheumatological, renal, hepatic or gastrointestinal, or other conditions).
2. Current or relevant history of physical or psychiatric illness, use of prohibited therapies during the study, or make the participant unlikely to fully comply with the requirements of the study or complete the study, or any condition that presents undue risk from the study intervention or study procedures.
3. Any other significant disease or disorder that, in the opinion of the Investigator, may put the participant at risk.
4. Clinically significant abnormal vital signs at Screening or predose on Day 1. If vital signs are significantly abnormal, up to 2 additional readings will be taken. If neither of the 2 replicates are normal or non-significantly abnormal, the participant will be excluded from study participation. Blood pressure should be taken after a minimum of 5 minutes in supine position. Standing (orthostatic) blood pressure will also be performed at Screening only to exclude participants who are prone to orthostatic hypotension.
5. Clinically significant abnormal ECG at Screening or 12-lead ECG (triplicate) predose on Day 1. If ECG values are significantly abnormal, up to 2 additional triplicate ECGs will be performed. If neither of the 2 replicates are normal or non-significantly abnormal, the participant will be excluded from study participation.
6. History of malignancy, apart from nonmelanoma skin cancer or carcinoma in situ of the cervix, that has been treated with no evidence of recurrence within 5 years.
7. HIV infection (evidenced by HIV-1 or HIV-2 antibody titer).
8. Acute or chronic hepatitis B virus infection (evidenced by positive hepatitis B surface antigen [HBsAg] or positive core antibody [HBcAb] with negative surface antibody [HBsAb]) at Screening will not be enrolled.
9. Acute or chronic hepatitis C virus infection (evidenced by antibody titer).
10. History of significant allergic reaction (eg, anaphylaxis or angioedema) to any product (eg, food, pharmaceutical).

Prior/Concomitant Therapy

11. Use or intended use of prescription medications (excluding oral contraceptives and paracetamol/acetaminophen at doses ≤ 3000 mg per day) within 14 days or 5 half-lives of the drug (whichever is longer) prior to Day -7, and/or intended use at any point over the duration of the study except with prior approval of Alexion.
12. Use of nonprescription/over-the-counter medications (excluding paracetamol/acetaminophen at doses ≤ 3000 mg per day), including herbal remedies and supplements, within 7 days to dosing Day 1, except with prior approval of Alexion.

13. Use of vitamin B6 (including vitamin supplements that contain vitamin B6) for at least 2 weeks prior to Screening.

Prior/Concurrent Clinical Study Experience

14. Current enrollment or past participation, within the last 90 days, before signing of consent in this or any other clinical study involving an investigational study intervention. Participants, involved in intervention studies using investigation or non-investigational drug with prolonged half-lives, are not eligible unless the time since last treatment has exceeded 90 days or 5 half-lives of the study intervention, whichever is longer.

Diagnostic Assessments

15. Presence of fever (confirmed body temperature > 37.6°C) (eg, a fever associated with a symptomatic viral or bacterial infection) within 14 days prior to dosing on Day 1.
16. Alkaline phosphatase greater than the ULN or lower than the lower limit of normal of the reference range of the testing laboratory at Screening or on Day -1.
17. Serum creatinine greater than the ULN of the laboratory reference range at Screening or on Day -1; estimated glomerular filtration rate < 90 mL/min/1.73 m^2.
18. ALT or aspartate aminotransferase > ULN of the reference range of the testing laboratory at Screening or on Day -1.
19. Any clinically significant abnormal hematological parameters (per the Investigator's discretion).
20. Positive urine drug toxicology screen at Screening or on Day -1.
21. Positive urine alcohol test at Screening or Day -1
22. Donation of plasma within 7 days prior to dosing; donation or loss of blood (excluding volume drawn at Screening) of more than 50 mL within 30 days of dosing on Day 1, or more than 499 mL of blood within 56 days of dosing on Day 1.

Other Exclusions

23. Female participants who are pregnant or breastfeeding.
24. Major surgery or hospitalization within 90 days prior to dosing on Day 1.
25. History of exposure to asfotase alfa.
26. History of allergy or hypersensitivity to excipients of asfotase alfa or ALXN1910 (eg, sodium phosphate, sodium chloride).
27. Use of tobacco in any form (eg, smoking or chewing) or other nicotine-containing products in any form (eg, gum, patch, electronic cigarettes) from 2 hours before admission through discharge from the CRU, for both inpatient and outpatient visits. (Former smokers may be permitted to enroll at the Investigator's discretion).
28. History of illicit drug abuse, history of alcohol abuse within 1 year prior to Screening, or clinical evidence of substance and/or alcohol abuse within the 2 years before Screening. Alcohol abuse is defined as regular weekly intake of more than 14 units for both men and women (https://www.nhs.uk/conditions/alcohol-misuse/).

5.3. Justification for Study Population

This is the first time that ALXN1910 will be administered to humans. Alexion considers that healthy participants are the appropriate population for this study, as they will enable PK and safety assessments without the potential of confounding effects due to other disease activity, comorbidities, or medications. Based on the available nonclinical data with ALXN1910, the sequential cohort study design with SAD administration of ALXN1910 IV or SC are expected to adequately assess safety, tolerability, and PK, and allow flexibility to change the injected dose as clinical data are generated.

The inclusion of a cohort of Japanese participants will meet regulatory requirements of the ICH Guidance E5(R1) and Japan Ministry of Health, Labour and Welfare guidance on Basic Principles on Global Clinical Trials. The ICH E5 guideline provides a general framework for evaluating the potential impact of ethnic factors on the acceptability of foreign clinical data, with the underlying objective of minimizing duplication of clinical data, and it also describes the requirement of bridging studies for extrapolation of foreign clinical data to a new region (ie, Japan).

5.4. Lifestyle Considerations

5.4.1. Meals and Dietary Restrictions

- Participants are required to abstain from ingesting food containing poppy seeds within 24 hours prior to admission to the CRU.
- No outside food or drink is permitted at the CRU. All meals and snacks will be provided. Participants will receive standard meals and snacks at scheduled times during confinement.

5.4.2. Activity

Participants will be required to remain in supine position for dosing and for approximately 15 minutes after study intervention administration. Vigorous activity will be prohibited at all times throughout confinement at the CRU.

5.4.3. Caffeine, Alcohol, and Tobacco

Participants will be required to abstain from the following:

- Ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) 24 hours before admission through discharge from the CRU and 24 hours before each outpatient visit.
- Ingesting alcohol 24 hours before admission through discharge from the CRU and 24 hours before each outpatient visit.
- Smoking nicotine or use of tobacco products from 2 hours before admission through discharge from the CRU.

5.5. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details (eg, failed eligibility criteria), and any AEs, including any SAEs and any related concomitant medication, occurring during the Screening Period.

Individuals who do not meet the criteria for participation in this study (screen failure) due to a reason that is expected to resolve or has resolved, may be rescreened based on discussion and agreement between the Investigator and the Medical Monitor. Rescreened participants are required to sign a new ICF.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Interventions Administered

The study intervention composition and doses to be administered in this study are presented in Table 7.

Table 7: Dose Reference Chart for Study ALXN1910-HV-101

Study Intervention Name	ALXN1910 IV	ALXN1910 SC	Placebo
Type	Biologic	Biologic	Placebo
Dose Formulation	ALXN1910 is formulated at pH 7.3 and each vial contains 100 mg of ALXN1910 in 10 mM sodium phosphate, 70 mM glycine, 210 mM sucrose, and 0.05% PS80.	ALXN1910 is formulated at pH 7.3 and each vial contains 100 mg of ALXN1910 in 10 mM sodium phosphate, 70 mM glycine, 210 mM sucrose, and 0.05% PS80	0.9% normal saline
Unit Dose Strength(s)/Dosage Level(s)	5 and 15 mg, single-dose	15, 45, and 135 mg, single-dose	0 mg, single-dose
Route of Administration	IV infusion	SC injection	IV infusion or SC injection
Use	Experimental	Experimental	Placebo
IMP and NIMP	IMP	IMP	IMP

Abbreviations: IMP = investigational medicinal product; IV = intravenous; NIMP = non-investigational medicinal product; PS80 = polysorbate 80; SC = subcutaneous

6.1.1. Study Intervention Packaging and Labeling

At minimum, bulk ALXN1910 vials supplied by Alexion will be labeled with:

A. Protocol number

B. Lot number/expiry date

C. Alexion name and address

D. Instructions for use and storage

ALXN1910 will be labeled according to the country's regulatory requirements. All packaging and labeling operations will be performed according to GMP and relevant regulatory requirements. Participant doses prepared by the site will be QP certified and released by the CRU.

6.2. Preparation/Handling/Storage/Accountability

Details regarding preparation, handling, storage, accountability, and administration of the study intervention are discussed below.

- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and that any discrepancies are reported and resolved before use of the study intervention.
    - Only participants enrolled in the study may receive the study intervention and only authorized site staff may supply or administer the study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
    - The Investigator (or designee), institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
    - This responsibility includes the reporting of any temperature excursions and product complaints to AlexionIMPTE@alexion.com and productcomplaints@alexion.com within 1 business day of awareness. A product complaint is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, usability, safety, effectiveness, or performance of a product or clinical study material and/or its packaging components after it is has been released for distribution to an end customer that affects the performance of such product.

Further guidance regarding preparation, handling, storage, and accountability and information for the final disposition of unused study intervention is provided in the pharmacy manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Up to approximately 48 participants will be randomized according to a randomization schedule generated prior to the start of the study. The participants in each dose cohort will be randomized in a 3:1 ratio to receive ALXN1910 or placebo.

The randomization codes will be maintained in a location with access restricted to pharmacy personnel only. Once a randomization number has been assigned to a participant, it may not be assigned to another participant.

This is a double-blind study. Participants and on-site medical/nursing staff at the study site will be blinded to study intervention/dose assignment. The pharmacy staff preparing the investigational products will not be blinded to study intervention/dose assignment, but all other site staff, including the Investigator, will be blinded.

As the treatment with ALXN1910 can cause increases in serum ALP, knowledge of the ALP results could jeopardize the double-blind design of the study. Therefore, ALP results for the post-dose time points will not be available to review by the Investigator; however, the ALP results will be available in a blinded manner for each cohort at the time of SRC meeting.

Alexion staff will be unblinded only when necessary (eg, to monitor that SC/IV dosing are being prepared appropriately, to determine reportability of SAEs for dose escalation decisions) and will refrain from sharing any information on study intervention assignment with the study center staff or others at Alexion, especially with regard to assessment and reporting of safety.

The study intervention assignment to each participant will be provided to the Investigator. This information will be retained by the Investigator (or representative) in a secured manner. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should contact Alexion prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for that participant. If a participant's intervention assignment is unblinded, Alexion must be notified within 24 hours after breaking the blind.

Additional details regarding the blinding/unblinding process (including masking techniques) will be included in the pharmacy manual.

As emerging PK and safety data from each cohort of this study will be needed for timely decisions about adjustments of doses or escalate dosing in subsequent cohorts, the emerging data will be unblinded for analysis. An independent unblinded team that is limited to key stakeholders will perform unblinded PK analyses and prepare preliminary summaries of PK and safety data as needed before data are more generally unblinded. These summaries will not reveal individual participant's treatment assignments. Except as noted above, other members of the study team will remain blinded.

6.4. Study Intervention Compliance

Participants will receive study intervention directly from the Investigator or designee, under medical supervision. Dosing date and time will be recorded in the source documents and recorded in the eCRFs. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a study site personnel other than the person administering the study intervention.

6.5. Concomitant Therapy

Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements), vaccine, or other specific categories of interest that the participant is receiving from 14 days prior to the dose of study intervention until the EOS Visit must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Allowed Medicine and Therapy

- Paracetamol/acetaminophen at doses of a maximum 3000 mg per day is permitted for use as an exception with the approval of the Investigator.

- Concomitant procedures are not allowed unless medically indicated and/or permitted by Alexion or the Investigator or designee.
- Concomitant medications may be used during the study if deemed medically indicated by the Investigator. The Investigator or designee will notify Alexion of any AEs requiring administration of prescription medication(s) while on study.

6.5.2. Disallowed Medicine and Therapy

- Participants must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the EOS Visit, unless, in the opinion of the Investigator and Alexion, the medication will not interfere with the study.
- Participants must abstain from taking prescription medications within 21 days or 5 half-lives (whichever is longer) of Day -1 or non-prescription drugs (including vitamins and dietary or herbal supplements) within 7 days or 5 half-lives (whichever is longer) before Day -1 and until completion of the EOS Visit.

6.6. Dose Modification

Decisions to continue or modify dosing will be made by the Investigator and/or SRC after review of the blinded data as described in Table 8. The SRC may also make recommendations regarding safety issues, study conduct, or study suspension.

Predicted ALXN1910 human PK exposure (Table 6) indicates Cohort 5 or Cohort 6 mean projected PK exposure should not exceed 50% of the NOAEL exposure established in the 28-day GLP toxicology study in monkeys. In the event that mean PK exposure in Cohort 5 or Cohort 6 is predicted to exceed 50% of the NOAEL exposure, a lower dose will be selected so the above criteria can be met. PK data will not be used for dose escalation from Cohort 1 to Cohort 2 as greater than 150-fold PK (safety) exposure margin is expected for Cohort 2.

Dose escalation requires agreement between the Investigator and Alexion; Alexion may not supersede the Investigator if there are concerns that dosing should be stopped.

Table 8: Detailed Dose Escalation Criteria for Each Cohort

Dosing Decision	Responsible Party	Data to be Reviewed	Documentation/ Communication Methods
Dose escalation from Cohort 1 to Cohort 2	SRC	• At minimum, 14 days of postdose safety and tolerability data from at least 7 participants in Cohort 1.	The SRC will document the decision on the escalation/progression approval form.
Dose escalation from Cohort 2 to Cohort 5 (in parallel with Cohort 3 and Cohort 4)	SRC	• At minimum, 14 days of postdose safety and tolerability data from at least 7 participants in Cohort 2. • Seven days of PK data from at least 7 participants in Cohort 1 and at least 7 participants in Cohort 2.	The SRC will document the decision on the escalation/progression approval form.
Dose escalation from Cohort 5 to Cohort 6	SRC	• At minimum, 14 days of postdose safety and tolerability data from at least 7 participants in Cohort 5. • Seven days of PK data from at least 7 participants in Cohort 5. • The cumulative PK data from Cohort 1 and Cohort 2.	The SRC will document the decision on the escalation/progression approval form.

Abbreviations: PK = pharmacokinetic; SRC = Safety Review Committee

6.7. Intervention After the End of the Study

This is a healthy participant study. No follow-up ALXN1910 administration is planned.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Although not anticipated for this study, if an acute infusion reaction occurs during IV infusion dosing, the research clinic should follow the steps outlined in the Acute Infusion Reaction Algorithm (Section 10.5). Participants who are unable to complete their IV dose on Day 1 should complete the scheduled safety assessments, if possible, but another participant must be enrolled.

7.2. Cohort Stopping Rules

In the event an acute safety event occurs in any cohort, dosing should be stopped until a causality assessment has taken place and an appropriate risk mitigation strategy is put into place before dosing the remainder of the cohort.

Assessment of AE intensity/severity should be performed by the Investigator using clinical judgment and according to criteria from NCI CTCAE version 5.0, published 27 Nov 2017 (see Section 10.3.3). As CTCAE grading is intended for oncology patients, study-specific modifications related to the liver, hematology, and QT interval prolongation have been made to ensure clear guidance and appropriate grading of AEs for this study in healthy participants (Table 11).

If a cohort stopping rule (Table 11) is met, no further dosing at the dose level or higher will proceed. Continuation of the cohort and/or study will require a substantial protocol amendment.

Unless a cohort stopping rule is met, dose continuation or escalation will proceed as scheduled and the study will continue as planned provided no prespecified toxicity events occur (as determined by the SRC).

7.3. Participant Discontinuation/Withdrawal from the Study

- All efforts should be made to ensure participants are willing to comply with study participation prior to conducting the screening procedures.
- The study staff should notify Alexion and their site monitor of all study withdrawals as soon as possible. The reason for participant discontinuation must be recorded in the source documents and eCRF.
- A participant may withdraw from the study at any time at their own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This activity is expected to be uncommon.
- At the time of discontinuing from the study, an early discontinuation visit should be conducted that includes the EOS assessments shown in the SoA, if possible (Section 1.3).
- All efforts will be made to contact participants who withdraw/are withdrawn from the study via phone for a safety follow-up call approximately 30 days (4.5 half-lives) after their dose to assess AEs.

- The first participant in each cohort to withdraw/be withdrawn from the study prior to completion of the EOS assessments may not be replaced; subsequent participants in that cohort to withdraw/be withdrawn before EOS completion will be replaced.
- If the participant withdraws consent for disclosure of future information, Alexion may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.4. Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant to reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, they will be considered lost to follow-up.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.8.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with Alexion immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).
- See Section 10.2 for the list of clinical laboratory tests.

8.1. Efficacy Assessments

No efficacy assessments will be performed during the study.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

- Complete or brief physical examinations will be performed according to the timepoints indicated in the SoA (Section 1.3). Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Complete physical examinations will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems.
- Brief physical examinations will include assessments at the Investigator's discretion.
- Height and BMI will be recorded only at Screening.
- Weight will be recorded at Screening and Day -1.

8.2.2. Vital Signs

- Oral temperature, pulse rate, respiratory rate, and systolic and diastolic blood pressure (mm Hg) will be assessed.
- Blood pressure and pulse measurements will be assessed using a completely automated device after the participant has been resting in the supine position for at

least 5 minutes. At Screening, supine and standing (orthostatic) blood pressures will be performed according to the CRU's typical procedure to exclude participants who are prone to orthostatic hypotension. Manual techniques will be used only if an automated device is not available.

- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones). Ideally, the same arm for each participant should be used for measurements.
- Vital signs taken postdose will be performed before the coinciding blood collection, whenever possible.

8.2.3. Electrocardiograms

- At each timepoint indicated in the SoA (Section 1.3), 12-lead ECGs will be performed in triplicate sequentially within 5 minutes, at least 1 minute apart to obtain heart rate, PR, QRS, QT, and QTc intervals.
- ECGs should not be performed within 1 hour after any major meal or major meals should be withheld until after ECG assessments.
- Participants should rest in supine position for at least 10 minutes before each ECG timepoint.
- Predose ECGs (Baseline) should be performed at least 1 minute apart after 10 minutes of bedrest in supine position (note, no bedrest is required post ECG), at 90, 75, and 60 minutes before dosing.
- Postdose ECGs will be performed before the coinciding blood collection, whenever possible.

8.2.4. Clinical Safety Laboratory Assessments

- See Section 10.2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and Alexion notified.
  - All protocol-required laboratory assessments, as defined in Section 10.2, must be collected in accordance with the Laboratory Manual and the SoA (Section 1.3).

  - Laboratory assessments performed at the institution's local laboratory that require a change in participant management or are considered clinically significant by the Investigator (eg, AE or SAE) must be recorded in the eCRF.

- The maximum total blood volume collected from participants in this study will not exceed 500 mL. The National Health Service blood donation policy at the time of completion of this protocol (http://www.blood.co.uk/who-can-give-blood/) states that women can give 470 mL of blood every 16 weeks. Therefore, the ≤ 500 mL of blood collected during this study of less than 16 weeks is permitted/consistent with current clinical practice.

8.2.5. Pregnancy

Pregnancy data from female participants and female spouses/partners of male participants will be collected from the time points specified in the SoA (Section 1.3). Any female participant who becomes pregnant during the study will be withdrawn from the study. If a pregnancy is reported, the Investigator must immediately inform Alexion within 24 hours of awareness of the pregnancy and follow the procedures outlined in Section 10.7.3.

8.3. Adverse Events and Serious Adverse Events Considerations

- The definitions of AEs and SAEs and specific reporting requirements can be found in Section 10.3.
- All AEs will be reported to the Investigator or qualified designee by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).
- The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).
- Procedures for recording, evaluating, follow-up, and reporting AEs and SAEs are outlined in Section 10.3.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

- All AEs and SAEs will be collected from the signing of the ICF until the EOS visit on Day 75 as specified in the SoA (Section 1.3).
- All SAEs will be recorded and reported to Alexion immediately and under no circumstance should this exceed 24 hours of the Investigator's awareness, as indicated in Section 10.3. The Investigator will submit any updated SAE data to Alexion within 24 hours of the date the investigational site became aware of the event.
- Investigators are not obligated to actively seek AE or SAE data after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and they

consider the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify Alexion.

8.3.2. Method of Detecting AEs and SAEs

- The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.
- Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow-up on each participant at subsequent visits/contacts. All SAEs will be followed up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is provided in Section 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification of an SAE by the Investigator to Alexion is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- Alexion has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. Alexion will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and Investigators.
- Alexion is required to submit individual suspected unexpected serious adverse reaction (SUSAR) reports (defined in Section 10.3.2) in the format of CIOMS I Form to health authorities and Investigators as required. Forms submitted to Investigators will be blinded to treatment assignment. In limited circumstances, the blind may be broken in the case of urgent safety issues that could compromise participant safety.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from Alexion will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Special Warnings and Precautions for Use

Please refer to the current ALXN1910 Investigator's Brochure for special warnings and precautions for use.

8.4. Treatment of Overdose

- For this study, any blinded dose of study intervention greater than that specified in the protocol will be considered a suspected overdose.

- Alexion does not recommend specific treatment for a suspected overdose and no antidote is currently available for ALXN1910.
- Overdoses are medication errors that are not considered AEs unless there is an untoward medical occurrence resulting from the overdose.
- In the event of a suspected overdose, the Investigator/Treating Physician should:
  - Contact the Medical Monitor immediately.
  - Closely monitor the participant for any AE/SAE.
  - Obtain a serum sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).
  - Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.
- Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

- Whole blood will be collected for measurement of serum concentrations of ALXN1910 as specified in the SoA (Section 1.3). Samples collected within ± 10% in minutes or 30 minutes of the scheduled time, whichever is less, will not be considered a protocol deviation. Additional samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and Alexion. The IV dose cohorts (1 and 3) will also have an end-of-infusion PK time point. The total blood volume will not exceed the volume limit for healthy participants (Section 8.2.4). To ensure appropriate monitoring, the timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak serum concentrations or to extend the study duration to capture sufficient PK elimination phase).
- Instructions for the collection and handling of biological samples will be provided by Alexion. The actual date and time (24-hour clock time) of each sample collection will be recorded.
- Samples will be used to evaluate the PK of ALXN1910. Samples collected for analyses of ALXN1910 serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

8.6. Pharmacodynamics

- Whole blood will be collected for measurement of plasma concentrations of PPi, PLP, PL, and PA as specified in the SoA (Section 1.3). Samples collected within ± 10% in minutes or 30 minutes of the scheduled time, whichever is less, will not be considered a protocol deviation. Additional samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and Alexion.

- Instructions for the collection and handling of biological samples will be provided by Alexion. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PD of ALXN1910. Samples collected for analyses of plasma concentrations of PPi, PLP, PL, and PA may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarker assays may be conducted as exploratory analyses on collected whole blood samples (details provided in Section 10.8).

8.9. Immunogenicity Assessments

Serum samples for ADA analysis will be collected at time points according to the SoAs (Section 1.3). All efforts will be made to obtain the immunogenicity samples at the exact nominal time relative to dosing. Out-of-window protocol deviation capture for immunogenicity samples follows that specified for PK sample collection (Section 8.5).

8.9.1. ADA Variables

ADA variables include ADA response category incidence and titer over the duration of the study as follows. ADA response category definitions and titer thresholds will be provided in the SAP.

ADA response categories

- ADA Negative
- ADA Positive

Participants that are ADA positive will be categorized as follows:

- Pre-existing Immunoreactivity
- Treatment-emergent ADA Responses
- Treatment-boosted ADA Responses

ADA Maximum Titer Value Categories:

- Lower Titer
- Moderate Titer
- High Titer

8.10. Health Economics Data and/or Medical Resource Utilization

Health economics data and/or medical resource utilization parameters are not collected or evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

No statistical hypotheses will be tested for this study.

9.2. Sample Size Determination

The sample size of up to approximately 48 participants is empirical and was selected to support the initial characterization of safety, tolerability, PK, PD, and immunogenicity for ALXN1910. Although the selected sample size was not based on statistical power considerations, the following table provides the probability of observing AEs under various underlying event incidence.

Incidence of AE in the Population	Probability to Observe at least 1 AE Occurrence in 6 Participants from Each Cohort
10%	46.9%
15%	62.3%
20%	73.8%
25%	82.2%
30%	88.2%
35%	92.5%
40%	95.3%

Abbreviation: AE = adverse event

9.3. Populations for Analyses

The population sets used for analysis are defined in Table 9.

Table 9: Populations for Analyses

Population	Description
Safety Set	All participants who receive any amount of study intervention will be included in the Safety Set. Participants will be analyzed according to the study intervention received.
PK Set	All treated participants for whom the PK profile of ALXN1910 can be adequately characterized will be included in the PK Set. PK analyses will be based upon the study intervention received.
PD Set	All treated participants for whom the PD profile of ALXN1910 can be adequately characterized will be included in the PD Set.
ADA Analysis Set	All randomized/enrolled participants who receive at least 1 dose of the study intervention and who after the dose have at least 1 reportable ADA result. Participants will be analyzed according to the study intervention they actually received.

Abbreviations: ADA = antidrug antibody; PD = pharmacodynamic; PK = pharmacokinetic

9.4. Statistical Analyses

Statistical methods described in this section will be further elaborated in the SAP. This SAP will be developed and finalized before first data cutoff if interim analysis is conducted or database lock. Summary statistics will be computed and displayed by treatment group and by visit, where applicable. Participants in the placebo group of each cohort will be pooled in the analysis.

Descriptive statistics for continuous variables will minimally include the number of participants, mean, standard deviation, minimum, median, and maximum. For categorical variables, frequencies, and percentages will be presented. Graphical displays will be provided as appropriate.

9.4.1. Safety Analyses

All safety analyses will be based on the Safety Set.

The primary objective of the study is to assess the safety and tolerability of ALXN1910. The endpoints to support the primary objective include incidence of TEAEs and TESAEs.

The incidence of TEAEs and TESAEs will be summarized by SOC and PT for each dose cohort overall, by intensity/severity, and by relationship to study intervention. Treatment-emergent AEs and TESAEs resulting in withdrawal from the study will be listed. Participants having multiple AEs within a category (eg, overall, SOC, PT) will be counted once in that category. For intensity/severity tables, a participant's most severe event within a category will be counted. Adverse events of special interest (such as ISRs and IARs) will be analyzed similarly.

Changes from baseline in vital signs and laboratory assessments (as displayed in Table 10) will be summarized by visit for each dose cohort and pooled placebo group. Laboratory parameter values will be assessed by the Investigator for intensity/severity grade by taking into consideration clinical judgment and using CTCAE version 5.0 (for grading see Section 10.3.3).

Shift tables by treatment group will be produced for these laboratory parameters. These tables will summarize the number of participants with each baseline intensity/severity grade relative to the normal ranges, and changes to the worst highest grade assessed postdose during the study

ECG parameters will be measured at the specified time points, including heart rate, PR, RR, QRS, QT, and QTcF intervals. Each 12-lead ECG will be performed in triplicate (sequentially within 5 minutes, at least 1 minute apart) and should not be assessed within 1 hour after any major meal or, major meals should be withheld until after ECG assessments. The average of the triplicate ECG readings at the time points collected will be calculated, and changes from baseline values will be assessed. Intensive cardiac assessments will be performed in the Safety Set using food effects on ECG to establish assay sensitivity. Analysis of drug related QT/QTc interval changes relative to serum PK concentrations may be conducted on all dose regimens. The principles of this analysis follow the statistical methods described by Garnett et al. (Garnett, 2018). The ECG utilized for this analysis requires adjudication by qualified cardiologists in accordance with principles set out in the ICH E14 guideline and subsequent Q&A documents. All ECG recordings will be in triplicate and compliant with the correct recording and manual adjudication of ECG in thorough QT/QTc studies. The ECG analyses will be based on adjudicated selected triplicates from each time point.

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

- QT, QTcF interval $\leq$ 450 msec
- 450 msec < QT, QTcF interval $\leq$ 480 msec
- 480 msec < QT, QTcF interval $\leq$ 500 msec

- QT, QTcF interval > 500 msec
- QT, QTcF interval increases from baseline ≤ 30 msec
- 30 msec < QT, QTcF interval increases from baseline ≤ 60 msec
- QT, QTcF interval increases from baseline > 60 msec

9.4.2. Other Analyses

9.4.2.1. Pharmacokinetic Analysis

All PK analyses will be performed on the PK Set and will be reported by each cohort. The individual serum concentration data from participants who receive ALXN1910 with actual sampling dates and times will be used to derive the PK parameters by non-compartmental analyses methods using Phoenix WinNonlin version 6.3 or higher.

The following PK parameters will be derived:

Parameter	Definition
C_{max}	Maximum observed serum concentration
t_{max}	Time to maximum observed serum concentration
AUC_t	Area under the serum concentration-time curve from time 0 (dosing) to the last quantifiable concentration
AUC_∞	Area under the serum concentration-time curve from time 0 (dosing) to infinity
$t_{½}$	Terminal elimination half-life
λ_z	Terminal-phase elimination rate constant
CL or CL/F	Total body clearance or apparent clearance
Vd or Vd/F	Volume of distribution or apparent volume of distribution
F	Absolute bioavailability

The F for the ALXN1910 SC cohorts will be defined by the ratio of the geometric means for the area under the serum concentration-time curve from time 0 (dosing) to infinity parameter for the ALXN1910 SC cohort over the ALXN1910 IV cohort. For the F estimates, a 95% CI for each of the ratios of the geometric means will be provided.

The PK parameters for ALXN1910 will be evaluated for Japanese and non-Japanese participants (Cohort 2 versus Cohort 4) on active treatment, using an analysis of variance statistical model with cohort as the fixed effects on the natural logarithms of the data. In addition, the Japanese versus non-Japanese cohorts will be evaluated using descriptive statistics; for each cohort, the geometric means and the associated 95% CIs of difference of PK parameters will be reported.

Dose-proportionality will be assessed and additional ALXN1910 PK parameters may be calculated if deemed appropriate with details to be provided in the SAP.

9.4.2.2. Pharmacodynamic Analysis

All PD analyses will be performed on the PD Set and will be reported by each cohort. Observed values and changes from baseline in plasma concentrations of PPi, PLP, PL, and PA versus time will be presented graphically by treatment over time compared with placebo-treated participants.

The PD parameters for ALXN1910 will be evaluated over time for Japanese and non-Japanese participants (Cohort 2 versus Cohort 4) on active treatment by using MMRM model with cohort,

visit, and cohort by visit interaction as fixed effects, subject as a random effect, and baseline value as a covariate. The unstructured covariance structure will be employed; however, if the model fails to converge, Toeplitz, heterogeneous compound symmetry, and compound symmetry covariance structure will be applied in the order listed until the model converges.

In the case that all covariance structures fail to converge, the analysis of variance statistical model with baseline and cohort as the fixed effects will be used. In addition, the Japanese versus non-Japanese cohorts will be evaluated using descriptive statistics; for each cohort, the geometric means and the associated 95% CIs of difference of PD parameters in observed value and CFB value will be reported. Figures of absolute values and change from baseline over time may be produced if needed.

Biomarker assays may be conducted as exploratory analyses on collected samples (Section 10.8).

9.4.2.3. Immunogenicity Analysis

All ADA analyses will be performed on the ADA Analysis Set Population using the ADA variables included in Section 8.9.1.

The incidence of ADA response categories will be summarized as absolute occurrence (n) and percent of all participants (%) by cohort. Participants in the placebo group will be pooled from each cohort for the summary analysis. Maximum ADA titer levels will be listed and summarized for ADA-positive participants as absolute occurrence (n) and percent of all participants (%). Additional details will be provided in the SAP.

Associations between ADA response categories and systemic exposure to study intervention may be explored for ALXN1910-treated participants by cohort, for analyzing the potential impact of immunogenicity on PK profiles. Additional details will be provided in the SAP.

Associations between ADA response categories and SAEs and severe adverse events may be explored, including SAEs such as systemic hypersensitivity, anaphylaxis, ISRs lasting more than 24 hours, and other immune-related SAEs.

Additional analysis may be performed with details to be provided in the SAP.

9.5. Interim Analyses

Interim analyses may be performed as needed. In particular, an interim analysis may be conducted after Cohort 5 completes Day 15. This analysis for further evaluation of the doses and for planning subsequent dosing will be included in the SAP finalized prior to analysis ALXN1910.

9.6. Safety Review Committee

The blinded SRC, consisting of the Investigator, Medical Monitor, Drug Safety Physician, Study Statistician, and Clinical Pharmacologist will evaluate the available study data at prespecified time points for participant safety and make recommendations on dose escalation, dose modification, or termination of the study. Decisions to continue, modify (explore the dose cohort further), or escalate dosing will be made by the Investigator and/or SRC.

The SRC will meet at minimum to support each cohort dose escalation after review of blinded data. Where review of unblinded data may be necessary in the event of emerging safety signals, additional ad hoc meetings will be scheduled without the Investigator/site staff in attendance. If dosing is stopped because of a safety event, continuation of the cohort and/or study will require a substantial amendment.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, substantial protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator/Alexion and reviewed and approved by the IRB/IEC before the study is initiated.
  - If any of these documents require regulatory/health authority approval per local regulations, Alexion will also obtain such approval before the study is initiated.
- Any substantial amendments to the protocol will require IRB/IEC and regulatory/health authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- For studies to be approved by the Medicines and Healthcare products Regulatory Agency: The Investigator will notify the IRB/IEC of deviations from the study protocol or GCP as defined by UK legislation as a serious breach or as required by IRB/IEC procedures.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to the requirements of ICH guidelines and the IRB/IEC, all regional and national regulations as applicable (eg, CFR Title 21, Regulation [EU] No 536/2014 on clinical trials on medicinal products for human use, Directive 2001/20/EC), and all other applicable local regulations.

10.1.2. Financial Disclosure

Investigators and Sub-Investigators will provide Alexion with sufficient, accurate financial information as requested to allow Alexion to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- It is the responsibility of the Investigator or designee to obtain signed (written or electronic signature) informed consent from all study participants prior to performing any study-related procedures including screening assessments.
- The Investigator or designee will explain the nature of the study (including but not limited to the objectives, potential benefits and risks, inconveniences, and the participant's rights and responsibilities) to the participant or their legally authorized representative, defined according to local and country regulations where the study is taking place, and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent or a certified translation, if applicable, that meets the requirements of 21 CFR 50, local regulations, EU General Data Protection Regulation, ICH GCP guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The participant's medical record must reflect/indicate a statement that signed (written or electronic) informed consent was obtained before any screening procedures were performed with a participant, and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF(s).
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study, as applicable.
- A copy of the signed (written or electronic) informed consent documentation (ie, a complete set of participant information sheets and fully executed signature pages) must be provided to the participant or the participant's legally authorized representative, as applicable. This document may require translation into the local language. Original signed (written or electronic) consent forms must remain in each participant's study file and must be available for verification at any time.
- Rescreened participants are required to sign a new ICF (Section 5.5).

10.1.4. Data Protection

- Participants will be assigned a unique identifier by Alexion. Any participant records or datasets that are transferred to Alexion will contain the identifier only; participant names, initials, or any information which would make the participant identifiable will not be transferred.

- Participants must be informed that their personal study-related data will be used in accordance with applicable data protection law, and participants must also be informed of any individuals rights they may have with regard to their personal data. Participants will be informed about how their personal study-related data will be disclosed, and will be required to agree to the information contained in the informed consent and provide consent to the processing of their personal data, if required by applicable data protection law.
- Participants must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Alexion, appropriate IRB/IEC members, and inspectors from regulatory authorities.
- Alexion as a data controller has implemented privacy and security controls designed to help protect participant personal data; including information security controls, firewalls, incident detection, and secure transfer measures.
- In the event of any accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data ("breach"), the controller has implemented procedures and measures to promptly address and mitigate any risk to the data participant. In the event of a breach, the controller will notify the appropriate regulatory authorities and/or the data participant in accordance with applicable data protection law.

10.1.5. Dissemination of Clinical Study Data

Study-related information and study results may be posted on publicly accessible clinical study databases (eg, the US website www.clinicaltrials.gov or the EU website www.clinicaltrialsregister.eu), as appropriate, and in accordance with national, regional, and local regulations.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on the eCRF. The Investigator is responsible for verifying that data entries are accurate and correct by signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Alexion or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

  - Remote source data verification may be employed where permitted by local regulations.
  - The scope of the source data verification will be described in detail in the Clinical Monitoring Plan.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator after study completion per local regulations or institutional policies. No records may be destroyed without the written approval of Alexion. No records may be transferred to another location or party without written notification to Alexion.
- QTLs will be predefined in the study-specific risk register to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The Investigator or designee will prepare and maintain adequate and accurate source documents (eg, medical records, ECGs, AE and concomitant medication reporting, raw data collection forms) designed to record all observations and other pertinent data for each participant.

Data reported on the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. eCRFs must be completed by the Investigator or designee as indicated in the site delegation log. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available to Alexion, Alexion delegates, and health authorities, as requested. Source documents are filed at the investigational site.

Per ICH E6 (R2) guidelines and good documentation practice requirements, source documents and study records in all media (eg, paper, electronic) must be attributable, legible, contemporaneous, original, accurate, and complete.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the first participant is consented.

Alexion reserves the right to close the study site or terminate the study at any time for any reason at its sole discretion. Study sites will be closed after the study is completed or following the decision to close or terminate the study. A study site is considered closed when all participants have completed the end of study or early discontinuation visit, all data have been collected and entered into the electronic data capture system, all required documents and study supplies have been collected and reconciled, and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by Alexion or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Alexion's procedures, or ICH GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

Alexion or health authority may terminate the study for reasonable cause. Conditions that may warrant termination of the study include, but are not limited to:

- Discovery of an unexpected, serious, or unacceptable risk of the study intervention to participants enrolled or continuing in the study
- Alexion decision to suspend or discontinue testing, evaluation, or development of the study intervention

If the study is prematurely terminated or suspended, Alexion shall promptly inform the Investigators, IRBs/IECs, regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.9. Publication Policy

- Where possible, primary manuscripts reporting results of the primary efficacy endpoint or the final results will be submitted for publication within 12 to 18 months of the primary evaluation date or end of study, whichever is earlier.
- Investigators who participate as authors in manuscripts derived from Alexion-sponsored studies will agree to the prerequisites as outlined in the Alexion author engagement agreement prior to engaging in manuscript development.
- The Investigator agrees to submit proposals for new manuscripts (whether or not the proposed analyses are derived from protocol-specified endpoints) to Alexion for review and consideration. All manuscripts or abstracts emanating from approved proposals are to be submitted to Alexion for review before submission to the journal/society. This allows Alexion to protect proprietary information and provide comments.
  - The proprietary nature of some development work may preclude publication. In some cases, it may be necessary to delay a publication to allow Alexion to ensure protection of intellectual property.
- Primary publications, including congress and journal publications, containing the protocol-specified results of a study should occur prior to the publication of individual study site results or case reports. Alexion's policy prohibits duplicate publication, whereby the same results must not be published in multiple peer-reviewed journal manuscripts.

  - Encore congress publications may be appropriate to allow communication of research findings to relevant audience and geographical regions.

- Alexion will comply with the requirements for publication of study results as defined by the Pharmaceutical Research and Manufacturers of America and the International Committee of Medical Journal Editors and per the Alexion Publication Policy. In accordance with standard editorial and ethical practice, Alexion will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Co-ordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements and per the Alexion Publication Policy.
- Alexion will publish Patient Lay Summaries and include participants and/or caregivers as reviewers for readability and understanding of lay person language.

10.1.10. Good Clinical Practice Compliance

Alexion and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH GCP Guideline E6 (R2), as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of Alexion and/or the company organizing/managing the research on behalf of Alexion to inspect study data, participants' medical records, and eCRFs in accordance with current GCP and respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

Alexion ensures that local regulatory authority requirements are met before the start of the study. Alexion (or designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of ALXN1910 for shipment to the site.

10.2. Clinical Laboratory Tests

Except ADAs, which will be analyzed via the central laboratory, the tests detailed in Table 10 will be performed by local laboratories.

If local laboratory results are used to make either a study intervention decision or response evaluation, the results must be available in the participant's source documents.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Pregnancy testing: WOCBP should only be enrolled after a negative serum pregnancy test result at Screening. Additional pregnancy testing (urine or serum) will be performed per the time points specified in the SoA (Section 1.3). Any female participant who becomes pregnant while participating in the study will be withdrawn from the study and the Investigator must immediately notify the Alexion Medical Monitor and follow the procedures outlined in Section 10.7.3.

Table 10: Protocol-required Laboratory Assessments

Laboratory Assessments	**Parameters**		
Hematology	White blood cell count Red blood cell count Hematocrit Hemoglobin	Red blood cell indices: Mean corpuscular volume Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Reticulocytes	Monocytes Eosinophils Basophils Neutrophils Lymphocytes Platelet count Mean platelet volume
Clinical chemistry	Blood urea nitrogen/urea Potassium Creatinine Sodium Chloride HbA1c[a] Creatine kinase eGFR[b]	AST/SGOT ALT/SGPT Gamma-glutamyltransferase Alkaline phosphatase[c]	Total and direct bilirubin Indirect bilirubin Total protein Albumin Calcium including ionized calcium Phosphate Magnesium Bicarbonate
Coagulation	Prothrombin time	Partial thromboplastin time	International normalized ratio
Other safety laboratory tests	• Antidrug antibodies (Alexion)	The following tests are to be conducted in case of an acute injection/infusion-associated reaction: • Tryptase (Alexion) • C5b-9 (Alexion) • Hematology, chemistry, and urinalysis panels	
Routine urinalysis (by dipstick)	• Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, and leukocyte esterase • Microscopic examination (if any leukocytes, trace protein, nitrites, and blood [if not menstruating] are abnormal)		
Urine electrolyte	Urine for calcium, phosphorus, and creatinine		

Laboratory Assessments	Parameters
Other screening tests	• Urine drug and alcohol tests • FSH (confirmation of postmenopausal state) • HIV-1 and HIV-2 antibodies, HBsAg, HBcAb, HBsAb and anti-HCV • Serum human chorionic gonadotropin pregnancy test • Serum or urine pregnancy test

[a] HbA1c will be assessed only at Screening.
[b] eGFR will be assessed only at Screening and admission.
[c] The results for ALP assessments for the post-dose time points will only be available in a blinded manner.

Abbreviations: ALT = alanine aminotransferase; anti-HCV = hepatitis C virus antibody; AST = aspartate aminotransferase; C5b-9 = terminal complement complex; eGFR = estimated glomerular filtration rate; FSH = follicle-stimulating hormone; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase

10.3. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity/severity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events Not Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): The condition that leads to the procedure is the AE. Situations in which an untoward medical occurrence did not occur (eg, hospitalization for elective surgery if planned before the signing the ICF, admissions for social reasons or for convenience). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. • A medication error (including intentional misuse, abuse, and overdose of the product) or use other than what is defined in the protocol is not considered an AE unless there is an untoward medical occurrence as a result of a medication error. • Cases of pregnancy that occur during maternal or paternal exposure to study intervention are to be reported within 24 hours of Investigator/site awareness. Data on fetal outcome and breastfeeding will be collected for regulatory reporting and safety evaluation. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
1. Results in death
2. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it was more severe.

3. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

4. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

5. Is a congenital anomaly/birth defect

6. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

A suspected unexpected serious adverse reaction (SUSAR) is defined as:

An event that is assessed as serious by the Investigator and/or Alexion that is not listed in the appropriate Reference Safety Information (IB) and has been assessed that there is at least a reasonable possibility that the event is related to the investigational medicinal product by the Investigator and/or Alexion.
Alexion has procedures that will be followed for the recording, medical assessment, and expedited reporting of SUSARs that are consistent with global regulations, legislation, and guidance documents.

Suspected unexpected serious adverse reactions will undergo expedited reporting to the national regulatory authorities, IRBs/IECs, and Investigators following local regulatory reporting requirements where applicable.

10.3.3. Recording and Follow-up of AE and/or SAE

Recording of AE and/or SAE

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF.
- It is not acceptable for the Investigator to send photocopies of the participant's medical records to Alexion in lieu of completion of the Alexion/AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by Alexion. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Alexion.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity/Severity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories from National Cancer Institute CTCAE version 5.0, published 27 Nov 2017:

- Grade 1: Mild (awareness of sign or symptom, but easily tolerated)
- Grade 2: Moderate (discomfort sufficient to cause interference with normal activities)
- Grade 3: Severe (incapacitating, with inability to perform normal activities)
- Grade 4: Life-threatening
- Grade 5: Fatal

Changes in the severity of an AE should be documented to allow an assessment of the AE duration at each level of intensity to be evaluated. AEs characterized as intermittent require documentation of onset and duration of each episode, if the severity of the intermittent event changes.
An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between the study intervention and each occurrence of each AE or SAE. An Investigator causality assessment must be provided for all AEs (both nonserious and serious). This assessment must be recorded in the eCRF and on any additional forms, as appropriate. The definitions for the causality assessments are as follows:
  - Not related: There is no reasonable possibility the study intervention caused the AE.
    - The AE has a more likely alternative etiology; it may be due to underlying or concurrent illness, complications, concurrent treatments, or effects of another concurrent drug.
    - The event does not follow a reasonable temporal relationship to administration of the study intervention.
  - Related: There is a reasonable possibility the study intervention caused the AE.
    - The AE has a temporal relationship to the administration of the study intervention.
    - The event does not have a likely alternative etiology.
    - The event corresponds with the known pharmaceutical profile of the study intervention.
    - There is improvement on discontinuation and/or reappearance on rechallenge.
    - AEs/SAEs assessed as "Probably Related" or "Possibly Related" will be grouped with "Related" AEs/SAEs.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB in their assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that they have reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to Alexion or designee. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Alexion or designee.
- The Investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Alexion or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide Alexion or designee with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.

- The Investigator will submit any updated SAE data to Alexion or designee within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Alexion or Delegate via Paper Safety Reporting Form

- All SAEs will be recorded and reported to Alexion or designee immediately and within 24 hours awareness.
- SAEs will be reported using the Safety Reporting Form and submitted to Alexion GDS. The Investigator must complete, sign, and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy via email or facsimile to the contact information provided below:
  - Email: clinicalsae@alexion.com or Fax: + 1.203.439.9347
- Additional follow-up information, if required or available, should be entered into the eCRF and sent to Alexion GDS within 24 hours of the Investigator or study site staff becoming aware of this additional information via the reporting process outlined above.
- For all SAEs, the Investigator must provide the following:
  - Appropriate and requested follow-up information in the time frame detailed above
  - Causality of the SAE(s)
  - Treatment of/intervention for the SAE(s)
  - Outcome of the SAE(s)
  - Medical records and laboratory/diagnostic information
- All paper forms and follow-up information submitted to Alexion GDS **must** be accompanied by a cover page signed by the Investigator.
- Paper source documents and/or reports should be kept in the appropriate section of the study file.

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; eCRF = electronic case report form; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; GDS = Global Drug Safety; Hb = hemoglobin; SAE = serious adverse event; ULN = upper limit of normal.

Table 11: Cohort and Study Stopping Rules

Adverse Events Related to Study Intervention	Showing Signs of Reversibility	Number of Participants	Action
Moderate (CTCAE Grade 2)	Yes	≥ 3 in 1 SOC ≥ 4 total in different SOCs	Cohort: Dosing of the remainder of the cohort suspended Study: Dosing of equal or higher doses suspended Dosing of lower dose levels can continue Continuation of dosing of equal or higher doses requires a substantial amendment[d]
	No	≥ 2 total in different SOCs	
Injection/infusion site reactions: Moderate (CTCAE Grade 2)	No[a]	≥ 3	
Injection/infusion related reactions (including hypersensitivity): Moderate (CTCAE Grade 2)	No[a]	≥ 3	
QT interval prolongation: A prolongation of the uncorrected QT interval of greater than 500 msec, using consistent, technically valid triplicate ECG (CTCAE Grade 2)	NA	≥ 2	
Hematology (CTCAE Grade 2): Hb drop to absolute values of < 10g/dL (100 g/L) Platelet count drop to absolute values of < 75,000/mm^3	NA	≥ 2	
Severe (CTCAE Grade 3) **Or** Serious AE (not fatal or life-threatening) **Or** Hy's law: ALT or AST value > 3 × ULN together with bilirubin increase > 2 × ULN, without other evidence of cholestasis (CTCAE Grade 3) **Or** ALT or AST value > 8 × ULN. ALT or AST value > 3 × ULN, and symptomatic (CTCAE Grade 3) **Or** Injection/infusion site reactions: Severe (CTCAE Grade 3) **Or** Injection/infusion related reactions (including hypersensitivity): Severe (CTCAE Grade 3) **Or** Hematology (CTCAE Grade 3): Hb drop to absolute values of < 8 g/dL	NA	2	Study suspended (all dosing [lower, equal, or higher doses] suspended) Continuation of the cohort or study requires a substantial amendment[b]
Serious (fatal or life-threatening, CTCAE Grades 4 and 5)	NA	1	

[a] For injection/infusion site reactions, a cohort and/or the study will be suspended when ≥ 3 participants are observed. If all but 1 affected participant show signs of recovery (at least to Grade 1), cohort and study continuation can then proceed. If ≥ 2 participants remain at Grade 2 after the minimum data review period, the period of observation should be extended for up to 168 hours. If all but 1 affected participant show sign of

recovery (at least to Grade 1), cohort and study continuation can then proceed. If ≥ 2 affected participants remain at Grade 2 after the first 168-hour extension period, the SRC will make the decision to either prolong further the observation period up to a maximum of another 168 hours or suspend the remainder of the cohort and study. At the end of the second extension period, if all but 1 participant show sign of recovery (at least to Grade 1), cohort and study continuation can then proceed. If, however, ≥ 2 affected participants remain at Grade 2, cohort and study will be suspended.

[b] A substantial amendment may include an amendment to the protocol, the ICF, or other study-related documents as appropriate.

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; Hb = hemoglobin; ICF = informed consent form; NA = not applicable; QT = interval between the start of the Q wave and the end of the T wave in an ECG; SOC = System Organ Class; SRC = Safety Review Committee; ULN = upper limit of normal

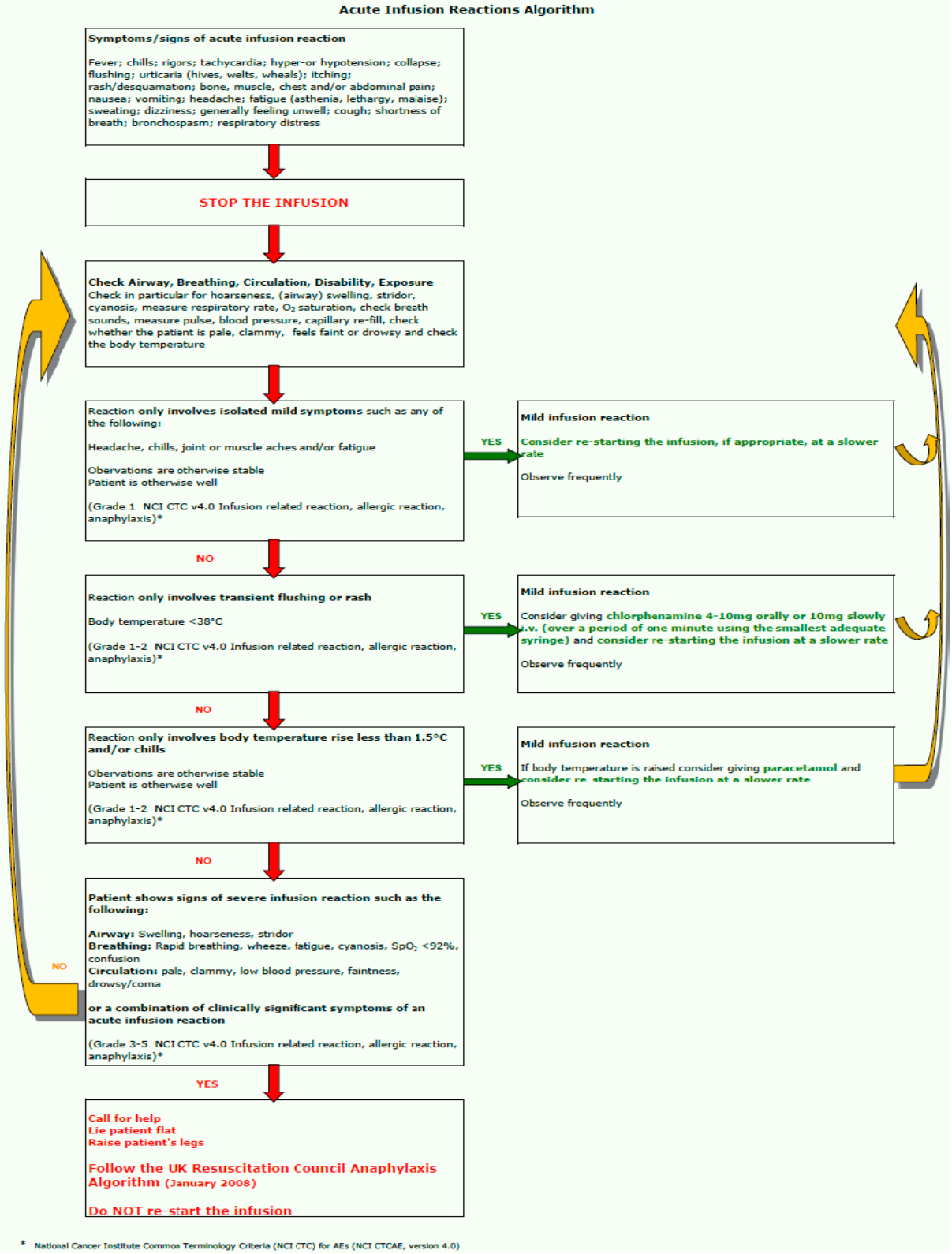
10.4. Management of Potential Adverse Events During Study Intervention Administration

Participants will be closely monitored during and after study intervention administration for any symptoms of anaphylaxis and other hypersensitivity reactions, including circulatory and/or respiratory changes or arrest, or urticaria, arthralgias, myalgias, or other signs of related reactions. Adequate treatment will be immediately available. Injection/infusion-associated AEs may occur, and depending on their type and intensity/severity, discontinuation of infusion may be required. Participants will be informed of early symptoms and signs of hypersensitivity reactions including hives, swollen face, eyelids, lips, or tongue, or trouble with breathing. An acute infusion reaction algorithm will be used to manage IARs (Section 10.5 [Acute Infusion Reaction Algorithm]). In this study, regular assessments to monitor IARs and ISRs will be done. To ensure that reactions can be dealt with promptly, there will be at least 30 minutes between the end of IV/SC infusion in 1 participant and the start of IV/SC infusion in the next participant. If anaphylactic reactions occur, the current "UK Treatment Guideline for Anaphylactic Reactions" of the UK Resuscitation Council will be followed (Section 10.6 [United Kingdom Resuscitation Council Anaphylaxis Algorithm]).

Decisions to continue or modify dosing will be made by the Investigator and SRC after review of the blinded data as described in Table 8. The SRC may also make recommendations regarding safety issues, study conduct, or study suspension.

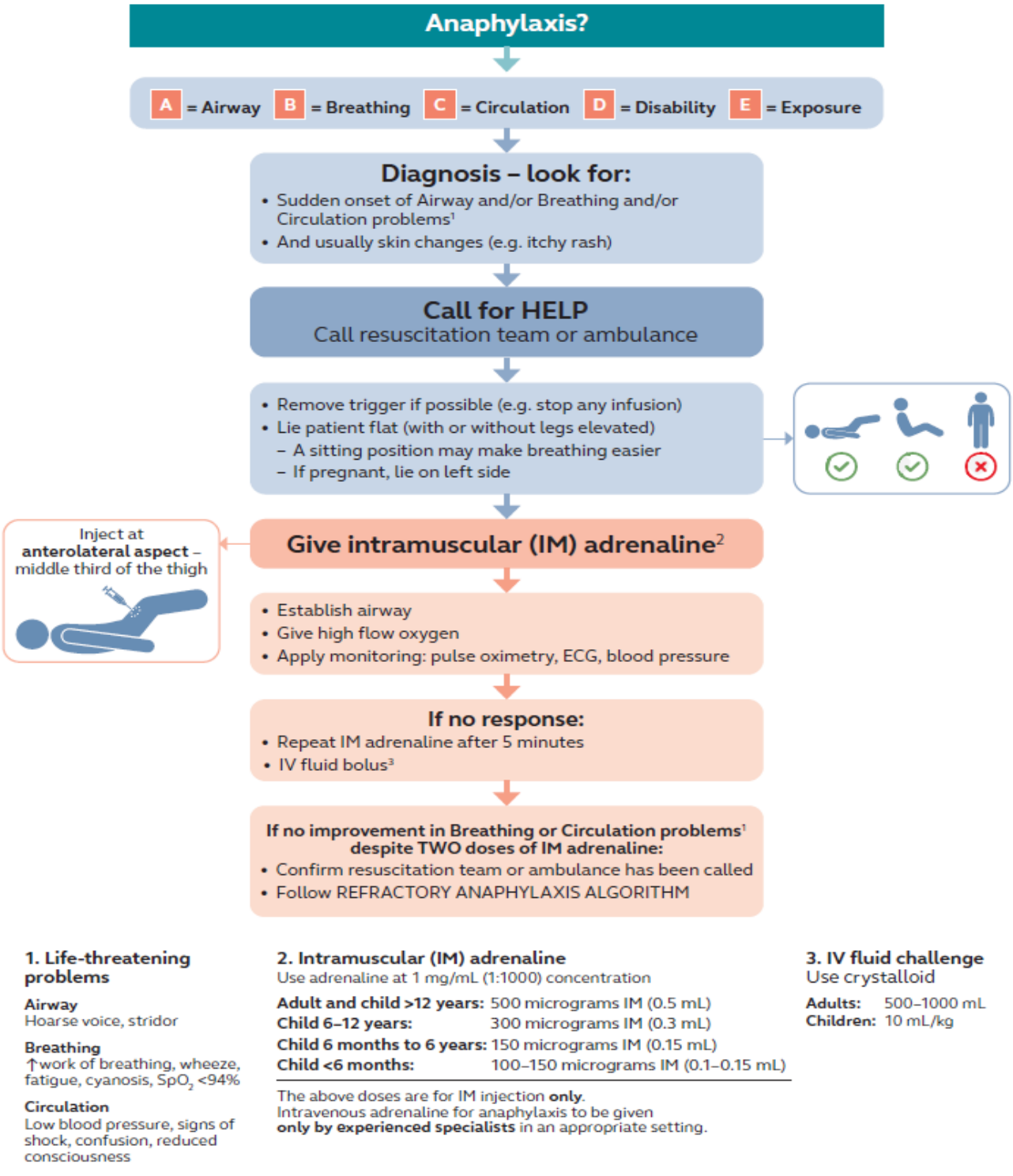
Participants who experience a severe reaction during administration of study intervention that results in discontinuation of study intervention should undergo all scheduled safety, immunogenicity, PK, and PD evaluations required by the protocol. Participants will therefore be instructed to attend all scheduled visits and undergo all procedures per protocol.

10.5. Acute Infusion Reaction Algorithm



Abbreviations: AE = adverse event; O2 = oxygen; SpO^2 = oxygen saturation

10.6. Country-specific Requirements: United Kingdom Resuscitation Council Anaphylaxis Algorithm - Guidelines 2021



Source: https://www resus.org.uk/library/additional-guidance/guidance-anaphylaxis/emergency-treatment
Abbreviations: ECG = electrocardiogram; IM = intramuscular; IV = intravenous; SpO_2 = oxygen saturation

10.7. Contraceptive Guidance and Collection of Pregnancy Information

10.7.1. Definitions

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the Following Categories Are Not Considered WOCBP

- Premenopausal female with one of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months prior to Day 1 without an alternative medical cause. A high FSH level in the postmenopausal range, as per local laboratory reference ranges, may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement may be required.
  - Female participants on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
- For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

10.7.2. Contraception Guidance

10.7.2.1. Guidance for Female Participants

Female participants of non-childbearing potential are exempt from contraception requirements. Female participants of childbearing potential, if heterosexually active, must use highly effective contraception as defined below. Antibiotic prophylaxis may be administered during this study, which can compromise the efficacy of hormonal contraception. Therefore, participants using hormonal contraception must also use barrier contraception (eg, condom or diaphragm with spermicide) for the duration of antibiotic prophylaxis.

Highly effective contraceptive methods for females are as follows:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation as follows:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation as follows:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized male partner (with documented evidence of azoospermia if possible)
- Sexual abstinence (in line with the preferred and usual lifestyle of the participant)

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. Calendar, ovulation, symptothermal, post-ovulation methods, and withdrawal do NOT meet the definition of abstinence. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Participants must use an appropriate form of highly effective contraception as stated for females of childbearing potential who are sexually active, from 1 complete menstrual cycle prior to the first intercourse with a male and continue until for at least 3 months after the dose.

10.7.2.2. Guidance for Male Participants

To prevent transfer of study intervention to a male or female partner or fetus/baby, all male participants including those who have had a vasectomy (even with documented evidence of azoospermia) must agree to use a barrier method (male condom) during intercourse with a male or female partner from the time of screening for up to 3 months after the dose.

Male participants, if sexually active and with a female spouse or partner of childbearing potential or a pregnant or breastfeeding spouse or partner, must agree to use barrier contraception (male condom). Barrier contraception is required even with documented medical assessment of surgical success of a vasectomy. Female spouses or partners of male participants who are of childbearing potential must use highly effective contraception as defined above.

Contraception for all cohorts must start during Screening and continue for up to 3 months after the dose.

Male participants must not donate sperm and female participants must not donate ova for up to 3 months after dose administration.

10.7.3. Collection of Pregnancy Information

- Pregnancy data will be collected during this study for all female participants and any female spouse/partner of a male participant, who become pregnant. Exposure during pregnancy (also referred to as exposure in utero) can be the result of either maternal exposure or transmission of drug product via semen following paternal exposure.
- If a female participant or a male participant's female sexual partner of childbearing potential becomes or is found to be pregnant while being treated or exposed to study intervention, the Investigator must submit the "Pregnancy/Breastfeeding Reporting and Outcome Form" to Alexion GDS or designee via the same method as SAE reporting (Section 10.3). When the outcome of the pregnancy becomes known, the form should be updated and submitted to Alexion Global Drug Safety or designee. If additional follow-up is required, the Investigator will be requested to provide the information.
- Exposure of an infant to an Alexion product during breastfeeding must also be reported (via the "Pregnancy/Breastfeeding Reporting and Outcome Form") and any AEs experienced by the infant must be reported to Alexion Global Drug Safety or designee via facsimile or email.
- A pregnancy in and of itself is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs and may meet the criteria for an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly). Elective abortions without complications should not be reported as AEs (Section 10.3).
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

10.8. Biomarkers

- Biomarker assays may be conducted as exploratory analyses on collected whole blood samples and the data used for research (eg, exploratory) related to ALXN1910. The samples may also be used to develop tests/assays including diagnostic tests related to ALXN1910 and/or others of this study intervention class.
- The samples may be analyzed as part of a multistudy assessment of biomarkers in the response to ALXN1910 to understand study disease or related conditions. Analyses may be done to establish normal range of values for biomarkers which may include, but are not limited to, markers of complement dysregulation (eg, Factor Ba), vascular inflammation (eg, soluble tumor necrosis factor receptors), and endothelial activation/damage (eg, soluble vascular cell adhesion molecule-1, thrombomodulin).
- The results of biomarker analyses may be reported in the CSR or in a separate study summary.
- Alexion or designee will store the samples obtained for biomarker analyses in a secure storage space with adequate measures to protect confidentiality.
- Samples will be retained no longer than 5 years from the end of the study (or another time period consistent with local requirements) while research on ALXN1910 continues.

10.9. Resuscitation Procedures, Equipment, Medicines, and Training

There must be procedures, equipment, medicines, and trained staff to deal with any medical emergency that might arise during the study (https://www.abpi.org.uk/media/4992/guidelines-for-phase-i-clinical-trials-2018-edition-20180626.pdf).

10.9.1. General Procedures

Study participants must:

- Have a call button by their bed and in places such as social areas, toilets, and showers to call study staff.
- Be given the names and telephone numbers of the study physicians, so that the participant (or another doctor who might see the participant) can call the 'on-call' physician or a study physician at any time.

Study staff must have access to and must be trained in the following:

- Medical cover throughout the study.
- An 'on-call' doctor who they can contact by telephone at any time.
- Alexion Medical Monitor or defined delegates whom they can contact by telephone at any time. A cascade of contactable personnel on the side of Alexion should be available to the Investigator site; this can be added to the study protocol or be detailed in a separate document.
- A procedure to report SAEs.
- A procedure to break the blind should a participant have an SAE
- An alarm system to call for assistance in case of a medical emergency.
- Continuous monitoring of vital signs such as ECG and pulse oximetry.
- Procedures for dealing with the most likely medical emergencies such as profound syncope, hypotension, anaphylaxis, and cardiopulmonary arrest.
- A procedure to transfer a participant to a hospital (see below)

10.9.2. Resuscitation Equipment and Medicines/Antidote

In each of the main clinical areas of the premises, there must be a resuscitation trolley with equipment and medicines that can be moved quickly to where they are needed in a medical emergency. Each trolley should have the same equipment and medicines, which must be checked at least weekly and after use, and records of the checks must be kept. The main items on each trolley should be as those recommended by the Resuscitation Council (https://www.resus.org.uk/library/additional-guidance/guidance-anaphylaxis/emergency-treatment), for example:

- Defibrillator with an ECG monitor (both mains and battery operated)
- Suction apparatus

- Oxygen cylinder and flowmeter
- Oropharyngeal airways and face masks
- Self-inflating bag
- Laryngoscope and endotracheal tubes or laryngeal mask/alternative supraglottic airway device
- Consumables such as IV cannula and fluid infusion sets
- Emergency medicines, including IV fluids
- Transcutaneous cardiac pacer (one should be enough for the whole premises)
- Waveform capnograph with appropriate tubing and connector

10.9.3. Resuscitation Training

Physicians, nurses, and other staff who help to care for participants must all be trained and hold a valid certificate in basic life support, ILS, or ALS procedures, as appropriate. For example, all physicians must be trained and hold a valid certificate in ALS or ILS. The medical director or another doctor with clinical expertise in resuscitation should set and maintain standards of training and assessment of the unit's staff and ensure that competence is maintained by regular refresher training. Appropriately trained people, such as doctors and resuscitation training officers, should carry out the training and assessment.

10.10. COVID-19 Risk Assessment

Based on the mechanism of action of ALXN1910, it is expected that participants will have the same risk to contract severe acute respiratory syndrome coronavirus 2 infection and develop COVID-19 of the same intensity/severity as the general population. Mitigation measures implemented to reduce the risk of transmission as per national and institutional guidances are to be followed.

The potential risks identified and mitigation measures put in place in light of the COVID-19 pandemic are provided in Table 12.

Table 12: Potential Risks and Mitigation Measures due to COVID-19

Risks Category	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential risks		
Healthcare institution availability for non-COVID-19-related activities	COVID-19 pandemic may impact the workload of healthcare institutions globally and may reduce staff availability to perform non-urgent activities and non-COVID-19-related activities.	During the time that the COVID-19 pandemic is active, Alexion will not open study sites or enroll new participants at sites unless the sites have the resourcing and capabilities to implement the study per protocol.
Data quality and integrity	Lack of availability of site personnel to perform study assessments and capture study-specific data in a timely manner and to maintain adequate quality standards. Lack of availability of site personnel to ensure adequate and continuous chain of custody, storage conditions, and monitoring for investigational product and biological samples. Inability of study monitors and quality personnel to conduct in-person visits to exercise adequate oversight of study execution at investigational sites. Missing data (COVID-19 pandemic may impact study visit schedules and increase missed visits and/or participant study discontinuations inadvertently resulting in missing data [eg, for protocol-specified procedures]).	During the time that the COVID-19 pandemic is active, Alexion will only open study sites that report enough personnel capacity to sufficiently conduct clinical study-related activities. During this timeframe, participants eligibility as well as site capacity will be reviewed by the site Investigator and the study Medical Monitor prior to screening. Each site is also evaluated for the capacity to perform remote safety monitoring. During the time that the COVID-19 pandemic is active, it will be important to capture specific information in the eCRF that explains the reason for missing data (eg, missed study visits or participant study discontinuations due to COVID-19).

Abbreviations: COVID-19 = coronavirus disease 2019; eCRF = electronic case report form

10.11. COVID-19 Vaccine Risk Assessment

Following a review of the available COVID-19 vaccine data (eg, Pfizer/BioNTech, Moderna, AstraZeneca, and Johnson & Johnson), it is unlikely that the immune response to a COVID-19 vaccine (and therefore the efficacy of the vaccination) would be diminished with concomitant ALXN1910 administration, based on ALXN1910's mechanism of action. There is currently no information available evaluating the safety and efficacy of COVID-19 vaccines in participants treated with ALXN1910.

Local and national guidelines should be consulted for recommendations related to COVID-19 vaccination. Alexion suggests that participants complete vaccination series before study participation, if feasible.

The potential risks identified and mitigation measures put in place in light of the COVID-19 vaccination rollout are provided in Table 13.

Table 13: Potential Risks and Mitigation Measures due to COVID-19 Vaccine

Risks Category	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential risks		
Data quality and integrity	Missing data due to appointments for COVID-19 vaccination or side effects of COVID-19 vaccine may impact study visit schedules and increase missed visits and/or participant study discontinuations, inadvertently resulting in missing data (eg, for protocol-specified procedures).	Capture specific information in the eCRF that explains the reason for missing data (eg, missed study visits due to appointments for COVID-19 vaccination or side effects of COVID-19 vaccine).

Abbreviations: COVID-19 = coronavirus disease 2019; eCRF = electronic case report form

10.12. Abbreviations

The following abbreviations and terms are used in this study protocol.

Table 14: Abbreviations and Specialist Terms

Abbreviation or Term	Explanation
ADA	antidrug antibody
AE	adverse event
AFF	atypical femoral fracture
ALP	alkaline phosphatase
ALS	advanced life support
ALT	alanine aminotransferase
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	coronavirus disease 2019
CRU	clinical research unit
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ED85	effective dose in 85% of the treated population
EMA	European Medicines Agency
EOS	end of study
ERT	enzyme replacement therapy
EU	European Union
F	absolute bioavailability
Fc	fragment crystallizable
FIH	first-in-human
FSH	follicle-stimulating hormone
GDS	Global Drug Safety
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GTP	Guanosine triphosphate
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
HPP	hypophosphatasia
HRT	hormonal replacement therapy
HV	healthy volunteer
IAR	injection/infusion-associated reaction
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG	immunoglobulin G
ILS	immediate life support

Abbreviation or Term	Explanation
IRB	institutional review board
ISR	injection/infusion site reaction
IV	intravenous(ly)
MABEL	minimum anticipated biological effect
MAPK	mitogen-activated protein kinase
NAb	neutralizing antibody
NCI	National Cancer Institute
NF1	neurofibromatosis type-1
NOAEL	no-observed-adverse-effect level
PA	pyridoxic acid
PD	pharmacodynamic(s)
Pi	inorganic phosphate
PK	pharmacokinetic(s)
PL	pyridoxal
PLP	pyridoxal-5′-phosphate
Pop-PK	population pharmacokinetic(s)
PPi	inorganic pyrophosphate
PT	Preferred Term
QT	interval between the start of the Q wave and the end of the T wave in an ECG
QTc	corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
QTL	quality tolerance limit
Ras	rat sarcoma virus family of related proteins
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
SoA	schedule of activities
SOC	System Organ Class
SRC	Safety Review Committee
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
t_{max}	time to maximum observed serum concentration
TNSALP	tissue nonspecific alkaline phosphatase
ULN	upper limit of normal
UK	United Kingdom
WOCBP	woman of childbearing potential

10.13. Protocol Amendment History

The protocol amendment summary of changes table for the current amendment is located directly before the Table of Contents.

DOCUMENT HISTORY	
Document	**Date**
Protocol Amendment 3	27 Jul 2022
Protocol Amendment 2	20 Apr 2022
Protocol Amendment 1	27 Jan 2022
Original protocol	06 Dec 2021

Amendment 2 (20 Apr 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and any applicable local regulations.

Overall Rationale for the Amendment

The main reasons for this amendment were to include an ECG assessment on the day of Screening, to add assessments to the clinical laboratory tests, and to clarify the timing of other assessments (brief physical examination, COVID-19 testing, hepatitis B testing). Changes implemented in Administrative Change Letter No.1 (15 Feb 2022), as well as some clarifications to wording and minor administrative changes, were also made.

Changes to the protocol are detailed below.

Section	Description of Change	Brief Rationale and/or Clarification
1.1 Synopsis	A paragraph on SRC Review Committee was deleted.	To eliminate redundancy.
1.3 Schedule of Activities, Table 2	Addition of ECG assessment on the day of screening.	Correction of Table 2 to align with Section 5.1 Inclusion Criteria.
1.3 Schedule of Activities, Table 2, Footnote k	Addition of text to stating that a brief physical examination will be conducted on Day 5 prior to discharge from the CRU.	To clarify when the brief physical examination will be performed on Day 5.
1.3 Schedule of Activities, Table 2, Footnote m 1.3 Schedule of Activities, Table 3, footnote d 8.2.3 Electrocardiograms 9.4.1 Safety Analyses	Addition of text stating the ECG should not be performed within 1 hour after any major meal.	To clarify the time period within which an ECG must not be measured after a major meal.
2.4.1.1 Coronavirus Disease	Correction to state that COVID-19 testing will be performed at Screening and “prior to admission”.	To clarify that COVID-19 testing will also be done prior to admission to the CRU.
5.2 Exclusion Criteria	Addition of text stating hepatitis B testing (evidenced by HBsAg, HBcAb and HBsAb) will be done at Screening. Removal of testing algorithm if HBsAg is negative.	To clarify and streamline how hepatitis B testing will be performed.

Section	Description of Change	Brief Rationale and/or Clarification
	Revised text in Exclusion Criteria # 27.	To clarify smoking is not allowed from 2 hours before admission through discharge from the CRU for both inpatient and outpatient visits.
5.5 Screening Failures 10.1.3 Informed Consent Process	Modified to state rescreened participants are required to sign a new ICF.	To clarify all participants who are rescreened are required to sign a new ICF.
6.3 Measure to Minimize Bias: Randomization and Blinding	Removal of text indicating files and envelopes containing study intervention assignment to each participant will be used. Deleted text stating SRC may be unblinded at summary level.	To clarify that study intervention assignment will be provided in a secured manner to the Investigator, without stating the format, because it may not be within envelopes. Corrections. SRC will not be unblinded.
6.6 Dose Modification	Revised text to indicate "mean" projected PK exposure should not exceed 50% of NOAEL exposure.	Revised for clarity.
6.6 Dose Modification, Table 8	Removal of text stating that at least 6 of each cohort will have received active treatment.	To ensure maintaining blind during dose escalation meeting.
8.2.3 Electrocardiograms	Removal of text stating that participants should rest for 5 minutes after each ECG measurement.	To clarify that no resting is required post ECG.
10.1.1 Regulatory and Ethical Considerations and 10.1.10 Good Clinical Practice Compliance	Modified text to remove specific reference to regional guidance and listed as examples only. Inclusion of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use as example.	To include a more general statement as not all regional guidances previously included are applicable.
10.2 Clinical Laboratory Tests, Table 10	Added the following parameters: white blood cell count, hemoglobin, mean corpuscular hemoglobin concentration, neutrophils, lymphocytes, eGFR. Added footnotes regarding HbA1c and eGFR and deleted glycated hemoglobin from the table. Removed erythrocytes and % of reticulocytes.	To further ensure participant safety.
Overall	Minor administrative changes.	For clarity.

Abbreviations: COVID-19 = coronavirus disease 2019; CRU = clinical research unit; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EU-CTR = European Union Clinical Trial Register; HbcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; ICF = informed consent form; NOAEL = no-observed-adverse-effect level

Amendment 1 (27 Jan 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and any applicable local regulations.

Overall Rationale for the Amendment

This protocol has been amended in response to queries raised by the UK MHRA regarding the inclusion of Japanese participants, wording on stopping rules, and the definition of abnormal laboratory findings.

In addition, a correction was made to the time that participants are required to be in the supine position prior to ECG timepoints, to align within the protocol.

Changes to the protocol are detailed below.

Section	Description of Change	Brief Rationale and/or Clarification
2.1 Study Rationale 4.1 Overall Design	Rationale included for the inclusion of Japanese participants in the study.	To clarify that Japanese participants have been included in the study to meet regulatory requirements of the ICH Guidance E5(R1), which provides a general framework for evaluating the potential impact of ethnic factors on the acceptability of foreign clinical data, with the underlying objective of minimizing duplication of clinical data, and it also describes the requirement of bridging studies for extrapolation of foreign clinical data to a new region.
7.1 Discontinuation of Study Intervention	Removal of "Individual Stopping Rules" from the section title, which previously read "Discontinuation of Study Intervention/Individual Stopping Rules". The following text has also been removed from the section: As each participant will receive 1 SC or IV dose in this study, discontinuation of study intervention/individual stopping rules apply only to participants who receive the IV dose.	To clarify that as this is a single dose study, individual stopping rules do not apply.
8.2.3 Electrocardiograms	The time that participants should be in the supine position before each ECG timepoint has been changed from 15 to 10 minutes.	To align with footnote m of Table 2, Schedule of Activities, which states 10 minutes before the ECG time point
8.2.4 Clinical Safety Laboratory Assessments	Removal of text stating that clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.	Removed because the study is conducted in healthy participants, not participants with a disease. All abnormal laboratory results will be considered clinically significant.

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