TITLE PAGE

Protocol Title:

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

Protocol Number: ALXN1850-HPP-101

Amendment Number: 5

Compound: ALXN1850

Study Phase: Phase 1

Short Title: Safety and Tolerability, Pharmacokinetic, and Pharmacodynamic Study of ALXN1850 in Participants with Hypophosphatasia (HPP)

Sponsor Name: Alexion Pharmaceuticals, Inc.

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Regulatory Agency Identifier Number(s)

NCT: NCT04980248

Approval Date:

Amendment 5	10 Mar 2022
Amendment 4	27 Oct 2021
Amendment 3	14 May 2021
Amendment 2	31 Mar 2021
Amendment 1	02 Feb 2021
Original protocol	12 Nov 2020

Sponsor Signatory:

[redacted]

11-Mar-2022 | 14:46:44 EST

Date

Medical Monitor Name and Contact Information will be provided separately.

INVESTIGATOR'S AGREEMENT

I have read the study Protocol Amendment 5 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.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 5 (10 Mar 2022)

This amendment is considered substantial according to 21 CFR part 312.30(b) and any applicable local regulations.

Overall Rationale for the Amendment

The protocol has been amended to address the recommendation from the FDA to clarify that if the initial triplicate ECG results are abnormal (Exclusion Criterion 5; both additional ECG triplicates must be normal for a participant to be enrolled in the study). Clarifications have also been added regarding the urine pregnancy test, physical examinations, exclusion criteria relating to GFR and eGRF, classification of infusion site reactions, and to the Schedules of Activities.

In addition, changes made in Administrative Change Letter 4 (dated 17 Nov 2021) have been incorporated into this amendment.

Changes to the protocol in Amendment 5 are detailed below.

Section	Description of Change	Brief Rationale and/or Clarification
Section 1.1 Synopsis, Intervention Groups and Duration	Revised the Screening duration from 6 to 8 weeks, bringing the total study duration for each participant to **22.5** ~~22.1~~ weeks.	To enable sufficient time for all screening procedures to be performed. The current health crisis sometime leads to delays in assays and tests, an extra 2 weeks are necessary to ensure enrollment and timely Screening
Section 1.1 Synopsis, Overall Design Section 4.1 Overall Design Section 6.6 Dose Modification	Deleted the "4" so that the sentence reads "remaining number of participants"	The 4 was removed, because there may be more than 4 remaining participants in a cohort.
Section 1.1 Synopsis, Number of Participants	Added "approximately" to the number of participants per cohort	To reflect that approximately 5 participants will be enrolled in each cohort.
Section 1.2 Schema	Revised the schema to reflect that Screening starts on Day -56.	To correct the start of Screening from Day -42 to Day -56.
Section 1.3 Schedule of Activities, Table 1 and Table 2	Revised the SoA tables to reflect that a urine pregnancy test is required on Day -1.	To enable a pre-dosing urine pregnancy test to be performed closer to dosing, rather than just during Screening. This change is also consistent with the urine pregnancy test performed on other pre-dosing days.
	Revised the SoA tables to reflect that urine PEA is optional. Optional collections were added to Screening and End of Treatment Visit (Day 65 for first participant in a cohort, Day 57 for all others).	Although PEA is a substrate of TNSALP, it is still an exploratory endpoint, because it is not known if it is correlated with clinical safety or efficacy. Due to logistical challenges at different sites in obtaining results for these samples, this assessment was changed to optional. Two additional collections were added to increase the sampling at sites.

Section	Description of Change	Brief Rationale and/or Clarification
	Added visits for the abbreviated physical examination and added a footnote to clarify that the predose and postdose abbreviated physical examinations are allowed at the predose or dosing day, and on the day after dosing or 2 days after dosing, depending on when the participant is admitted and discharged.	To align with the site's requirement to perform a physical examination when participants are admitted and discharged for each of the inpatient periods of the study.
	Added the visit window of ±1 day for the first participant's Day 36 visit and subsequent participants' Day 29 visit.	The window was mistakenly removed in Protocol Amendment 4.
	In the footnote for ophthalmological and renal assessments, the timeframe during which, if a potential participant is rescreened, ophthalmological and renal assessments do not need to be performed again, changed from 6 months to 12 months between each test and enrollment.	In clinical practice these tests are only done once per year. Since there will not be any IP exposure for the participant since the initial screening, the tests can still be considered baseline for re-screens.
	Changed "PCP result" to **drug screen**. Removed "3-5 days" from the footnote for drug screening. A negative ~~PCP result~~ **drug screen** ~~at Screening~~ is required for participant enrollment. **Table 1 only text**: Drug screens collected at timepoints prior to dosing (Days -1, 14, 21, 28) are not required to confirm a negative drug screen prior to dosing. The ~~PCP~~ **drug screen** results ~~are~~ received ~~3–5 days~~ after sampling will be noted, and if positive, the participant will be discontinued from the study. **Table 2 only text**: : Drug screens collected at timepoints prior to dosing (Days -1, 7, 14, 21) are not required to confirm a negative drug screen prior to dosing. The ~~PCP~~ **drug screen** results ~~are~~ received ~~3–5 days~~ after sampling will be noted, and if positive, the participant will be discontinued from the study.	The drug screen test panel includes additional screening for other drugs besides PCP. Also removed the duration for receipt of drug screen results, because the turnaround time for results is variable.
	Updated the numbering of footnotes.	Footnotes renumbered to take into account addition and deletion of footnotes.
Section 1.3 Schedule of Activities, Table 1 and Table 2 Section 8.2.2 Vital Signs	Deleted text relating to assessment of orthostatic hypotension.	Criterion relating to orthostatic hypotension was removed in Protocol Amendment 4; therefore, text relating to assessment of orthostatic hypotension should also have been removed.
Section 1.3 Schedule of Activities, Table 3	Revised footnote "c" to state that at least the last of the 3 predose triplicate 12-lead ECGs will be performed within half an hour prior to dosing.	To clarify that at least the last of the 3 predose triplicate ECGs will be performed within half an hour prior to dosing, rather than exactly at 30 minutes prior to dosing.

Section	Description of Change	Brief Rationale and/or Clarification
Section 4.3 Justification for Dose, Table 5	Revised N from 4 to 5.	To correct the N from 4 to 5.
Section 5.1 Inclusion Criteria	Revised inclusion criterion 2b to add "at Screening" so that it reads as follows: Serum ALP level below the laboratory age- and sex-adjusted normal range **at Screening.**	To clarify that the value for serum ALP is the value at Screening, rather than historical ALP values.
Section 5.2 Exclusion Criteria	Revised Exclusion Criterion 5 to clarify that if the results of the first triplicate ECG are abnormal, both subsequent ECG triplicates must be normal. In addition, reference to vital signs has been removed.	Revised as per a request by the US FDA for clarification. Removal of the reference to vital signs was because the vital signs criterion was removed in Protocol Amendment 4.
	Revised Exclusion Criterion 13 to clarify that this criterion is only required for patients with a history of asfotase alfa use.	Revised for clarity and alignment with SoA.
	Revised exclusion criterion 18 to state eGFR instead of GFR and removal of the term "renal insufficiency".	Based on the following FDA guidance, this study will utilize the eGFR for evaluation of renal function: "There are different ways to assess renal function. Measurement of the GFR provides a more accurate assessment of renal function than estimating equations. However, these methods are not routinely used in clinical practice and estimation of renal function using a widely accepted serum creatinine-based equation is usually sufficient for PK studies."
	Deleted exclusion criterion 19.	Removed as exclusion criterion 18 relates to eGFR. It is not necessary to have both GFR and eGFR tests because they measure the same parameter. eGFR is an estimate of the GFR and requires only a blood sample to perform.
	Deleted "or > 1.5 × ULN of the reference range of the testing laboratory on Day -1" from Exclusion Criterion 21 (formerly Exclusion Criterion 22): • Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > ULN of the reference range of the testing laboratory at Screening ~~**or > 1.5 × ULN of the reference range of the testing laboratory on Day -1**~~"	The value required to pass Screening is more stringent, so the Day -1 assessment is not needed.
Section 5.4 Screen Fails	Removed the restriction of one-time rescreening.	Removed restriction on one-time rescreening to allow participants to be enrolled if the eligibility criteria are met as described in this amendment of the protocol.

Section	Description of Change	Brief Rationale and/or Clarification
Section 7.2 Participant Discontinuation/ Withdrawal from the Study	Removal of "or completes it out of window" from the following: • If a participant misses a dosing visit ~~**or completes it out-of-window**~~, they do not need to be withdrawn or discontinued from treatment or the study; however, they will not be considered "completed" even if they continue on to complete the end-of-treatment assessments. These participants should be replaced unless at least 3 participants in their cohort have already "completed" or are on track to "complete.	Removed because participants cannot make up a missed dose. Therefore, dosing visits should not be conducted out of window.
Section 8.2.3.1 Safety Review of 12-lead Electrocardiograms	Removed of reference to Holter	Holter was removed in Protocol Amendment 4.
Section 8.3.6.1 Injection/Infusion Site Reactions	Removed Infusion site reactions from section. Added/deleted text as follows: Deleted text in ~~strikethrough~~, new text in **bold**. ~~Antibodies have been associated with injection/infusion reactions, with onset typically during or shortly after completion of the injection/infusion. For this reason, participants will be carefully observed during each injection/infusion.~~ ~~Injection/infusion site reactions are defined as AEs localized to the site of IV or SC route of study drug administration, occurring at any time during study participation that are assessed by the Investigator to be related to study drug.~~ **Injection site reactions (ISRs) are defined as AEs localized to the site of study drug administration that occur at any time during study participation that are assessed by the Investigator as possibly, probably, or definitely related to study drug. AE intensity reporting procedures are outlined in Section 10.3.4.** **Injection site reactions may occur at any timepoint after study drug administration. There is no additional laboratory testing required for ISRs. The Investigator is responsible for monitoring for ISRs in patients throughout the duration of the study. As part of the study-required physical examinations, Investigators should evaluate injection sites for signs of reaction(s).**	To clarify descriptions of and symptoms associated with the severity of injection site reactions and to provide cross reference to section of protocol describing reporting of AEs and SAEs.

Section	Description of Change	Brief Rationale and/or Clarification
Section 8.3.6.2 Injection/Infusion-associated Reactions	Removed Infusion site reactions from section. Removed reference to IV administration. Added following sentence as final sentence in the section: **AE intensity reporting procedures are outlined in Section 10.3.4.**	To clarify for this study, as drug will be administered SC only, and to provide cross reference to section of protocol describing reporting of AEs and SAEs.
Section 8.6 Pharmacodynamics	Whole blood samples will be collected for measurement of PLP/PL, **PA**, and PPi.	Addition of PA to PLP/PL and PPi
Section 10.2 Clinical Laboratory Tests	Calcium, calcium/creatinine have been removed from routine urinanalysis	Calcium and calcium/creatinine are not part of a routine urinalysis. However, they assessed via a separate collection, and the table has been updated for clarity.
All	Minor edits to wording.	For clarification and consistency.

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; CTCAE = Common Terminology Criteria for Adverse Events; electrocardiogram ECG = electrocardiogram; (e)GFR = (estimated) glomerular filtration rate; FDA = Food and Drug Administration; ISR = injection site reaction; IV = intravenous; PA = pyridoxic acid; PCP = phencyclidine PD = pharmacodynamics(s); PEA = phosphoethanolamine; PK = pharmacokinetic(s); PL = pyridoxal; PLP = pyridoxal-5'-phosphate; PPi = inorganic pyrophosphate; SAE = serious adverse event; SoA = Schedule of Assessments; SC = subcutaneous; TNSALP = tissue non-specific isoenzyme of alkaline phosphatase; ULN = upper limit of normal

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1. PROTOCOL SUMMARY

1.1. Synopsis

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

Short Title: Safety and Tolerability, Pharmacokinetic, and Pharmacodynamic Study of ALXN1850 in Participants with Hypophosphatasia (HPP)

Rationale:

Hypophosphatasia (HPP) is a rare, inherited, metabolic disease caused by deficient activity of the tissue non-specific isoenzyme of alkaline phosphatase (TNSALP), typically due to loss-of-function mutation(s) in the *ALPL* gene. 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. Asfotase alfa (STRENSIQ®) is currently the only approved treatment for patients with pediatric-onset HPP. ALXN1850 is an investigational enzyme replacement therapy (ERT) that addresses the underlying cause of HPP by replacing the defective enzyme, thus reversing the mineralization defects of the skeleton and improving systemic manifestations of HPP. ALXN1850 is a human recombinant TNSALP-fragment crystallizable (Fc)-deca-aspartate fusion protein. It is a soluble glycoprotein comprised of 2 polypeptide chains of 724 amino acids made from the catalytic domain of human TNSALP (SwissProt, P05186), the human immunoglobulin (Ig) G2/4 Fc domain (SwissProt P01859 and Genebank K01316; to facilitate purification and extend half-life), and a deca-aspartate peptide (to target the bone).

The purpose of this first-in-human (FIH), open-label, dose-escalating study is to assess the safety and tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) parameters and immunogenicity of ALXN1850 when given intravenously (IV) and subcutaneously (SC) to adult participants with HPP. This FIH study is designed to support an efficient and tolerable pharmacologically effective dose in participants with HPP for whom ALXN1850 has been designed to deliver the required enzyme with less frequent SC administration than asfotase alfa, and therefore reduce the burden of treatment for this group of patients.

Objectives and Endpoints

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

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

Overall Design

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

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

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

Disclosure Statement: This is a sequential dose-escalating treatment study with 3 cohorts that is open-label.

Number of Participants: Approximately 15 eligible participants (approximately 5 in each Cohorts 1, 2, and 3), will be enrolled to allow for at least 9 participants (3 per cohort) to "complete" (ie, participant completed EoT assessments, all PK/PD sampling was performed within window, and all doses were received per the SoA). Participants who withdraw/are

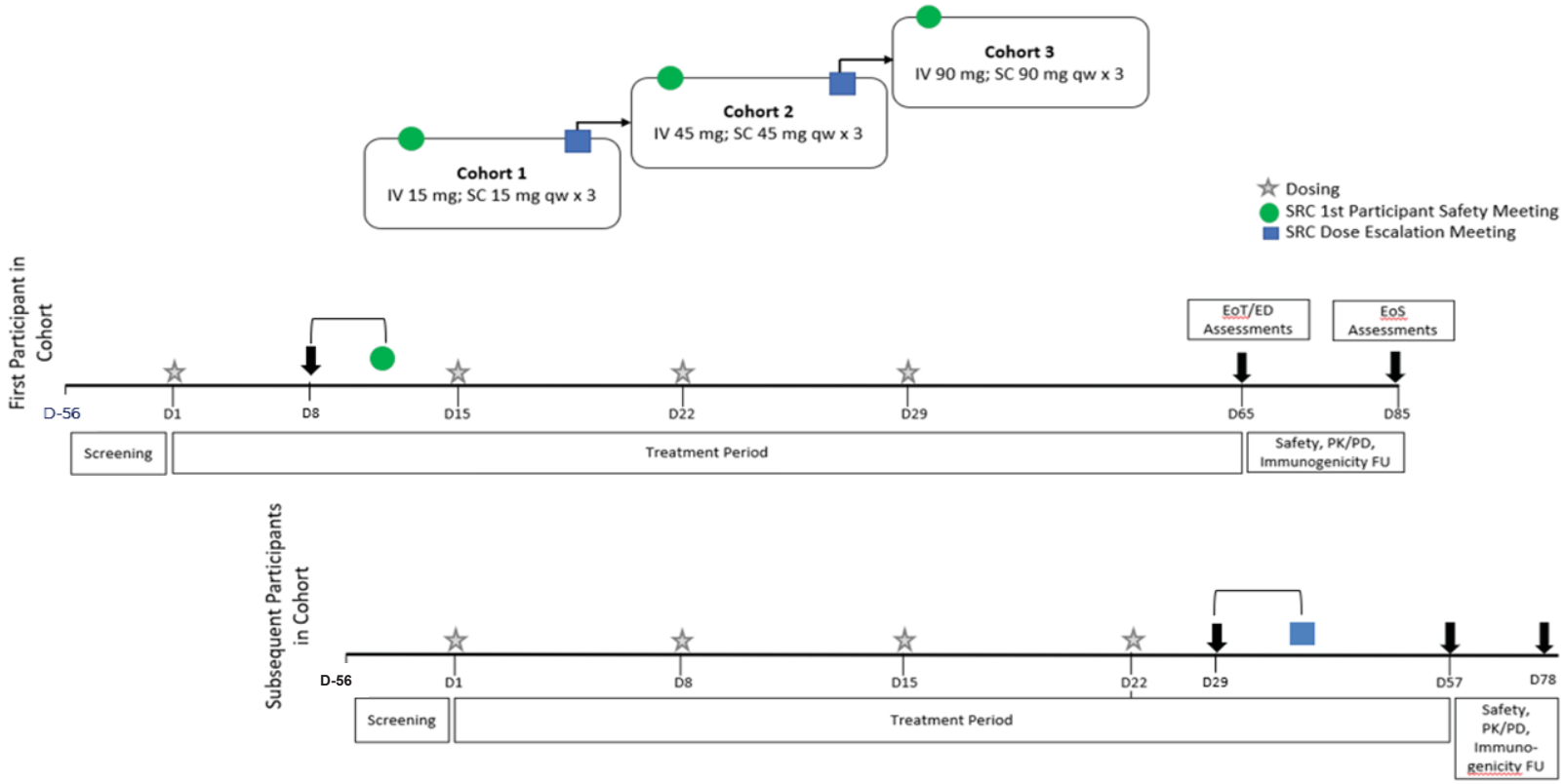
withdrawn from the study after "completion" but before the EoT Visit do not need to be replaced unless at least 3 participants in their cohort have "completed" or are on track to "complete".

Intervention Groups and Duration: The planned study duration for each participant is up to 22.5 weeks (approximately 5 months) in total: up to 8 weeks for Screening, 71 days for first participants and 63 days for subsequent participants for the Treatment Period, and 34 days for the post-dosing Follow-up Period to further monitor safety/tolerability, PK/PD, and immunogenicity. Dosing will be staggered within and between cohorts. The end of study is anticipated to be Day 85 (-7/+14 days) for the first participant in each cohort and Day 78 (-7/+14 days) for subsequent participants in each cohort.

Safety Review Committee: A SRC will assess all available data and will provide recommendations for cohort clearance and dose escalation decisions.

1.2. Schema

Figure 1: Study Schema



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

1.3. Schedule of Activities

Assessment details can be found in the following SoA tables: Study Overview for the First Participant in Each Cohort (Table 1), Study Overview for Subsequent Participants in Each Cohort (Table 2), and Each Dosing Day for All Participants (Table 3).

Table 1: Schedule of Activities - Study Overview for the First Participant in Each Cohort

Assessments	Screening		Treatment Period																			EoT/ED Assessment	FU/ EoS Assessment
Inpatient (I) or Outpatient (O)[a]	O	I/O	I	I	I/O	O	O	I/O	I	I	I/O	O	I/O	I	I	I/O	I	I	I/O	O	O	O	O
Study Day	-56 to -2	-1	1	2	3	5	8	14	15	16	17	19	21	22	23	28	29	30	31	36	51	65	85
Permitted Day(s) Window						±1	± 1					± 1								± 1	± 3	-3/ +7	-7/ +14
Hours postdose[b]			IV Dosing Day (See Table 3)	24	48	96	168		SC Dosing Day (See Table 3)	24	48	96		SC Dosing Day (See Table 3)	24		SC Dosing Day (See Table 3)	24	48	168			
Informed consent[c]	X																						
Inclusion/ Exclusion Criteria	X	X																					
Medical history	X																						
Demographics	X																						
Genetic testing (*ALPL* gene mutation)[d]	X																						
25-OH vitamin D	X																						
Hepatitis B and C screen	X																						
HIV (Types 1 and 2) screen	X																						
FSH test[e]	X																						
Weight	X	X						X					X			X							
Height and BMI	X																						
Alcohol test	X																						
Urine drug screen[f]	X	X						X					X			X							
Serum pregnancy test[g]	X																						
Urine pregnancy test[g]		X	IV D					X	S C				X	S C		X	S C			X	X	X	X

Table 1: Schedule of Activities - Study Overview for the First Participant in Each Cohort

Assessments	Screening		Treatment Period																			EoT/ED Assessment	FU/ EoS Assessment
Inpatient (I) or Outpatient (O)[a]	O	I/O	I	I	I/O	O	O	I/O	I	I	I/O	O	I/O	I	I	I/O	I	I	I/O	O	O	O	O
Study Day	-56 to -2	-1	1	2	3	5	8	14	15	16	17	19	21	22	23	28	29	30	31	36	51	65	85
Permitted Day(s) Window						±1	± 1					± 1								± 1	± 3	-3/ +7	-7/ +14
Hours postdose[b]				24	48	96	168			24	48	96			24			24	48	168			
Full PE	X																						
Abbreviated PE[h]		X		X	X			X		X	X		X		X	X		X	X				
Vital sign measurements	X			X	X	X	X			X	X	X			X			X	X	X	X	X	X
Ophthalmological examination[i]	X																					X	
Renal ultrasound[i]	X																					X	
Glycated hemoglobin (HbA1c)	X																						
Hematology labs (except HbA1c)	X	X		X			X	X		X			X		X	X		X		X		X	
Chemistry labs	X	X		X			X	X		X			X		X	X		X		X		X	
Coagulation labs	X	X		X			X	X		X			X		X	X		X		X		X	
Urinalysis	X	X		X			X	X		X			X		X	X		X		X		X	
PK[j]				X	X	X	X			X	X	X			X			X	X	X	X	X	X
PD (PPi, PLP, PL, PA)[j]			IV Dosing Day/Sca	X	X	X	X		SC Dosing Day/Sca	X	X	X		SC Dosing Day/Sca	X		SC Dosing	X	X	X	X	X	X
Bone biomarkers (sCTX, P1NP, osteocalcin)																				X		X	X

Table 1: Schedule of Activities - Study Overview for the First Participant in Each Cohort

Assessments	Screening		Treatment Period																			EoT/ED Assessment	FU/ EoS Assessment
Inpatient (I) or Outpatient (O)[a]	O	I/O	I	I	I/O	O	O	I/O	I	I	I/O	O	I/O	I	I	I/O	I	I	I/O	O	O	O	O
Study Day	-56 to -2	-1	1	2	3	5	8	14	15	16	17	19	21	22	23	28	29	30	31	36	51	65	85
Permitted Day(s) Window						±1	± 1					± 1								± 1	± 3	-3/ +7	-7/ +14
Hours postdose[b]				24	48	96	168			24	48	96			24			24	48	168			
Blood for PTH	X																			X			
Immunogenicity test (ALXN1850 ADA and NAb)[k]							X													X	X	X	X
Immunogenicity test (asfotase alfa ADA and NAb)[k]	X																						
CRIM (Day 1 only)																							
Urine for calcium, phosphorus, and creatinine		X		X	X		X			X	X				X			X	X	X			
Urine PEA (optional)	X	X		X	X		X			X	X				X			X	X	X		X	
12-lead ECG[l]	X			X	X	X	X			X	X	X			X			X	X	X		X	
ALXN1850 administration																							
Injection/ infusion site evaluation[m]				X	X		X			X	X				X			X	X	X			
Hypersensitivity rxn monitoring			←Monitor continually after 1st dose→																				

Table 1: Schedule of Activities - Study Overview for the First Participant in Each Cohort

Assessments	Screening		Treatment Period																			EoT/ED Assessment	FU/ EoS Assessment
Inpatient (I) or Outpatient (O)[a]	O	I/O	I	I	I/O	O	O	I/O	I	I	I/O	O	I/O	I	I	I/O	I	I	I/O	O	O	O	O
Study Day	-56 to -2	-1	1	2	3	5	8	14	15	16	17	19	21	22	23	28	29	30	31	36	51	65	85
Permitted Day(s) Window						±1	± 1					± 1								± 1	± 3	-3/ +7	-7/ +14
Hours postdose[b]				24	48	96	168			24	48	96			24			24	48	168			
Hypersensitivity rxn labs (tryptase, IgE, C5b-9)[n]			←See footnote [m] →																				
Concomitant medications	← Monitor continually after ICF is signed →																						
Adverse events review/evaluation	← Monitor continually after ICF is signed →																						

Note: Participants who complete the EoT assessments but withdraw/are withdrawn prior to completion of the end-of-study assessments will be considered "completed" and do not require replacement if they completed all prior PK/PD sampling within window and received all doses per the SoA. Participants who withdraw/are withdrawn prior to the end-of-treatment visit should have the end-of-treatment assessments performed, if possible, and will be replaced unless 3 participants in their cohort have already "completed" or are on track to "complete".

[a] Visits designated "I/O" may be performed Inpatient or Outpatient at the Investigator's discretion.

[b] All postdose timepoints are relative to the start of the IV infusion/time of the SC injection (ie, Time 0) except the vital signs measurements, PK and PD sample, and infusion site evaluation performed/collected at the EoI (see Table 3).

[c] Signed and dated IEC-approved ICF must be obtained before any study-specific screening procedures are performed.

[d] If available, historical results are acceptable, and a confirmatory test is not required.

[e] Female participants who claim postmenopausal status will have an FSH test to confirm status.

[f] A negative drug screen is required for participant enrollment. Results from drug screens collected at timepoints prior to dosing (Days -1, 14, 21, 28) are not required to confirm a negative result prior to dosing. The drug screen results received after sampling will be noted, and if positive, the participant will be

discontinued from the study. If negative, the results will serve as clearance to proceed with dosing for future pre-dosing days. A positive drug test result for a non-prescribed substance received at any visit will lead to discontinuation

[g] Pregnancy test must be performed on all participants of child-bearing potential at the specified time points. Additional pregnancy tests may also be performed at any time at the Investigator's discretion.

[h] Predose and postdose abbreviated PEs are allowed at the predose or dosing day, and on the day after dosing or 2 days after dosing, depending on when the participant is admitted and discharged.

[i] If a potential participant is rescreened, these assessments do not need to be performed again unless more than 12 months will have elapsed between each test and enrollment.

[j] A window of ± 30 minutes from each time point is permitted for PK/PD timepoints except the PK sample collected at end of infusion (+ 15 minutes). Predose PK/PD windows are -1 hour (SC doses) and 3 hours (IV dose). For all assessments, their window and the visit window should not be calculated together to determine the permitted assessment time.

[k] Asfotase alfa ADA and NAb will only be tested in participants who have previously received asfotase alfa. Participants do not need to be retested for ADAs and NAbs if they are re-screened.

[l] Each 12-lead ECG will be performed in triplicate (sequentially within a 15-minute period) and should not be assessed after any major meal (ie, major meals should be withheld until after ECG assessments). All ECGs should be performed before the vital signs assessment and PK/PD sampling (in that order if 1 or both of the latter are also scheduled during an ECG timepoint). Each ECG shown in this table has a window of ± 30 minutes.

[m] Injection/infusion site evaluations will be performed within 15 minutes (± 5 minutes) after injection/EoI and ± 15 minutes of the rest of the timepoints.

[n] If the participant is in the clinic, collect the first sample ASAP (preferred) or within 1 hour of the suspected hypersensitivity reaction. The 2 subsequent samples also have a permitted + 1 hour window. If the participant is not in the clinic, these samples do not need to be collected and suspected hypersensitivity reaction will be reported as an AE only. If the suspected hypersensitivity reaction persists beyond 8 hours, the CRU should contact the MM for guidance.

Abbreviations: ADA = antidrug antibody; AE = adverse event; ALPL = alkaline phosphatase; ASAP = as soon as possible; BMI = body mass index; C5b-9 = terminal complement complex C5b-9; CRIM = cross-reactive immunological material; CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; EoI = end of infusion; EoS = end-of-study; EoT = end-of-treatment; FSH = follicle stimulating hormone; FU = follow-up; HIV = human immunodeficiency virus; I = inpatient; ICF = informed consent form; IEC = Independent Ethics Committee; IgE = immunoglobulin E; IV = intravenous; MM = medical monitor; NAb = neutralizing antibody; O = outpatient; PA = pyridoxic acid; PCP = phencyclidine; PD = pharmacodynamics; PE =physical examination; P1NP = N-terminal propeptide of type I procollagen; PEA = phosphoethanolamine; PK = pharmacokinetics; PL = pyridoxal; PLP = pyridoxal 5′-phosphate; PPi = inorganic pyrophosphate; PTH = parathyroid hormone; rxn = reaction; CTX-1 (sCTX) = serum Ctelopeptide cross-link of type 1 collagen; SoA = schedule of activities; SC = subcutaneous.

Table 2: Schedule of Activities - Study Overview for Subsequent Participants in Each Cohort

Assessments	Screening		Treatment Period																		EoT Assessments	FU/ EoS
Inpatient (I) or Outpatient (O)[a]	O	I/O	I	I	I/O	O	I/O	I	I	I/O	O	I/O	I	I	I/O	I	I	I/O	O	O	O	O
Study Day	-56 to -2	-1	1	2	3	5	7	8	9	10	12	14	15	16	21	22	23	24	29	43	57	78
Permitted Day(s) Window						±1					±1								± 1	±3	-3/ +7	-7/ +14
Hours postdose[b]				24	48	96			24	48	96			24			24	48	168			
Informed consent[c]	X		IV Dosing Day (See Table 3)					SC Dosing Day (See Table 3)					SC Dosing Day (See Table 3)			SC Dosing Day (See Table 3)						
Inclusion/ Exclusion Criteria	X	X																				
Medical history	X																					
Demographics	X																					
Genetic testing (*ALPL* gene mutation)[d]	X																					
25-OH vitamin D	X																					
Hepatitis B and C screen	X																					
HIV (Types 1 and 2) screen	X																					
FSH test[e]	X																					
Weight	X	X					X					X			X							
Height and BMI	X																					
Alcohol test	X																					
Urine drug screen[f]	X	X					X					X			X							
Serum pregnancy test[g]	X																					
Urine pregnancy test[g]		X					X					X			X				X	X	X	X
Full PE	X																					
Abbreviated PE[h]		X		X	X		X		X	X		X		X	X		X	X				
Vital sign measurements	X		I V	X	X	X		S C	X	X	X			X		S C	X	X	X	X	X	X

Table 2: Schedule of Activities - Study Overview for Subsequent Participants in Each Cohort

Assessments	Screening		Treatment Period																		EoT Assessments	FU/ EoS
Inpatient (I) or Outpatient (O)[a]	O	I/O	I	I	I/O	O	I/O	I	I	I/O	O	I/O	I	I	I/O	I	I	I/O	O	O	O	O
Study Day	-56 to -2	-1	1	2	3	5	7	8	9	10	12	14	15	16	21	22	23	24	29	43	57	78
Permitted Day(s) Window						±1					±1								± 1	±3	-3/ +7	-7/ +14
Hours postdose[b]				24	48	96			24	48	96			24			24	48	168			
Ophthalmological examination[i]	X																				X	
Renal ultrasound[i]	X																				X	
Glycated hemoglobin (HbA1c)	X																					
Hematology labs (except HbA1c)	X	X		X			X		X			X		X	X		X		X		X	
Chemistry labs	X	X		X			X		X			X		X	X		X		X		X	
Coagulation labs	X	X		X			X		X			X		X	X		X		X		X	
Urinalysis	X	X		X			X		X			X		X	X		X		X		X	
PK[j]				X	X	X			X	X	X			X			X	X	X	X	X	X
PD (PPi, PLP, PL, PA)[j]				X	X	X			X	X	X			X			X	X	X	X	X	X
Bone biomarkers (sCTX, P1NP, osteocalcin)																			X		X	X
Blood for PTH	X																		X			
Immunogenicity test (ALXN1850 ADA and NAb)[k]																			X	X	X	X
Immunogenicity test (asfotase alfa, ADAs, and NAbs)[k]	X		IV Dosing					SC Dosing					SC Dosing			SC Dosing						
CRIM (Day 1 only)																						

SC Dosing Day (See Table 3)

Table 2: Schedule of Activities - Study Overview for Subsequent Participants in Each Cohort

Assessments	Screening		Treatment Period																		EoT Assessments	FU/ EoS
Inpatient (I) or Outpatient (O)[a]	O	I/O	I	I	I/O	O	I/O	I	I	I/O	O	I/O	I	I	I/O	I	I	I/O	O	O	O	O
Study Day	-56 to -2	-1	1	2	3	5	7	8	9	10	12	14	15	16	21	22	23	24	29	43	57	78
Permitted Day(s) Window						±1					±1								± 1	±3	-3/ +7	-7/ +14
Hours postdose[b]				24	48	96			24	48	96			24			24	48	168			
Urine for calcium, phosphorus, and creatinine		X		X	X				X	X				X			X	X	X			
Urine PEA (optional)	X	X		X	X				X	X				X			X	X	X		X	
12-lead ECG[l]	X			X	X	X			X	X	X			X			X	X	X		X	
ALXN1850 administration																						
Injection/infusion site evaluation[m]				X	X				X	X				X			X	X	X			
Hypersensitivity rxn monitoring			←Monitor continually after 1st dose→																			
Hypersensitivity rxn labs (tryptase, IgE, C5b-9)[n]			←See footnote[n] →																			
Concomitant medications	← Monitor continually after ICF is signed →																					
Adverse events review/evaluation	← Monitor continually after ICF is signed →																					

Note: Participants who complete the end-of-treatment assessments but withdraw/are withdrawn prior to completion of the end-of-study assessments will be considered "completed" and do not require replacement if they completed all prior PK/PD sampling within window and received all doses per the SoA. Participants who withdraw/are withdrawn prior to the end-of-treatment visit should have the end-of-treatment assessments performed, if possible, and will be replaced unless 3 participants in their cohort have already "completed" or are on track to "complete".

[a] Visits designated "I/O" may be performed Inpatient or Outpatient at the Investigator's discretion.

[b] All postdose timepoints are relative to the start of the IV infusion/time of the SC injection (ie, Time 0) except the vital signs measurements, PK and PD sample, and infusion site evaluation performed/collected at the EoI (see Table 3).

[c] Signed and dated IEC-approved ICF must be obtained before any study-specific screening procedures are performed.

[d] If available, historical results are acceptable, and a confirmatory test is not required.

[e] Female participants who claim postmenopausal status will have an FSH test to confirm status.

[f] A negative drug screen is required for participant enrollment. Results from drug screens collected at timepoints prior to dosing (Days -1, 7, 14, 21) are not required to confirm a negative result prior to dosing. The drug screen results received after sampling will be noted, and if positive, the participant will be discontinued from the study. If negative, the results will serve as clearance to proceed with dosing for future pre-dosing days. A positive drug test result a non-prescribed substance received at any visit will lead to discontinuation.

[g] Pregnancy test must be performed on all participants of child-bearing potential at the specified time points. Additional pregnancy tests may also be performed at any time at the Investigator's discretion.

[h] Predose and postdose abbreviated PEs are allowed at the predose or dosing day, and on the day after dosing or 2 days after dosing, depending on when the participant is admitted and discharged.

[i] If a potential participant is rescreened, these assessments do not need to be performed again unless more than 12 months will have elapsed between each test and enrollment.

[j] A window of ± 30 minutes from each time point is permitted for PK/PD timepoints except the PK sample collected at end of infusion (+ 15 minutes). Predose PK/PD windows are -1 hour (SC doses) and 3 hours (IV dose). For all assessments, their window and the visit window should not be calculated together to determine the permitted assessment time.

[k] Asfotase alfa ADA and NAb will only be tested in participants who have previously received asfotase alfa. Participants do not need to be retested for ADAs and NAbs if they are re-screened.

[l] Each 12-lead ECG will be performed in triplicate (sequentially within a 15-minute period) and should not be assessed after any major meal (ie, major meals should be withheld until after ECG assessments). All ECGs should be performed before the vital signs assessment and PK/PD sampling (in that order if 1 or both of the latter are also scheduled during an ECG timepoint). Each ECG shown in this table has a window of ± 30 minutes.

[m] Injection/infusion site evaluations will be performed within 15 minutes (± 5 minutes) after injection/EoI and ± 15 minutes of the rest of the timepoints.

[n] If the participant is in the clinic, collect the first sample ASAP (preferred) or within 1 hour of the suspected hypersensitivity reaction. The 2 subsequent samples also have a permitted + 1 hour window. If the participant is not in the clinic, these samples do not need to be collected and suspected hypersensitivity reaction will be reported as an AE only. If the suspected hypersensitivity reaction persists beyond 8 hours, the CRU should contact the MM for guidance.

Abbreviations: ADA = antidrug antibody; AE = adverse event; ALPL = alkaline phosphatase; ASAP = as soon as possible; BMI = body mass index; C5b-9 = terminal complement complex C5b-9; CRIM = cross-reactive immunological material; CRU = clinical research unit; ECG = electrocardiogramEoI = end of infusion; EoS = end-of-study; EoT = end-of-treatment; FSH = follicle stimulating hormone; FU = follow-up; HIV = human immunodeficiency virus; I = inpatient; ICF = informed consent form; IEC = Independent Ethics Committee; IgE = immunoglobulin E; IV = intravenous; MM = medical monitor; NAb = neutralizing antibody; O = outpatient; PA = pyridoxic acid; PCP = phencyclidine; PE =physical examination; P1NP = N-terminal propeptide of type I procollagen; PD = pharmacodynamics; PEA = phosphoethanolamine; PK = pharmacokinetics; PL = pyridoxal; PLP = pyridoxal 5′-phosphate; PPi = inorganic pyrophosphate; PTH = parathyroid hormone; rxn = reaction; CTX-1 (sCTX) = serum Ctelopeptide cross-link of type 1 collagen; SoA = schedule of activities; SC = subcutaneous

Table 3: Schedule of Activities – Each Dosing Day for All Participants

Assessments	**Each Dosing Day (Inpatient Visits)**								
Study Day (First Participant)	**Days 1, 15, 22, 29**								
Study Day for (Subsequent Participants)	**Days 1, 8, 15, 22**								
Day/Time	**Day 1 Only**	**Each Dosing Day**							
		Predose		**Dose**	**Postdose[a]**				
	Predose	**Per Window (if specified)**	**-0.5 hr**	**0 hr**	**EoI (IV Dose Only)**	**Every 15 min for 1st hr**	**2**	**6**	**12**
Admission to IP Unit[b]		X							
12-lead ECG (triplicate)[c]			X		X[d]		X	X	X
Vital signs measurements		X				X[e]	X	X	X
PK[f]		X			X[d]		X	X	X
PD (PPi, PLP, PL, PA) [f]		X			X[d]				
Bone biomarkers (sCTX, P1NP, osteocalcin)	X								
Immunogenicity testing (ALXN1850 ADA and NAb)		X							
CRIM assay	X								
ALXN1850 administration				X					
Injection/infusion site evaluation[g]				X	X	X	X	X	X
Abbreviated PE [h]		X							
Hypersensitivity reaction monitoring				←Monitor continually→					
Hypersensitivity reaction labs (tryptase, IgE, C5b-9, chemistry, hematology, and urinalysis)	X			← X[i]→					
Concomitant medications	←Monitor continually after ICF is signed→								
Adverse events review/evaluation	←Monitor continually after ICF is signed→								

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

[a] All postdose timepoints are relative to the start of the IV infusion/time of the SC injection (ie, time 0 hr) except the ECG, PK/PD sample, and infusion site evaluation performed/collected at the EoI (see footnote d).

[b] Only if the Investigator approves the day prior as an Outpatient Visit.

[c] Each 12-lead ECG will be performed in triplicate (sequentially within a 15-minute period) and should not be assessed after any major meal (ie, major meals should be withheld until after ECG assessments). At least the last of the 3 predose triplicate 12-lead ECG will be performed within half an hour prior to dosing. The ECGs at 2, 6, and 12 hours postdose have a window of ± 30 minutes.

[d] ECG and PK/PD (in that order) performed/collected at EoI (t_{max}) each have a window of + 15 minutes.

[e] Vital signs will be measured every 15 minutes for the first hour after dosing, with a window of ± 5 minutes. Other vital signs measurements have a window of ± 15 minutes.
[f] A window of ± 30 minutes from each postdose time point is permitted for all PK/PD timepoints except EoI. Predose PK/PD windows are -1 hour (SC doses) and -3 hours (IV dose).
[g] Injection/infusion site evaluations will be performed during the infusion, after I/EoI, and then within 15 minutes (+ 5 minutes) after I/EoI. The rest of the timepoints have a window of ± 15 minutes.
[h] Predose and postdose abbreviated PEs are allowed at the predose or dosing day, and on the day after dosing or 2 days after dosing, depending on when the participant is admitted and discharged.
[i] If a hypersensitivity reaction is suspected, samples should be collected as soon as possible (within 1 hour of the reaction) and again at 2 and 8 hours (+ 1 hour window each) after the 1st sample. The Day 1 predose sample will only be analyzed for participants with a reported suspected hypersensitivity reaction at any time following the first dose.

Abbreviations: ADA = antidrug antibody; C5b-9 = terminal complement complex C5b-9; CRIM = cross-reactive immunological material; ECG = electrocardiogram; EoI = end of infusion; hr = hour; ICF = informed consent form; IgE = immunoglobulin E; IV = intravenous; min = minutes; NAb = neutralizing antibody; PA = pyridoxic acid; P1NP = N-terminal propeptide of type I procollagen; PD = pharmacodynamics; PE = physical examination; PK = pharmacokinetics; PL = pyridoxal; PLP = pyridoxal 5′-phosphate; PPi = inorganic pyrophosphate; CTX-1 (sCTX) = serum Ctelopeptide cross-link of type 1 collagen; SC = subcutaneous; t_{max} = time to maximum observed plasma concentration

2. INTRODUCTION

2.1. Study Rationale

ALXN1850 is a human recombinant TNSALP-Fc-deca-aspartate fusion protein being developed as an investigational ERT to address the underlying cause of HPP by replacing the defective TNSALP enzyme. It is a soluble glycoprotein comprised of 2 polypeptide chains of 724 amino acids made from the catalytic domain of human TNSALP (SwissProt, P05186), the human Ig G2/4 Fc domain (SwissProt P01859 and Genebank K01316; to facilitate purification and extend half-life), and a deca-aspartate peptide (to target the bone). ALXN1850 is designed for SC administration. Nonclinical pharmacology, PK, and toxicology studies of ALXN1850 have been conducted to support the clinical testing of ALXN1850 in humans. The Phase 1 FIH study is designed to evaluate the safety, tolerability, PK, and PD of ALXN1850 when given IV and SC to adults with HPP.

This FIH study will enroll adult participants with HPP who have a confirmed mutation for the gene (*ALPL*) that encodes the enzyme TNSALP, resulting in the presence of decreased serum alkaline phosphatase (ALP) activity and elevated serum pyridoxine and inorganic pyrophosphate, which are the genetic and biochemical hallmarks of the disease. The characteristics of this population represent patients with HPP who currently do not require ERT but could qualify for future Phase 2 and Phase 3 studies, depending on the disease burden. This study has been designed to minimize risk to participants; it is a study with strict inclusion/exclusion criteria and there is a robust safety monitoring and risk mitigation plan in place to address potential safety and tolerability findings. Because of the potential for immunogenicity, this study will enroll participants with HPP who are not anticipated to require continued treatment with ERT, based on their signs and symptoms, and the Investigator's clinical assessment of their current condition.

ALXN1850 and asfotase alfa, the only approved treatment for HPP, have the same mechanism of action and address the underlying cause of HPP by replacing the defective enzyme, thus reversing the mineralization defects of the skeleton and improving systemic manifestations of HPP. ALXN1850 differs from asfotase alfa in the following ways: it is altered by an amino acid change to enhance substrate hydrolysis by its active site; its Fc domain is an IgG2/4, to improve half-life and bioavailability; 2 N-linked glycans have been removed from each TNSALP polypeptide chain via asparagine to glutamine mutations, and other enhancements to its glycan profile which should alter the PK of the active moiety and increase its exposure and half-life.

Currently, the recommended dosage regimen of asfotase alfa for the treatment of pediatric-onset HPP is 6 mg/kg per week administered SC as either 2 mg/kg 3 times per week, or 1 mg/kg 6 times per week. However, patients using asfotase alfa are burdened with a high rate of injection site reactions and an inconvenient administration frequency (3 to 6 times per week). ALXN1850 is a next-generation HPP therapy developed with the intent to deliver a molecule with equivalent potency and improved activity compared to asfotase alfa, providing higher exposure, longer half-life, and better bioavailability. These improvements may address current asfotase alfa limitations and support lower doses and longer dosing intervals. Patient experience is expected to improve by reducing injection volumes and dosing frequency, which may also translate to fewer injection site reactions and higher patient compliance.

2.2. Background

A detailed description of the chemistry, pharmacology, and toxicology data available for ALXN1850 is provided in the Investigator's Brochure (IB).

2.2.1. Hypophosphatasia

Hypophosphatasia is a rare, inherited, metabolic disease caused by deficient activity of the TNSALP, typically due to loss-of-function mutation(s) in the *ALPL* gene. TNSALP is a glycosylphosphatidylinositol anchored ectoenzyme, which although widely expressed, is expressed at particularly high concentrations on the surface of osteoblasts. During normal bone mineralization, TNSALP dephosphorylates inorganic pyrophosphate (PPi), producing inorganic phosphate (Pi). Inorganic phosphate then precipitates calcium (Ca^{2+}) in the extracellular matrix to form calcium phosphate that is then transformed into hydroxyapatite crystals, which give bones their strength and rigidity. Other known endogenous substrates for ALP include pyridoxal-5′-phosphate (PLP) and phosphoethanolamine (PEA) (Whyte, 2012; Whyte, 1994).

In HPP, low TNSALP activity leads to extracellular accumulation of PPi, which inhibits bone mineralization by blocking hydroxyapatite crystal formation (Russell, 1965; Fleisch, 1966; Rockman-Greenberg, 2013). Consequently, Ca^{2+} and PPi accumulate in the bloodstream, causing disturbances in calcium/phosphate homeostasis (Linglart, 2016). In addition, TNSALP dephosphorylates PLP, the circulating form of vitamin B_6, producing pyridoxal (PL), which crosses the blood-brain barrier and is rephosphorylated into PLP, where it plays an important role in the synthesis of multiple neurotransmitters (Whyte, 1994; Whyte, 2012). The role of PEA is not completely understood but may be a component of the phosphatidylinositol-glycan linkage apparatus that couples TNSALP and many other proteins to cell surfaces.

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. Hypophosphatasia 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. Severe disease associated with 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 in the central nervous system in patients with HPP can result in infantile seizures which are responsive to pyridoxine (Baumgartner-Sigl, 2007; Whyte, 1985).

2.2.2. ALXN1850

2.2.2.1. Chemistry

ALXN1850 is a human recombinant tissue nonspecific alkaline phosphate (TNSALP)-Fc-aspartate fusion protein. It is expressed by a vector in Chinese Hamster Ovary (CHO) cells using cell culture technology in bioreactors and is formulated to a concentration of 100 mg/mL. ALXN1850 has a deglycosylated molecular weight of 160 KDa confirmed by electrospray ionization mass spectrometry. The purified soluble Fc fusion protein is modified by an amino acid change to enhance substrate hydrolysis by its active site; its Fc domain is an

IgG2/4, to improve half-life and bioavailability; 2 N-linked glycans have been removed from each TNSALP polypeptide chain via asparagine to glutamine mutations, and other enhancements to its glycan profile which were designed to improve the PK of the active moiety and increase its exposure and half-life.

2.2.2.2. Pharmacology

Preclinical efficacy studies with ALXN1850 were conducted in a murine knockout model (designated Akp2GW-/-) of human HPP created by inactivating the *TNSALP* gene according to the homologous recombination method used by the laboratory of Dr José Millán (Narisawa, 1997) to generate the Akp2-/- mouse model which supported the Investigational New Drug (IND) filing for asfotase alfa. The Akp2GW-/- model was similarly maintained on a mixed background of C57BL6 and 129J strains. As occurs in human infantile HPP and Akp2-/-mice, Akp2GW-/- mice demonstrate a range of mineralization and bone deficits with shortened survival. Compared to wild-type littermates, Akp2GW-/- mice display excess unmineralized matrix early in life, experience seizures likely due to defective vitamin B6 metabolism, and die before postnatal day 26 despite dietary pyridoxine (B6 vitamer) supplementation (Study RTR-0032).

The efficacy of ALXN1850 in Akp2GW-/- mice was evaluated in prophylactic SC injection treatments initiated 1 day after birth. The efficacy endpoints evaluated in preclinical studies with Akp2GW-/- mice were bone mineralization defects, growth (body weight and bone lengths of femur and tibia), and survival. Additional outcome measures included plasma and femur alkaline phosphate enzymatic activity.

ALXN1850 increased bone mineralization and had a beneficial effect on bone length, body weight gain, and survival time. ALXN1850 improved upon the potency of asfotase alfa, with higher enzymatic activity on bone, higher frequency of normalized bone mineralization, and increased bone length, at lower doses and at less-frequent dosing intervals than asfotase alfa.

2.2.2.3. Toxicology

Nonclinical safety/toxicology studies conducted to date to support ALXN1850 FIH study consisted of definitive/Good Laboratory Practices (GLP) nonclinical safety studies in rats (Study 1727-227) and monkeys (Study 1727-228). The GLP toxicology studies evaluated the systemic toxicity of the administration of SC ALXN1850 in rat and monkeys; these studies included safety pharmacology endpoints (cardiovascular, respiratory in monkey study and neurofunctional in rat study), toxicokinetic evaluations, immunogenicity evaluations, and a recovery period to assess the reversibility of any treatment-related effects. ALXN1850 did not result in any systemic organ toxicity in rats or monkeys. ALXN1850 was well tolerated locally following SC administration to rats and monkeys, with no adverse findings observed at injection sites. The no observed adverse effect levels (NOAELs) in rat and monkey studies were the highest doses evaluated in rats (30 mg/kg/dose) and monkeys (20 mg/kg/dose). In conclusion, SC administered ALXN1850 to rats and monkeys did not identify any new or unexpected systemic toxicity or local tolerability findings in rats or monkeys.

In rat 28-day toxicity study, administration of ALXN1850 via SC injection once every 3 days (q3d) for 28 days (Days 1, 4, 7, 10, 13, 16, 19, 22, 25, and 28) for a total of 10 doses to male and female CD® rats was well tolerated up to 30 mg/kg/dose, the highest SC dose evaluated in this

study. Additionally, administration of ALXN1850 at 10 mg/kg IV was also well tolerated after a single injection. There were no ALXN1850-related changes in clinical observations, body weights, body weight gains, quantitative food consumption, ophthalmology, functional observational battery observations, hematology, urinalysis, gross pathology, and organ weights. At the end of the dosing phase, there were dose-related increases in ALP activity (anticipated pharmacology effect) at ≥ 2 mg/kg/dose ALXN1850 SC which were fully resolved following a 28-day recovery period. Non-adverse microscopic changes were related to the injection procedures with associated reactive changes in the draining lymph nodes. There was no discernible ALXN1850-associated alteration in the incidence, severity, or microscopic character of the changes at the injection sites or draining lymph nodes. Microscopic changes in the injection sites and draining lymph nodes of recovery animals were similar to those noted in the terminal necropsy animals, although less pronounced in the recovery group animals. In conclusion, the dose level of 30 mg/kg/dose is considered to be the NOAEL for SC administration that corresponds to Day 24 males and females combined maximum observed serum concentration (C_{max}) value of 43.9 µg/mL and area under the concentration-time curve from time zero to 72 hours (AUC_{0-72h}) value of 2120 h*µg/mL.

Single IV bolus injection of ALXN1850 at 10 mg/kg was well tolerated in rats with no noteworthy toxicity or injection site reactions and resulted in an AUC_{0-72h} of 3690 h*µg/mL. The SC bioavailability for ALXN1850 (based on SC AUC_{0-72h} values at 10 mg/kg/dose) in rats was approximately 44.2%.

In a monkey 28-day toxicity study, administration of ALXN1850 via SC injection once q3d for 28 days (Days 1, 4, 7, 10, 13, 16, 19, 22, 25, and 28) for a total of 10 doses to male and female cynomolgus monkeys was well tolerated up to 20 mg/kg/dose, the highest dose evaluated in this study. There were no ALXN1850-related changes in injection site reactions (dermal scoring), body weights, body weight gains, qualitative food consumption, ophthalmology, manual respiratory rates, indirect blood pressures, qualitative electrocardiography, hematology, urinalysis, gross pathology, and organ weights. At the end of the dosing phase, there were dose-related increases in ALP activity (anticipated pharmacology effect) which were fully (1 mg/kg/dose) or mostly (≥5 mg/kg/dose) resolved following a 28-day recovery period. Non-adverse ALXN1850 related microscopic changes were confined to the injection sites and included minimal to mild degeneration/necrosis, mineralization, and mixed cell inflammation/infiltration. Partial recovery of degeneration/necrosis and mixed cell inflammation/infiltration of the injection site(s) were observed within the recovery groups, while minimal to mild mineralization persisted in recovery males at ≥ 1 mg/kg/dose and females at 20 mg/kg/dose. Heart rate increases were observed in all animals at 1 mg/kg/dose and in some of the animals at ≥ 5 mg/kg/dose. Heart rate and electrocardiogram (ECG) values remained within a normal range of biological variation for monkeys of this age, and therefore these heart rate increases were not considered to be adverse, given the incongruity with systemic exposure data. In conclusion the dose level of 20 mg/kg/dose is considered to be the NOAEL that corresponds to Day 24 males and females combined mean C_{max} value of 254 µg/mL and mean AUC_{0-72h} value of 15400 h*µg/mL, respectively.

In conclusion, SC administration of ALXN1850 to rats or monkeys did not identify any new or unexpected systemic toxicity or local tolerability findings. The NOAEL dose of 20 mg/kg/dose from the ALXN1850 GLP monkey toxicity study was used to select the Phase 1 study starting dose. The observed exposure of the NOAEL at 20 mg/kg/dose from the GLP SC monkey toxicity

study is approximately 113× (for IV) and 83× (for SC) of the projected AUC exposure of the proposed human starting single dose of 15 mg IV or 15 mg qw × 3 SC (Section 4.3). Given the exposure margins and the lack of systemic toxicity or local tolerability findings in 28-day rat and monkey toxicology studies with ALXN1850, the safety risk for humans on the 15 mg starting dose is considered to be very low.

As per the current FIH study design the fourth dose will be administered by Day 28 (1 IV dose followed by 3 SC doses; Section 1.2). The 28-day toxicology studies in rats and monkeys with 10 SC doses administered with q3d dosing frequency are sufficient to support the FIH duration of dosing (ICH M3 [R2] and ICH S6 [R1] guidance).

2.3. Benefit/Risk Assessment

Identified potential risks are described below. More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of ALXN1850 may be found in the IB.

2.3.1. Risk Assessment

Potential risks of study participation include:

- Injection/infusion site reactions (ISRs)
- Injection/infusion associated reactions (including hypersensitivity)
- Formation of anti-ALXN1850 antibodies
- Ectopic calcifications

2.3.1.1. Coronavirus Disease 2019

The coronavirus disease 2019 (COVID-19) pandemic is active in many countries at the time of the original protocol and this protocol amendment. Given this unique circumstance, specific consideration has been given to the risks and benefits of the study as they relate to COVID-19, and the global and local changes that exist as a result of the pandemic. This assessment is described in Section 10.7.

2.3.2. Benefit Assessment

No direct medical benefit is anticipated in participants in any of the cohorts during this short course of treatment with ALXN1850. HPP is a chronic systemic disease that requires long term ERT in patients for whom it is indicated. The decision to continue ERT for HPP after the patient has ended the study will be made by the patient and their physician and, if requested, treatment with asfotase alfa will be made available.

2.3.3. Overall Benefit Risk Conclusion

This is the first time that ALXN1850 will be administered to humans. Because of the potential for immunogenicity, this study will enroll adults with HPP who are not anticipated to require continued treatment with ERT, based on their signs and symptoms, and the Investigator's clinical assessment of their current condition.

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. A SRC 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. There is no added medical benefit for the participants.

3. OBJECTIVES AND ENDPOINTS

The study objectives and corresponding endpoints are presented in Table 4.

Table 4: Objectives and Endpoints

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

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

4. STUDY DESIGN

4.1. Overall Design

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

Study participants will be enrolled into 3 cohorts in a sequential fashion. The first participant in each cohort will begin dosing before the rest of the cohort. A SRC will convene after the first participant in each cohort has completed the first IV dose to assess safety and tolerability, and to endorse initiation of SC study drug administration to the first participant as well as IV and SC study drug administration to the remaining participants in the cohort.

Once Cohort 1 participants have received a single IV dose and 3 qw SC doses, the SRC will convene again to review safety and tolerability data, and to determine if the dose escalation may proceed. If the SRC endorses dose escalation, Cohort 2 will begin dosing at the next dosing level. Cohort 3 will begin dosing after the SRC has reviewed all relevant safety, tolerability, and PK data from participants in Cohorts 1 and 2 and endorsed dose escalation. The study design is presented in Figure 1. Further details are provided in Section 6.6.1 and in the SRC charter.

4.2. Scientific Rationale for Study Design

As this is the first time ALXN1850 will be dosed in humans, an open-label dose escalating design was chosen for initial assessment of the safety, tolerability, PK, and PD of ALXN1850 IV and SC in adults with HPP.

The scientific rationale for each aspect of the study design is discussed below:

- This study will be conducted in adult participants with HPP because ALXN1850 is designed as a TNSALP ERT that is expected to lead to improvement in this patient population. Because of the potential for immunogenicity, this study will enroll adults with HPP who are not anticipated to require continued treatment with ERT, based on their signs and symptoms, and the Investigator's clinical assessment of their current condition.
- A single ALXN1850 IV dose will provide the reference necessary for assessing absolute bioavailability.
- Weekly SC dose will provide the PK and PD information that will support the intended dose regimen in this patient population.
- Three weekly doses of SC ALXN1850 will provide accumulation information for this study drug.
- The qw SC dose range proposed for this study (15 to 90 mg) is expected to cover the therapeutic range in humans.
- An 8-week follow-up will provide enough time to assess immunogenicity and possible risks to the participants.

4.3. Justification for Dose

First-in--human dose selection was based on PK data collected from a wild-type mouse study; rat and monkey dose range finding studies; 4-week GLP toxicology studies in rats and monkeys; and efficacy data from 2 Akp2GW -/- mouse efficacy studies. A model-based approach employing dose response and population PK (PopPK) models was used to characterize the SC dose (15 mg [0.15 mL], 45 mg [0.45 mL], and 90 mg [0.90 mL]) after performing body weight-based forecasting to humans for the FIH study. A NOAEL based approach was used to determine the starting dose (15 mg IV). A summary of the expected exposure margin and- expected percentage of population with normalized mineralization response in humans for ALXN1850 is provided in Table 5. Given previous experience with asfotase alfa, it is expected that the ALXN1850 safety multiple will support flat dosing. The trade-off of flat dosing versus mg/kg dosing is some increase in PK variability (within a cohort) with a gain of reduction in potential errors in dosing and operational factors.

The 15 mg IV starting dose is considered the maximum recommended starting dose (MRSD). The starting dose was selected based on NOAEL from the 4-week GLP toxicology study in monkeys dosed SC q3d. Monkey was selected because it has relevant biology with humans. The monkey NOAEL was determined to be 20 mg/kg/q3d or 46 mg/kg/week. Assumptions of 1) no allometric scaling for a molecule with molecule weight > 100 kDa (Food and Drug Administration (FDA) guidance: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Health Volunteers, 2005), 2) applying safety factor of 150, and 3) SC bioavailability (75%), 4) adult body weight of 70 kg, were factored into the calculation of the starting dose. Based on dose simulation results, the observed exposure of the NOAEL at 20 mg/kg/dose from the GLP monkey toxicity study is approximately 113-fold of projected exposure from the 15 mg IV starting dose (Table 5).

Cohort 1 will receive 15 mg as a single IV dose, followed by 15 mg SC at 1-week intervals for 3 doses. The 15 mg SC dose was calculated (based on dose-response modeling of mouse data) to produce normalized bone mineralization in 66% of a treated population.

Cohort 2 will receive 45 mg as a single IV dose, followed by 45 mg SC at 1-week interval for 3 doses. A 45 mg SC dose is expected to achieve normal bone mineralization in 85% of a treated population and is selected as the target effective dose. Based on the asfotase alfa clinical definition for this efficacy endpoint, the dose producing normal bone mineralization in 85% of the treated population (ED85) is considered as the target effective dose. Mouse ED85 was calculated using a dose response model developed using ALXN1850 preclinical efficacy studies in Akp2GW (-/-) mouse model of HPP and allometrically scaled to a weekly flat dose of 45 mg/week in humans.

Cohort 3 will receive 90 mg as a single IV dose, followed by 90 mg SC at 1-week intervals for 3 doses. A 90 mg SC dose is projected to achieve normalized bone mineralization in 91% of a treated population and is expected to cover the therapeutic range in humans.

In the monkey 28-day toxicology study, a total of 10 doses were administered SC at a dose interval of once every 3 days (q3d). The proposed Phase 1 dosing schedule includes administering a total of 4 doses (1 IV and 3 SC doses) once-a-week (qw) (see Section 4.1 for more details), resulting in a total dosing duration of 3 weeks (4 weeks for first participant of the cohort) for ALXN1850 administration. Although, the total duration of ALXN1850 proposed

administration in the Phase 1 study is at most the same duration as the monkey toxicology study, more doses were administered in the monkey toxicology study at a more frequent dosing interval (10 doses at q3d) than the proposed dosing regimen in this Phase 1 study (4 qw doses). Therefore, the existing nonclinical toxicology data (rat and monkey) support the proposed Phase 1 dosing regimen in a clinical setting.

Table 5: Predicted ALXN1850 PK Exposure, Exposure Margin, and Percentage of Population with Normalized Mineralization Response in Humans

Cohort	N	Dose	Predicted $AUC_{0\text{-}168h}$ (µg × hour/mL)	Predicted C_{max} (µg/mL)	Expected exposure margin for $AUC_{0\text{-}168h}$	Expected exposure margin for C_{max}	Expected % of population with normalized mineralization response
1	5	15 mg IV	325	4.3	113	59	NA
		15 mg SC qw × 3	441	3.2	83	26	66%
2	5	45 mg IV	1084	13	38	18	NA
		45 mg SC qw × 3	1318	9.6	28	13	85%
3	5	90 mg IV	1951	26	19	10	NA
		90 mg SC qw x 3	2645	19	14	13	91%

Note: A NOAEL dose of 20 mg/kg/dose was derived from a 4-week SC monkey toxicology study.
Abbreviations: $AUC_{0\text{-}168h}$ = area under the concentration-time curve from time zero to 168 hours; C_{max} = maximum observed serum concentration (measured after dosing); HPP = hypophosphatasia; IV = intravenous; N = number of participants; NA = not available; NOAEL = no- observed- adverse- effect level; PK = pharmacokinetic(s); q3d = every 3 days; SC = subcutaneous; qw = weekly

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all visits including the last scheduled visit specified in the SoA (Section 1.3).

Details on participant withdrawal from the study as well as stopping rules can be found in Section 7.

The end of the study is defined as the date of the last scheduled visit (including follow-up) as shown in the SoA [Section 1.3]).

5. STUDY POPULATION

Participants will be enrolled in the study if all inclusion criteria and no exclusion criteria are met. Because of the potential for immunogenicity, this study will enroll adults with HPP who do not currently require asfotase alfa and are not anticipated to require ERT after study completion, based on their signs and symptoms, and the Investigator's clinical assessment of their current condition and disease burden.

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

5.1. Inclusion Criteria

Age

1. Male or female aged ≥ 18 years at the time of signing the informed consent form (ICF).

Type of Participant and Disease Characteristics

2. Clinical diagnosis of HPP confirmed by the following:
    a. Documented *ALPL* gene mutation(s) (pathogenic or likely pathogenic variant, or a variants of unknown significance) from the certified laboratory;
    b. Serum ALP level below the laboratory age- and sex-adjusted normal range at Screening.
3. Not anticipated to require further treatment with ERT to treat their HPP after study completion.

Pregnancy and Contraception

4. Female participants of childbearing potential and male participants must follow protocol-specified contraception guidance as described in Section 10.4.

Informed Consent

5. Must be willing and able to give written informed consent and to comply with all study visits and procedures as well as requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

Medical Conditions

1. Primary or secondary hyperparathyroidism or hypoparathyroidism.
2. Current or recurrent concomitant disease that could affect clinical assessments or clinical laboratory evaluations.
3. Current or relevant history of physical or psychiatric illness that is not stable or may require a change in treatment, 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 drug or study procedures.

4. Any other significant disease or disorder which, in the opinion of the Investigator, may put the participant at risk.
5. ECGs showing a PR value of less than 120 ms or greater than 240 ms, QRS > 110 ms, and QT interval corrected using Fridericia's formula (QTcF) > 450 ms for men and QTcF > 470 ms for women at Screening. If the results of the first triplicate ECG are abnormal, 2 additional triplicate ECGs will be performed. Both of the subsequent triplicate ECGs must be within normal ranges or the participant is not eligible for the study.
6. Heart rate > 120 beats per minute (bpm) at Screening.
7. Human immunodeficiency virus (HIV) infection (evidenced by HIV type 1 or type 2 antibody titer), acute or chronic hepatitis B virus (HBV) infection (evidenced by hepatitis B surface antigen), or acute or chronic hepatitis C virus (HCV) infection (evidenced by antibody titer)
8. Fracture within 12 weeks of screening.
9. History of significant allergic reaction (eg, anaphylaxis or angioedema) to any product (eg, food, pharmaceutical).

Prior/Concomitant Therapy

10. Use of nonprescription/ over-the-counter medications, including herbal remedies and supplements, within 7 days before dosing Day 1, except with prior approval of Alexion.
11. Use of vitamin B6 (including vitamin supplements that contain vitamin B6) within 2 weeks prior to screening.
12. Oral bisphosphonate use within 6 months (depending on the half-life of the drug as assessed by the Investigator) and IV bisphosphonate use within 12 months prior to screening.
13. Asfotase alfa use within 6 months or positive for asfotase alfa antidrug antibody (ADA)/neutralizing antibodies (NAbs) [only required for patients with a history of asfotase alfa use].
14. Teriparatide/parathyroid hormone (PTH) analog use within 2 months prior to screening.
15. Treatment with strontium or sclerostin inhibitors within 6 months prior to the first dose of study drug.
16. History of allergy or hypersensitivity to excipients of asfotase alfa or ALXN1850 (eg, sodium phosphate, sodium chloride).

Prior/Concurrent Clinical Study Experience

17. Current enrollment or past participation, within the last 30 days, before signing of informed consent form in any other clinical study involving an investigational study drug. Participants, involved in interventional studies, are not eligible unless the time since last treatment has exceeded 30 days or 5 half-lives of the study drug, whichever is longer.

Diagnostic Assessments

18. Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2.

19. Serum 25-hydroxy (25-OH) vitamin D below 20 ng/mL,
20. PTH levels > ULN of the laboratory reference range at Screening.
21. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > ULN of the reference range of the testing laboratory at Screening.
22. Any clinically significant abnormal hematological parameters (per the Investigator's discretion).
23. Positive urine drug toxicology screen for non-prescribed substances at Screening.

Weight

24. Body mass index (BMI) > 40 kg/m^2 at baseline.

Other Exclusions

25. Female participants who are pregnant, planning to become pregnant, or breastfeeding.
26. Current employees of Alexion.
27. Investigational site personnel involved directly in the study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
28. Major surgery or hospitalization within 90 days prior to dosing on Day 1.
29. Currently smokes nicotine or tobacco products in any form and is unwilling to refrain from smoking during inpatient stays.
30. History of drug and/or alcohol abuse (according to current Diagnostic and Statistical Manual of Mental Disorders) within 1 year of Screening that would limit patient participation in the study as determined by the Investigator.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

- Participants are required to abstain from ingesting food containing poppy seeds within 48 hours prior to each dose.

5.3.2. Alcohol, and Tobacco

Participants will be required to abstain from:

- Ingesting alcohol 48 hours before each dose through discharge from the inpatient facility, and 24 hours before each study follow-up visit.
- Smoking nicotine or tobacco products from 2 hours before admission through discharge from the inpatient facility.

5.3.3. Activity

Participants will be required to remain in supine position for dosing and for approximately 15 minutes after study drug administration. Vigorous activity (strenuous, beyond the

participant's routine physical activities) will be prohibited at all times throughout confinement at the inpatient unit.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered into 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 serious adverse events (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. Investigational sites are permitted to rescreen participants who do not meet inclusion/exclusion criteria.

6. STUDY INTERVENTION

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

6.1. Study Interventions Administered

The study drug composition and doses to be administered in this study are presented in Table 6. Detailed description of the study drug is provided in the Pharmacy Manual.

Table 6: Dose Reference Chart for Study ALXN1850-HPP-101

Intervention Name	**ALXN1850 SC**	**ALXN1850 IV**
Type	Biologic	Biologic
Dose Formulation	ALXN1850 is formulated at pH 7.3 and each vial contains 100 mg of ALXN1850 in 10 mM sodium phosphate, 140 mM proline, 140 mM sucrose, 0.05% w/v polysorbate 80. The concentration is 100 mg/mL.	ALXN1850 is formulated at pH 7.3 and each vial contains 100 mg of ALXN1850 in 10 mM sodium phosphate, 140 mM proline, 140 mM sucrose, 0.05% w/v polysorbate 80. The concentration is 100 mg/mL.
Unit Dose Strength(s)/Dosage Level(s)	15, 45, and 90 mg (3 × qw),	15, 45, and 90 mg single dose
Route of Administration	SC	IV
Use	Experimental	Experimental
Dosing Instructions	ALXN1850 will be administered via the SC route once a week (qw) over 3 weeks (a total of 3 doses) at a 15, 45, or 90 mg dose. SC doses will be administered as a manual SC injection in either the abdomen or thigh at the Investigator's discretion. For more detailed instructions on study drug dosing refer to the Pharmacy Manual.	A single dose of ALXN1850 at 15, 45, or 90 mg will be administered as an IV infusion per cohort. For more detailed instructions on study drug dosing refer to the Pharmacy Manual.
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by Alexion	Provided centrally by Alexion
Packaging and Labeling	Study drug will be provided in kits. There will be 1 vial per kit. Both kits and vials will be labeled according to the protocol and local regulatory requirements.	Study drug will be provided in kits. There will be 1 vial per kit. Both kits and vials will be labeled according to the protocol and local regulatory requirements.

Abbreviations: IMP = investigational medicinal product; IV = intravenous; NIMP = non-investigational medicinal product; qw = weekly; SC = subcutaneous

6.2. Preparation/Handling/Storage/Accountability

Details regarding preparation, handling, storage, accountability, and administration of the study drug are discussed below. Additional guidance is provided in the Pharmacy Manual.

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive the study drug and only authorized site staff may supply or administer the study drug. All study drug 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.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance regarding preparation, handling, storage, administration (including infusion rate), 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

This is a Phase 1, open-label study; therefore, there will be no randomization of study participants in this study. Approximately 15 participants will be enrolled in the study to allow for at least 9 participants (3 per cohort) to complete the study. Participants presenting during the Screening Period who meet all the eligibility criteria will be offered participation in the study. Those that accept will be assigned to the next available cohort.

6.4. Study Intervention Compliance

Participants will be administered study drug in a controlled setting under the supervision of the Investigator or designee, thereby ensuring compliance with study drug administration. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the electronic case report form (eCRF).

For additional information on study intervention compliance and management, refer to the Pharmacy Manual.

6.5. Concomitant Therapy

A concomitant therapy is any drug or substance (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency
- Any AEs related to concomitant drug administration

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

6.5.1. Allowed Medicine and Therapy

The use of hormonal contraceptives will be allowed and recorded in the eCRFs.

Prescription medications will be permitted during the study at the Investigator's discretion and recorded in the eCRFs.

The occasional use of nonprescription medications, over-the-counter, herbal preparations, and multivitamins, antipyretics, or analgesics (eg, acetaminophen) may be allowed during the study, at the discretion of the Investigator and documented.

6.5.2. Disallowed Medicine and Therapy

Use of vitamin B6 (including vitamin supplements that contain vitamin B6) must be discontinued at least 2 weeks before Screening.

Use of oral bisphosphonate and IV bisphosphonate must be discontinued 6 months and 12 months, respectively, before Screening. Treatment with strontium or sclerostin inhibitors must be discontinued at least 6 months before the first dose of study drug. Use of teriparatide/ PTH analog must be discontinued at least 2 months before Screening.

Use of asfotase alfa within 6 months of Screening and throughout the study is prohibited.

A concomitant procedure is any therapeutic intervention (eg, surgery/biopsy, physical therapy) or non-study diagnostic assessment (eg, blood gas measurement, bacterial cultures) performed from the time the participant is screened for the study until the last study visit. Concomitant procedures are not allowed unless medically indicated.

6.6. Dose Modification

Decisions to continue, modify (explore the dose cohort further), or escalate dosing will be made by the SRC.

The SRC will meet to review safety data after the first participant in each cohort completes IV dosing to assess for safety and to support multiple dosing for the first participant as well as study drug administration for the remaining participants in each cohort. Initiation of Cohort 2 can only occur after review of accumulated safety data from Cohort 1. Initiation of Cohort 3 can only occur after review of accumulated safety and PK data from Cohorts 1 and 2. If dosing is stopped because a safety event occurs or a stopping criterion is met, dosing may not resume until there is documented agreement between the Investigator and Alexion's Medical Monitor.

After review of the safety data, the SRC may agree to any of the following options:

- Continue dose escalation as described in the protocol
- Administer the same dose to an additional cohort
- Administer a higher intermediate dose between the current dose and the next protocol specified dose level
- Administer a lower intermediate dose between the current dose and the previously administered dose
- Discontinue further dosing in the study

Safety review and decisions of the SRC will be documented in a memorandum that must be approved by Alexion and Investigator prior to initiating dosing of the next cohort. The study design is presented in Figure 1. Further details are provided in Section 6.6.1 and in the SRC charter.

6.6.1. Dose Escalation

Before initiating Cohort 2, accumulated safety data from Cohort 1 will be reviewed. After at least 3 participants in Cohort 1 have received a single IV dose and 3 weekly (qw) SC doses, the SRC will convene again to review safety and tolerability data, and to determine if the dose escalation may proceed. The SRC will review available data including treatment emergent adverse events (TEAEs), safety laboratory results, 12-lead ECG findings, and vital sign measurements.

For dose escalation between Cohort 1 and Cohort 2, PK data will not be provided.

The decision to begin Cohort 3 will be determined by the SRC, who, at minimum, will review the following data (see SRC charter for full description of data required for each safety review):

- All available accumulated safety data from all participants in Cohorts 1 and 2
- Up to Day 36 PK data from the first participant in Cohort 1
- Up to Day 29 PK data from the 2nd and 3rd participants in Cohort 1
- Up to Day 22 (168 hours post SC dose) PK data from the first participant in Cohort 2
- Up to Day 8 (168 hours post IV dose) PK data from the 2nd and 3rd participants in Cohort 2

Predicted ALXN1850 human PK exposure (Table 5) indicates Cohort 3 PK exposure will not exceed 50% of the NOAEL exposure ($AUC_{0\text{-}168h}$ = 36800 h*µg/mL and C_{max} = 254 µg/mL) established in the GLP 4week monkey toxicology study. In the event that PK exposure in Cohort 3 is predicted to exceed 50% of the NOAEL exposure, a lower dose may be selected so that the above criteria can be met.

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

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

6.7. Intervention After the End of the Study

Upon completion of the last study visit, participants will return to the care of their treating physician.

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Stopping rules provide explicit guidance for the discontinuation of treatment cohorts and discontinuation of individual participants. The following rule sets apply to TEAEs that are assessed by the Investigator to be related to study drug (unless specified otherwise). While stopping rules provide an explicit guide for dose discontinuation, the Investigator and/or Alexion may elect to discontinue dosing at any time. 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).

The entire study will be suspended if any severe or life-threatening treatment-emergent serious adverse events (TESAEs) occur.

Participants who do not complete the study but have been dosed should make every effort to undergo all scheduled safety, PK, and PD evaluations required by the protocol (refer to SoA, Section 1.3) in relation to the last dose they received. Alexion and site monitor will be notified as soon as possible.

If a participant withdraws consent and is unwilling to attend all scheduled procedures, every attempt will be made to encourage them to complete the ED visit at a minimum.

7.1. Discontinuation of Study Intervention

7.1.1. Cohort Stopping Rules

Within cohort dosing will be temporarily halted if any of the following are observed:

- Two or more participants experience CTCAE Grade 2 TEAE (excluding ISR and injection/infusion associated reactions) with the same PT or medical concept that are considered to be related to study drug and do not show signs of reversibility by the following visit.
- One participant experiences a CTCAE Grade 3 (or higher) TEAE considered to be related to study drug.
- Severe (Grade 3) injection site reaction in more than 50% of a cohort, assessed by the Investigator to be related to the study drug
- The PK stopping limit defined as 50% of the NOAEL exposure (mean C_{max} and $AUC_{0\text{-}168h}$ values) established in the GLP 4-week monkey toxicology study. This stopping rule will only be assessed before dose-escalating between Cohort 2 and Cohort 3.

In the event of suspension of dosing, continuation of the study will require a protocol amendment.

7.1.2. Individual Participant Stopping Rules

Individual participant dosing will be temporarily halted if any of the following are observed:

- Participant experiences any CTCAE Grade 3 (or higher) TEAE considered to be related to study drug.
- Participant experiences any CTCAE Grade 2 TEAE considered to be related to study drug and is considered to be a safety concern by the Investigator.
- Severe (Grade 3) ISR assessed by the Investigator to be related to the study drug.

See the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

Dosing may continue if appropriate risk mitigation steps are enacted to allow for safe continuation of the study. Assessment of adverse event intensity should be performed by the Investigator taking into consideration clinical judgment as described in the clinical protocol.

7.2. 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 his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- At any visit, a positive drug test result for a non-prescribed substance will lead to participant discontinuation.
- A positive pregnancy test result at any time during the study will lead to participant discontinuation.
- Participants diagnosed with COVID-19 with clinical manifestations of the disease will be evaluated for potential treatment and/or study discontinuation according to the CRU's COVID-19 protocol.
- At the time of discontinuing from the study, if possible, an Early Discontinuation visit should be conducted, as shown in the SoA. See SoA (Section 1.3) for data to be collected at the time of discontinuation and follow-up and for any further evaluations that need to be completed.
- 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, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.
- Participants who withdraw/are withdrawn from the study following completion of EoT assessments but prior to completion of EoS assessments will be considered "completed" if all PK/PD sampling was performed within window and all doses were administered per the SoA. "Completed" participants do not need to be replaced.

- Participants who withdraw/are withdrawn from the study prior to completion of the end-of-treatment assessments should be replaced unless at least 3 participants in their cohort have already “completed” or are on track to “complete”.
- If a participant misses a dosing visit, they do not need to be withdrawn or discontinued from treatment or the study; however, they will not be considered “completed” even if they continue on to complete the end-of-treatment assessments. These participants should be replaced unless at least 3 participants in their cohort have already “completed” or are on track to “complete.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she 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, he/she 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 this 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

- A full physical examination will be performed at Screening and will include assessments of the general appearance; skin; head, ears, eyes, nose, and throat; neck; lymph nodes; chest; heart; abdominal cavity; limbs; central nervous system; and musculoskeletal system.
- At all other timepoints indicated in Section 1.3, an abbreviated physical examination will be performed that will target certain assessments listed above at the Investigator's discretion.
- During both full and abbreviated physical examinations, Investigators or designee should pay special attention to clinical signs related to previous serious illnesses.
- Height and weight will be measured and recorded at the timepoints indicated in Section 1.3.

8.2.2. Vital Signs

Vital sign measurements will be taken after the participant has been resting in the supine or semi-recumbent position for at least 5 minutes and will include temperature (°C; tympanic or oral), respiratory rate, blood pressure, and pulse.

The timing of vital sign measurements is described in the SoA (Section 1.3). Of note, vital signs measurements will be performed every 15 minutes for the first hour after dose administration to monitor for anaphylaxis.

Out of range blood pressure or pulse measurements will be repeated at the Investigator's discretion. Confirmed, clinically significant vital sign measurements will be recorded as AEs.

8.2.3. Electrocardiograms

Triplicate 12-lead ECGs will be recorded at the time points described in the SoA (Section 1.3) but should not be performed after any major meal (ie, major meals should be withheld until after ECG assessments). All ECGs should occur before the vital signs assessment and PK/PD sampling (if 1 or both are scheduled in addition to an ECG during a timepoint).

Electrocardiograms recorded during Screening will be stored electronically. Only ECGs recorded electronically will be valid ECGs for any purpose other than safety assessment. Each ECG recorder will be set up to the required technical specifications and containing the information required to identify the records. Each ECG recording will be clearly identified (participant ID, visit date, and the actual times of ECG recordings).

Recording of each 12-lead ECG will be made after the participants have been resting in a supine position for at least 10 minutes. The participants will avoid postural changes during the ECG recording and clinical staff will ensure that participants are awake during the ECG recording.

At each time point, the ECG will be recorded in triplicate, to reduce variance and improve the precision of measurement. The triplicates will be performed sequentially within a 15-minute window and each ECG recording (trace) will last 10 seconds; repeat ECGs will be performed until these criteria are met.

ECGs will be assessed per applicable standard operating procedure to enable reading and analyzing at least 5 complexes per derivation.

8.2.3.1. Safety Review of 12-lead Electrocardiograms

All recorded ECGs will be reviewed by the Investigator or qualified designee. If a participant shows a clinically significant abnormal ECG, additional safety recordings may be made, and the abnormality will be followed to resolution.

8.2.4. Clinical Safety Laboratory Assessments

All protocol-required assessments, as defined in Section 10.2, must be conducted in accordance with the SoA (Section 1.3) and the Laboratory Manual. Clinical and laboratory assessments to assess safety will be performed by a central laboratory.

- 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. 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.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study will 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.
  - If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

The maximum total blood volume collected from participants in the study will not exceed 500 mL in 16 weeks. The American Red Cross at the time of completion of this protocol (https://www.redcrossblood.org/faq.html) states that people can give up to 470 mL every 56 days. Therefore, the 500 mL per 16 weeks permitted in this study is approximately consistent with current clinical practice.

8.2.5. Drug and Alcohol Screen

A urine sample for drug screen will be analyzed for the substances listed in Section 10.2. Timing for urine drug screen and alcohol tests is specified in the SoA (Section 1.3).

8.2.6. Pregnancy

Pregnancy data from female participants and female spouses/partners of male participants will be collected from the first dose of ALXN1850 and at the time points specified in the SoA (Section 1.3). Any female participant who becomes pregnant during the study should be considered for discontinuation from the study intervention. 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 10.4.3.

8.2.7. Injection or Infusion Site Evaluation

Subcutaneous injection- or IV infusion-site evaluations will be performed at the time points specified in the SoA (Section 1.3).

8.2.8. Ophthalmological Examination

Ophthalmological examinations will be performed at the timepoints indicated in Section 1.3.The examination will assess for papilledema and signs of ectopic calcification and will include slit-lamp examination and fundoscopy. The ophthalmology examination should be performed by a qualified ophthalmologist or an optometrist (ie, Doctor of Optometry) as long as the optometrist works under the supervision of an ophthalmologist.

8.2.9. Renal Ultrasound

A renal ultrasound will be performed at the timepoints indicated in Section 1.3 to assess for the presence of nephrocalcinosis.

8.3. Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs can be found in Section 10.3. All AEs will be reported to the Investigator or qualified designee by the participant.

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 drug (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

All AEs and SAEs will be collected from the signing of the ICF until the final follow-up- visit (See Section 1.3).

Medical occurrences that begin before the start of study drug but after obtaining informed consent will be considered as pretreatment AEs.

All SAEs will be recorded and reported to Alexion immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The Investigator will submit any updated SAE data to Alexion within 24 hours of awareness.

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 he/she considers 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 nonleading 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 7.3). 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 toward 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, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and Investigators.
- Alexion is required to submit individual suspected unexpected serious adverse reaction (SUSAR) reports (defined in Section 10.3.3) in the format of MedWatch 3500 or Council for International Organizations of Medical Sciences (CIOMS) I Form to health authorities and Investigators as required.
- 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. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Any increase on frequency and/or intensity in the signs/symptoms of the disease under study will be reported as AEs.

8.3.6. Adverse Events of Special Interest

8.3.6.1. Injection Site Reactions

Injection site reactions (ISRs) are defined as AEs localized to the site of study drug administration that occur at any time during study participation that are assessed by the Investigator as possibly, probably, or definitely related to study drug. AE intensity reporting procedures are outlined in Section 10.3.4.

Injection site reactions may occur at any timepoint after study drug administration. There is no additional laboratory testing required for ISRs.

The Investigator is responsible for monitoring for ISRs in patients throughout the duration of the study. As part of the study-required physical examinations, Investigators should evaluate injection sites for signs of reaction(s).

8.3.6.2. Injection-associated Reactions

Injection-associated reactions are defined as systemic AEs (eg, fever, chills, flushing, alterations in heart rate and blood pressure, dyspnea, nausea, vomiting, diarrhea, and generalized skin rashes) occurring during or within 24 hours of the start of SC injection that are assessed by the Investigator to be related to the study drug. AE intensity reporting procedures are outlined in Section 10.3.4.

8.4. Treatment of Overdose

For this study, any dose of ALXN1850 greater than that specified in this protocol will be considered an overdose.

Overdoses are medication errors that are not considered AEs unless there is an untoward medical occurrence resulting from the overdose. There is no specific treatment for an overdose.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE.
3. Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

8.5. Pharmacokinetics

- Whole blood samples will be collected for measurement of plasma concentrations of ALXN1850 as specified in the SoAs (see Section 1.3). Additional samples may be collected 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. Permitted collection windows are specified in the SoAs (see Section 1.3).
- Samples will be used to evaluate the PK of ALXN1850. Samples collected for analyses of ALXN1850 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study. Unused samples may be retained for a period of up to 5 years (or per regional requirements) to perform additional PK assessments as necessary.
- Samples may be used for research to develop methods, assays, for prognosis, diagnostics, and/or treatment monitoring related to the mechanism of action of ALXN1850.

8.6. Pharmacodynamics

- Whole blood samples will be collected for measurement of PLP/PL, PA, and PPi as specified in the SoA (see Section 1.3). Additional samples may be collected 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. Permitted collection windows are specified in the SoAs (see Section 1.3).
- Samples will be used to evaluate the PD of ALXN1850. Samples collected for analyses of ALXN1850 concentration may also be used to evaluate safety or efficacy

aspects related to concerns arising during or after the study. Unused samples may be retained for a period of up to 5 years (or per regional requirements) to perform additional PD assessments as necessary.

- Samples may be used for research to develop methods, assays, for prognosis, diagnostics, and/or treatment monitoring related to the mechanism of action of ALXN1850.

8.7. Genetics

To confirm eligibility, genetic testing for *ALPL* gene mutation will be performed during the Screening Period. No additional samples will be obtained for other genetic analysis during this study.

8.8. Biomarkers

Hypophosphatasia is characterized by interdependent clinical manifestations, emanating from a failure to mineralize bone matrix due to elevated concentrations of the TNSALP substrates, including PPi and PLP. Failure to mineralize bone matrix results in osteomalacia (softening of bones). Bone turnover markers such as osteocalcin, N-terminal propeptide of type I procollagen (P1NP), and serum C-telopeptide cross-link of type 1 collagen (sCTX) are a series of protein or protein derivative biomarkers released during bone remodeling due to activity of osteoblasts or osteoclasts. Bone turnover markers respond rapidly to changes in bone physiology; therefore, they have utility in determining patient response to and compliance with therapies for bone metabolic disorders (Greenblatt, 2017).

Blood samples for bone turnover marker analysis (osteocalcin, P1NP, and sCTX) will be collected at the time points indicated in Section 1.3.

Unused samples may be retained for a period of up to 5 years (or per regional requirements) to perform additional assessments as necessary.

Samples may be used for research to develop methods, assays, for prognosis, diagnostics, and/or treatment monitoring related to the mechanism of action of ALXN1850.

8.9. Immunogenicity Assessments

Antibodies to ALXN1850 (ie, ADA) will be evaluated in serum samples collected from all participants according to the SoA (see Section 1.3). Additionally, serum samples should also be collected at the final visit from participants who discontinued the study intervention or were withdrawn from the study. These samples will be tested by Alexion or Alexion's designee.

Serum samples will be screened for antibodies binding to ALXN1850 and the titer of confirmed positive samples will be reported. Other analyses may be performed to further characterize the immunogenicity of ALXN1850.

The detection and characterization of antibodies to ALXN1850 will be performed using a validated assay method by or under the supervision of Alexion. Samples collected at the same time points as those collected for detection of ALXN1850 antibodies will be evaluated for ALXN1850 concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study drug.

Samples will be analyzed on a per batch basis. In the event that a participant experiences an SAE potentially related to immunogenicity, that participant's sample or set of samples will be sent for analysis at the time of the event and data will be provided to the SRC. Unused samples may be retained for a period of up to 5 years (or per regional requirements) to perform additional assessments as necessary.

Samples may be used for research to develop methods, assays, for prognosis, diagnostics, and/or treatment monitoring related to the mechanism of action of ALXN1850.

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

Antibodies to asfotase alfa will also be evaluated in participants who have previously received asfotase alfa at Screening.

8.10. Health Economics Data and Medical Resource Utilization

Health economics data and medical resource utilization will not be collected or evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

No statistical hypotheses are planned for this study.

9.2. Sample Size Determination

The sample size is empiric and selected to support assessment of safety, tolerability, and PK parameters. Approximately 15 participants will be enrolled to allow for at least 9 participants (3 per cohort) to "complete" (ie, participant completed EoT assessments, all PK/PD sampling was performed within window, and all doses were received per the SoA) the study. It is expected that 9 "completed" participants will support adequate characterization of safety, tolerability, and PK/PD for the ALXN1850 compound.

9.3. Populations for Analyses

The population sets used for analysis sets are defined in the following:

Population	Description
Safety Set	All participants who receive any amount of study drug will be included in the Safety Set. Participants will be analyzed according to the study drug received.
Pharmacokinetic Set	All treated participants for whom the PK profile of ALXN1850 can be adequately characterized will be included in the PK Set. Pharmacokinetic analyses will be based upon the study drug received.
Pharmacodynamic Set	All treated participants for whom the PD profile of ALXN1850 can be adequately characterized will be included in the PD Set.
Immunogenicity Set	All treated participants for whom pre and postdose anti-ALXN1850 antibody samples are obtained will be included in the Immunogenicity Set.

9.4. Statistical Analyses

In general, descriptive statistics for continuous variables will include number of non-missing values, arithmetic mean, standard deviation, median, minimum, and maximum. Descriptive statistics for PK parameters will include number of observations, arithmetic mean, standard deviation, arithmetic coefficient of variation (%CV), median, minimum, maximum, geometric mean, and geometric %CV. Categorical variables will be summarized using percentages and frequency counts, by cohort and time point.

A statistical analysis plan (SAP) will be developed and finalized before first data cutoff/database lock and will further describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data as appropriate. This section is a high-level summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Efficacy Analyses

No efficacy analyses will be performed for this study.

9.4.2. Safety Analyses

The primary objective of the study is to assess the safety and tolerability of ALXN1850. The endpoints to support the primary objective include incidence of TEAEs and treatment-emergent serious adverse events (TESAEs). The incidence of TEAEs and TESAEs will be summarized by System Organ Class (SOC) and Preferred Term by administration and cohort overall, by severity, and by relationship to study intervention. Adverse events will be categorized by the type of administration being received at the date of onset (ie, IV or SC). Treatment-emergent AEs and TESAEs resulting in withdrawal from the study will be listed. Participants having multiple AEs within a category (eg, overall, SOC, Preferred Term) will be counted once in that category. For severity tables, a participant's most severe event within a category will be counted. Adverse events of special interest will be analyzed similarly.

Changes from baseline in vital signs and laboratory assessments (as displayed in Table 7) will be summarized by visit for each cohort. Laboratory parameter values will be graded based on the National Cancer Institute CTCAE grading for severity (v5.0, published 27 Nov 2017). Shift tables by treatment group will be produced for these laboratory parameters. These tables will summarize the number of participants with each baseline grade relative to the normal ranges and changes to the worst highest grade assessed postdose during the study.

Electrocardiogram parameters will be measured at the specified time points, including heart rate, PR, RR, QRS, QT, and QTcF intervals. The average of the triplicate ECG readings at the time points collected will be calculated, and changes from pretreatment baseline values will be assessed.

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.

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

Physical examination results will be classified as Normal, Abnormal Not Clinically Significant (NCS), Abnormal Clinically Significant (CS), and Not Examined. The results will be summarized by visit for each administration.

All concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary, and the frequency and percentage of concomitant medications will be summarized.

While safety analyses will be performed on the Safety Set (defined in Section 9.3), all safety data collected will be listed by participant.

9.4.3. Other Analyses

9.4.3.1. Pharmacokinetic Analyses

All PK analyses will be performed on the PK Set and will be reported by each cohort. The individual plasma concentration data from participants who receive ALXN1850 with actual sampling dates and times will be used to derive the PK parameters by noncompartmental analyses methods using Phoenix WinNonlin 8 or higher.

The following PK parameters will be derived:

PK Parameters	Definition
C_{max}	Maximum observed plasma concentration
t_{max}	Time to maximum observed plasma concentration
AUC_t	Area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration
AUC_{tau}	Area under the plasma concentration versus time curve during the dosing interval
AUC_∞	Area under the plasma concentration versus time curve from time 0 (dosing) to time infinity
$t_{½}$	Terminal elimination half-life
λ_z	Terminal-phase elimination rate constant
CL or CL/F	Total body clearance
Vd or Vd/F	Volume of distribution
R	Subcutaneous accumulation ratio (Dose 3/Dose 1)
F	Absolute bioavailability after subcutaneous administration

9.4.3.2. Pharmacodynamic Analyses

All PD analyses will be performed on the PD Set and will be reported by each cohort.

Absolute, change, and percent change from the baseline in plasma PLP, PLP/PL ratio, and PPi concentration versus time data will be presented graphically by treatment over time.

Biomarker assays may be conducted as exploratory analyses on collected samples.

9.4.3.3. Immunogenicity Analysis

Immunogenicity, as measured by ADAs and NAbs to ALXN1850 and asfotase alfa (at Screening, only for participants who have previously received asfotase alfa), will be summarized.

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

9.4.3.4. Exploratory Analysis

Change in ionized calcium, phosphorus, magnesium, PTH, PA, sCTX, P1NP, and osteocalcin versus time will be presented graphically by treatment over time.

9.5. Interim Analyses

Interim analyses may be performed as needed. In particular, an interim analysis may be conducted for each cohort at the end of the Day 29 after all participants in the corresponding cohort have completed or withdrawn. This analysis will allow for further evaluation of the doses and for subsequent ALXN1850 Phase 2/3 studies planning purpose.

The SAP will describe the planned interim analyses in greater detail.

9.6. Safety Review Committee (SRC)

An SRC consisting of, but not limited to, the Investigator, Safety Monitor, Medical Monitor, Study Statistician, and Clinical Pharmacologist, will evaluate the study data at prespecified time points for participant safety and make recommendations on dose escalation, dose modification, or termination of the study. The SRC charter will include a description of membership, schedule of meetings, data required for each safety review, and requirements for documenting meeting discussions and outcome. For more details refer to Section 6.6.

In addition to planned meetings, ad hoc SRC meetings may be held to discuss urgent issues should the need arise. The ad hoc SRC must convene within 48 hours in the case of a treatment-emergent SAE or the withdrawal of any participant due to an adverse reaction.

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 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (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 and reviewed and approved by the IRB/IEC before the study is initiated.
- Any substantial amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- 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 requirements of 21 CFR, ICH guidelines, the IRB/IEC, Directive 2001/20/EC, European regulation 536/2014 for clinical studies (if applicable), 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 his/her 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 (GDPR), ICH GCP guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The participant's medical record must include 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.

Participants who are rescreened outside of the screening window are required to sign a new ICF (see Section 5.4).

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 printed CRF or eCRF unless transmitted to Alexion or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- 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.

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. Electronic case report forms 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
- Decision on the part of Alexion to suspend or discontinue testing, evaluation, or development of the study drug
- Discovery of an unexpected, serious, or unacceptable risk to participants enrolled in the study

If the study is prematurely terminated or suspended, Alexion shall promptly inform the Investigators, the IECs/IRBs, the 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 Coordinating 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, EU Directive 2001/20/EC, 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 ALXN1850 for shipment to the site.

10.2. Clinical Laboratory Tests

- The clinical safety tests detailed in Table 7 will be performed by a local laboratory or by Alexion, as indicated.
- 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.
- The results of each test must be entered in the eCRF.
- Pregnancy testing: Women of childbearing potential should only be enrolled after a negative serum pregnancy test result at Screening. Urine pregnancy testing will be performed for women of childbearing potential at all subsequent timepoints specified in the SoA (Section 1.3). Additional pregnancy tests may also be performed at any time at the Investigator's discretion.

Table 7: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**		
Hematology	Red blood cell count Hematocrit	Red blood cell indices: Mean corpuscular volume Mean corpuscular hemoglobin %Reticulocytes Glycated hemoglobin (HbA1c)[a]	White blood cell count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils Platelet count
Clinical chemistry[b]	Blood urea nitrogen Potassium Creatinine Sodium Chloride Glucose Total carbon dioxide	Aspartate aminotransferase /serum glutamic-oxaloacetic transaminase Gamma glutamyltransferase Alanine aminotransferase /serum glutamic-pyruvic transaminase Alkaline phosphatase (ALP)[a]	Total and direct bilirubin Indirect bilirubin Total protein Albumin Calcium[c] Phosphate Magnesium
Coagulation	Prothrombin time	Partial thromboplastin time	International normalized ratio
Other safety laboratory tests	Parathyroid hormone, intact 25-OH Vitamin D Antidrug antibodies (Alexion) Neutralizing antibodies (Alexion)	The following tests are to be conducted in case of an acute injection-associated reaction: Tryptase (Alexion) C5b-9 (Alexion) IgE (Alexion) Hematology, chemistry, and urinalysis panels	
Other urine tests	Routine urinalysis: Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, erythrocytes, leukocyte esterase (by dipstick) Microscopic examination (if any leukocytes, trace protein, nitrites, and blood [if not menstruating] are abnormal)		

Table 7: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
	Further urinalysis for calcium, phosphorus, creatinine and calcium/creatinine Urine pregnancy tests (after Screening, for women of childbearing potential)
Other screening tests	Alcohol test Urine drug screen (to include amphetamines; barbiturates; benzodiazepines; cocaine; opiates; phencyclidine; methamphetamine; 3,4 methylenedioxy-methamphetamine; and methadone) FSH test (confirmation of post-menopausal state) HIV-1 and HIV-2 antibodies, hepatitis B surface antigen (HbsAg), anti-HBC IgG + IgM (if IgG positive) and hepatitis C virus antibodies (anti-HCV) Serum human chorionic gonadotropin pregnancy test (for women of childbearing potential)

[a] Only collected at Screening.
[b] Clinical chemistry must be fasting only at Screening.
[c] Includes ionized calcium.
Abbreviations: 25-OH = 25-hydroxy; C5b-9 = terminal complement complex C5b-9; eCRF = electronic case report form; FSH = follicle-stimulating hormone; HBC = hepatitis B core antigen; HIV = human immunodeficiency virus IgG = immunoglobulin G; IgM = immunoglobulin M; PLP = pyridoxal 5'-phosphate

Investigators must document their review of each laboratory safety report.

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 or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment (ICH E2A). • **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 the study intervention, whether or not considered related to the 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 signs 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 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. • Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • 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.

10.3.3. Suspected Unexpected Serious Adverse Reactions Definition

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.

10.3.4. 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.

Recording of AE and/or SAE

- 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 or designee in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by Alexion or designee. 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 or designee.
- 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

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories from National Cancer Institute CTCAE v5.0, 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. Adverse events 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 criteria as described in the definition of 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.
- 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 and/or Product Information, for marketed products, in his/her assessment.

Assessment of Causality

- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has 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 his/her 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.

10.3.5. Reporting of SAEs

SAE Reporting to Alexion via Paper Safety Reporting Form

1. All SAEs will be recorded and reported to Alexion immediately and within 24 hours of awareness.
2. All SAEs will be reported using the Safety Reporting Form and submitted to Alexion Global Drug Safety (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
3. 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.
4. 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
5. All paper forms and follow-up information submitted to Alexion GDS **must** be accompanied by a cover page signed by the Investigator.
6. Paper source documents and/or reports should be kept in the appropriate section of the study file.

10.4. Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions

Woman of Childbearing Potential (WOCBP)

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

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the Following Categories Are Not Considered WOCBP

1. Premenarchal
2. Premenopausal female with one of the following:
    - Documented hysterectomy
    - Documented bilateral tubal ligation or bilateral salpingectomy
    - Documented bilateral oophorectomy

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.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause prior to the Day 1 Visit.
        - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement may be required. In the absence of 12 months of amenorrhea the reason for not obtaining FSH levels should be documented by the Investigator at the time of Screening.
    - Females 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.
4. Permanent sterilization at least 6 weeks prior to the Day 1 Visit.

10.4.2. Contraception Guidance

Contraceptive use by male or female participants should be consistent with local regulations regarding the methods of contraception utilized for those participating in clinical studies. If

teratogenic effects are suspected to be transferred to a fetus/embryo from a female spouse/partner of a male participant, pregnancy follow-up information will be obtained for the partner who becomes pregnant (refer to Section 10.4.3.1). In these cases, follow-up will be conducted on the pregnant partner in the same manner as a female participant who becomes pregnant during the study.

10.4.2.1. Guidance for Female Participants

Female participants of childbearing potential must have a negative pregnancy test (serum) at Screening. Additional requirements for pregnancy testing during and after dosing with ALXN1850 are indicated in the SoA (Section 1.3).

The Investigator is responsible for the review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

The Investigator should evaluate the potential for contraceptive method in relationship to the first dose of ALXN1850.

Female participants of childbearing potential must use a highly effective method of contraception, including at least 1 of the following until at least 3 months after the final dose of ALXN1850.

1. Intrauterine device in place for at least 6 weeks prior to first dose of ALXN1850.
2. Progestogen-only hormonal contraception associated with inhibition of ovulation (either oral, injectable, or implantable) for at least 6 weeks prior to first dose of ALXN1850.
3. Intrauterine progestogen releasing system for at least 6 weeks prior to first dose of ALXN1850.
4. Bilateral tubal occlusion for at least 6 weeks prior to first dose of ALXN1850.
5. Combined (estrogen- and progestogen-containing) hormonal contraception (either oral, intravaginal, or transdermal) for at least 6 weeks prior to first dose of ALXN1850.
6. Surgical sterilization of the male partner (medical assessment of azoospermia is required if vasectomy was performed within 6 months prior to first dose of ALXN1850). Male partner is still required to use condom during sexual intercourse.
7. Sexual abstinence for female participants:
    a. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse. In this study, abstinence is only acceptable if consistent with the participant's preferred and usual lifestyle. Abstinent female participants must refrain from heterosexual intercourse for at least 3 months after the final dose of ALXN1850.

The following methods of contraception are considered unacceptable in this study:

- Periodic abstinence (calendar, symptothermal or post ovulation methods
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhea method

- Female condom and male condom should not be used together

10.4.2.2. Guidance for Male Participants

Contraception is the responsibility of the heterosexually active male participants in the study, regardless of his female partner's method of contraception.

Male participants who have had a vasectomy > 6 months prior to the first dose of ALXN1850 must use a condom during heterosexual intercourse. Male participants who have had a vasectomy < 6 months prior to the first dose of ALXN1850 and those who have not had a vasectomy must use a condom with spermicide during heterosexual intercourse for at least 3 months after their final dose of ALXN1850.

10.4.2.2.1. Sexual Abstinence for Male Participants

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse. In this study, abstinence is only acceptable if consistent with the participant's preferred and usual lifestyle. Abstinent male participants who become heterosexually active must use a condom with spermicide during intercourse.

Periodic abstinence (eg, calendar, symptothermal, or post ovulation methods for a female partner) is not considered a highly effective method of contraception for male participants.

Male participants must not donate sperm from the Day 1 Visit until at least 3 months after their final dose of ALXN1850.

10.4.3. Collection of Pregnancy Information

Pregnancy data will be collected during this study for all female participants and female spouses/partners of male participants from the first dose of ALXN1850 until 3 months after the final dose of ALXN1850 is administered. Any female participant who becomes pregnant during the study should be considered for discontinuation from the study intervention. Exposure during pregnancy (also referred to as exposure in utero) can be the result of either maternal exposure or transmission of study intervention via semen following paternal exposure. If a female participant or a male participant's female spouse/partner becomes pregnant during the conduct of this study, the Investigator must submit the "Pregnancy/Breastfeeding Reporting and Outcome Form" to Alexion GDS via facsimile or email. When the outcome of the pregnancy becomes known, the form should be updated and submitted to Alexion GDS. If additional follow-up is required, the Investigator will be requested to provide the information.

Exposure of an infant to study intervention 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 GDS via email or facsimile.

Pregnancy 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.

10.4.3.1. Male Participants with Partners Who Become Pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive ALXN1850.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate "Pregnancy/Breastfeeding Reporting and Outcome Form" and submit it to Alexion within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Alexion. Generally, the follow-up will be no longer than 3 months following the delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

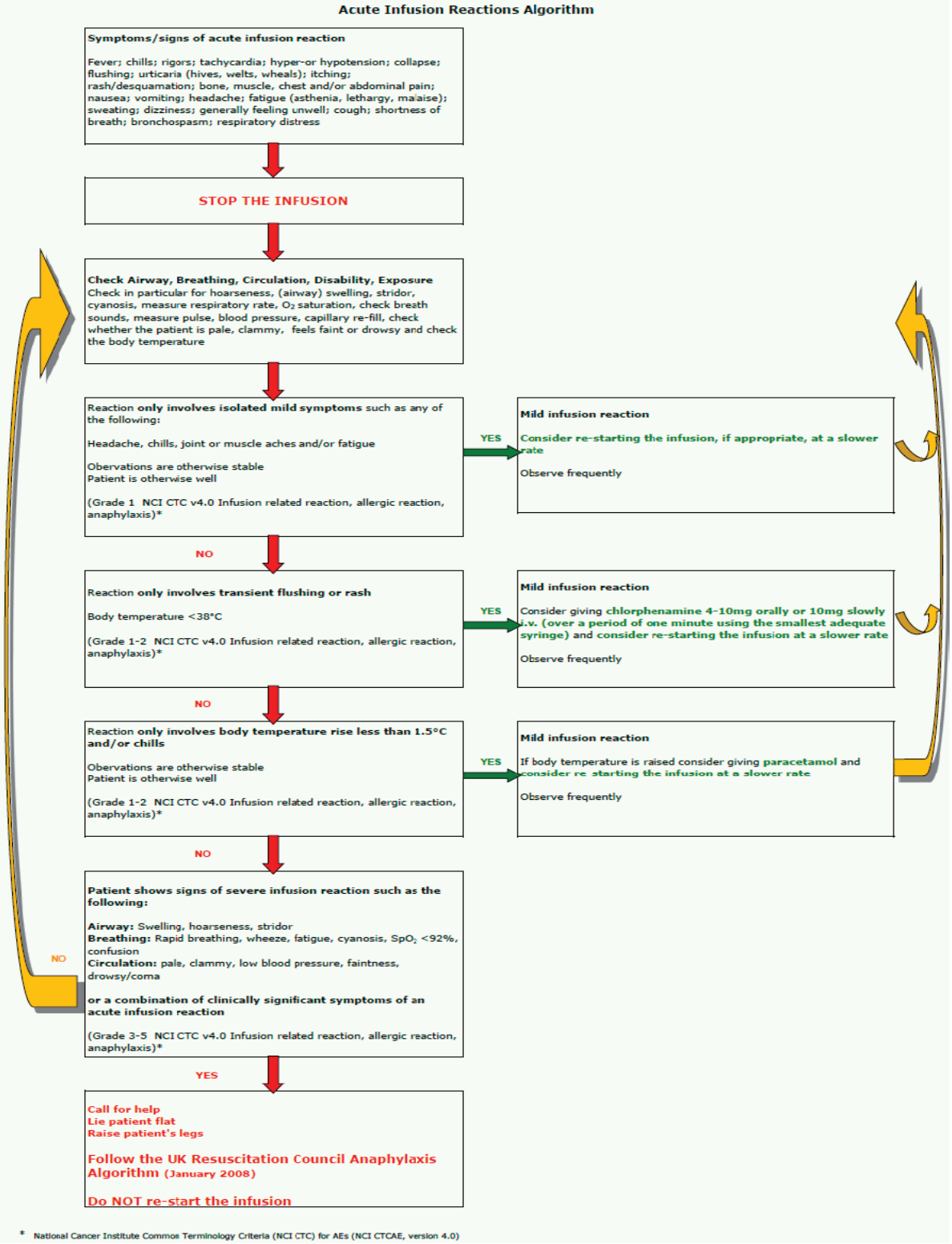
10.4.3.2. Female Participants Who Become Pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial Information will be recorded on the appropriate form and submitted to Alexion within 24 hours of learning of a participant's pregnancy.
- For all Alexion products, both in development or post approval, exposure during pregnancy must be recorded and the pregnancy followed, until the outcome of the pregnancy is known (ie, spontaneous miscarriage, elective termination, normal birth, or congenital abnormality), even if the participant discontinues the study intervention or withdraws from the study. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to Alexion. Generally, follow-up will not be required for longer than 3 months beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Pregnancy is not considered as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such. Any poststudy pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to Alexion. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention but will not be withdrawn from the study.

10.5. Biomarkers

- Blood samples will be collected for biomarker analyses and the data will be used for research (eg, exploratory) related to ALXN1850 or HPP and related diseases. The samples may also be used to develop tests/assays including diagnostic tests related to ALXN1850 and/or other TNSALP ERT interventions and HPP.
- The samples may be analyzed as part of a multistudy assessment of biomarkers in response to ALXN1850 or TNSALP ERT interventions to understand study disease or related conditions.
- The results of biomarker analyses may be reported in the clinical study report (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.
- The samples will be retained while research on ALXN1850, TNSALP ERT interventions, or HPP continues but no longer than 5 years or other period as per local requirements.

10.6. Acute Infusion Reaction Algorithm



Abbreviations: NCI CTC = National Cancer Institute Common Terminology Criteria; i.v. = intravenous.

10.7. COVID-19 Risk/Benefit Assessment

Hypophosphatasia can cause irreversible morbidity and even mortality, if untreated. As such, and due to the limited number of available treatment options, the benefit a participant may receive from joining a clinical study with a new investigational treatment, which may improve current treatment options available for adults with HPP, is potentially significant. In this case, the fact that the study is open-label and every participant is treated with the study interventional drug also contributes to the potential benefit a participant may derive from partaking in the study. The site Investigator will balance the risk/benefit considerations in the study participant taking these factors into account.

The potential risks identified and mitigation measures put in place in light of the COVID-19 pandemic are provided in Table 8.

Table 8: Potential Risks and Mitigation Measures Due to COVID-19

Risks category	Summary of Data/ Rationale for Risk	Mitigation Strategy
Potential risks		
Potentially higher risk population for SARS-CoV-2 infection	Based on Alexion's understanding of the mechanism of action for asfotase alfa and the currently collected safety data, it does not appear that participants treated with ALXN1850 have a higher risk of developing a viral infection.	During the time that the COVID-19 pandemic is active, Alexion will recommend that sites in a position to start the study and enroll participants follow the national and institutional guidances regarding prevention of SARS-CoV-2 infection. Additionally, during that time period, it is expected that Investigators and their staff will take all possible precautions in order to minimize a participant's potential exposure to SARS-CoV-2 infection. Depending on the site, this will consist of measures such as social distancing, temperature screening, enhanced cleaning, and use of personal protective equipment for participants, staff, and caregivers as necessary.
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	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

Table 8: Potential Risks and Mitigation Measures Due to COVID-19

Risks category	Summary of Data/ Rationale for Risk	Mitigation Strategy
	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]).	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).

Abbreviation: COVID-19 = coronavirus disease 2019; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

10.8. Abbreviations

Table 9: Abbreviations and Specialist Terms

Abbreviation or Term	Explanation
%CV	arithmetic coefficient of variation
ADA	antidrug antibodies
AE	adverse event
$AUC_{0\text{-}72h}$	area under the concentration-time curve from time zero to 72 hours
$AUC_{0\text{-}168h}$	area under the concentration-time curve from time zero to 168 hours
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum observed serum concentration
COVID	coronavirus disease 2019
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
eCRF	electronic case report form
ED85	85% of the treated population
ERT	enzyme replacement therapy
Fc	fragment crystallizable
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GDS	Global Drug Safety
GLP	Good Laboratory Practices
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HPP	hypophosphatasia
HRT	hormonal replacement therapy
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
IND	Investigational New Drug
IRB	Institutional Review Board
IV	intravenous(ly)
NAb	neutralizing antibodies
NOAEL	no observed adverse effect level
P1NP	N-terminal propeptide of type I procollagen
PA	pyridoxic acid
PCP	phencylidine
PD	pharmacodynamic(s)
PEA	phosphoethanolamine
PK	pharmacokinetic(s)
PLP	pyridoxal 5'-phosphate
Pop-PK	population pharmacokinetic(s)
PPi	inorganic pyrophosphate

Table 9: Abbreviations and Specialist Terms

Abbreviation or Term	Explanation
PTH	parathyroid hormone
q3d	every 3 days
QTcF	QT interval corrected using Fridericia's formula
qw	every week/weekly
TNSALP	tissue non-specific isoenzyme of alkaline phosphatase
SAE	serious adverse event
SC	subcutaneous(ly)
SoA	schedule of activities
SOC	System Organ Class
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse events
TESAE	treatment-emergent serious adverse event
TNSALP	tissue nonspecific alkaline phosphatase
ULN	upper limit of normal
WHO	World Health Organization

10.9. Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

DOCUMENT HISTORY	
Protocol/Amendment Updates	**Release Date**
Amendment 4	27 Oct 2021
Amendment 3	14 May 2021
Amendment 2	31 Mar 2021
Amendment 1	02 Feb 2021
Original protocol	12 Nov 2020

Amendment 1 (02 Feb 2021)

Overall Rationale for the Amendment

The protocol was amended to address comments by the US FDA regarding monitoring of ectopic calcification, anaphylaxis, and ADAs. In addition, minor changes for clarification, consistency, and accuracy were made.

Changes to the protocol in Amendment 1 are detailed below.

Section	Description of Change	Brief Rationale and/or Clarification
1.1 Synopsis, Overall Design 8.9 Immunogenicity Assessments 9.4.3.3 Immunogenicity Analysis	Addition of text stating that participants who are positive for ADAs at the last assessment of the study will be given options to enable further monitoring of their ADA values after the end of the study; these options may include enrollment in the Global HPP Registry.	In response to a suggestion by the US FDA to continue monitoring participants who develop ADAs until the ADAs return to baseline values.
1.2 Schedule of Activities, Table 1 and Table 2 10.2 Clinical Laboratory Tests, Table 6	Removal of alcohol test from visits, except for at Screening. "Breath" removed from "alcohol breath test" so that the type of test is not specified.	An alcohol test is required as part of the assessment of exclusion criterion 35 (ie, whether participants have a history of alcohol abuse) but is not required after Screening during the study. The type of test is not specified as site may not have access to an alcohol breath test.
1.2 Schedule of Activities, Table 1	Addition of text stating that the ophthalmological examination occurs during Screening and must be completed by Day -1.	To clarify when the ophthalmological examination must take place.
1.2 Schedule of Activities, Table 2	Text added noting that PTH is only measured at Screening and the Day 36 visit.	To clarify the time points at which PTH will be measured.
	Addition of calcium to the urine test.	In response to a suggestion by the US FDA to monitor ectopic calcification.
	Addition of PEA to the urine test.	In response to a request by the planned Principal Investigator as PEA has been shown to have potential as a marker of treatment efficacy.

Section	Description of Change	Brief Rationale and/or Clarification
1.2 Schedule of Activities, Table 2 8.2.2 Vital Signs	Addition of text stating that vital signs measurements will be performed every 15 minutes for the first hour after dose administration.	In response to a suggestion by the US FDA to monitor participants closely for anaphylaxis following dose administration.
2.1 Study Rationale 2.3.3 Overall Benefit Risk Conclusion 4.2.2 Scientific Rationale for Study Design 5 Study Population	Addition of rationale for the population that will be enrolled in the study.	In response to a suggestion by the US FDA, the rationale has been included. Because of the potential for immunogenicity, this study will enroll participants with HPP who are not anticipated to require further treatment with ERT, based on their signs and symptoms, and the Investigator's clinical assessment of their current condition.
5.2 Exclusion Criteria	Exclusion criterion 21 amended so that the glomerular filtration rate in exclusion criterion changed from < 30 to < 60 mL/min/1.73m^2.	A cutoff of < 30 mL/min/1.73m^2 was considered to be too low as 60 – 90 mL/min/1.73m^2 is considered to be mildly decreased function.
9.6 Safety Review Committee (SRC)	Addition of provision for ad hoc SRC meetings.	To allow for ad hoc meetings if safety issues arise during the study.
All	Minor edits to text.	For consistency and accuracy.

Abbreviations: ADA = antidrug antibodies; ERT = enzyme replacement therapy; FDA = Food and Drug Administration; HPP = hypophosphatasia; PEA = phosphoethanolamine; PTH = parathyroid hormone; SRC = Safety Review Committee

Amendment 2 (31 Mar 2021)

This amendment is considered to be substantial according to 21 CFR part 312.30(b) and any applicable local regulations.

Overall Rationale for the Amendment

This protocol has been amended to address a request by the US Food and Drug Administration (FDA) to update the protocol inclusion criteria to clarify that participants are not anticipated to require further treatment with enzyme replacement therapy (ERT). In addition, the assessments at the 60-hour time point were removed.

Changes to the protocol in Amendment 2 are detailed below.

Section	Description of Change	Brief Rationale and/or Clarification
5.1 Inclusion Criteria	Addition of the following to the inclusion criteria: • Not anticipated to require further treatment with ERT to treat their HPP after study completion.	To address a request by the US FDA to clarify the participant population.
1.2 Schema, Figure 1	Study schema updated to account for removal of time point at 60 hours.	Per Principal Investigator recommendation, the time point at 60 hours has been removed because participants will be monitored for 48 hours post-first administration of study intervention, which is considered sufficient for monitoring for safety purposes. Removal of this time point will also reduce participant burden.
	Visit window of +/- 1 day added for Outpatient Visits.	To address a request by the site to enable flexibility around holidays and weekends.

Section	Description of Change	Brief Rationale and/or Clarification
	Inclusion of footnote noting that some visits may be conducted by a home healthcare professional at the participant's home	To limit participant travel, some visits may be conducted at the participant's home.
	Lines denoting SRC meetings removed. Terminology aligned with the SRC charter added, and reference to the SRC charter and Table 1 included in the Figure 1 footnote.	For alignment with the SRC charter and to improve the readability of Figure 1.
1.3 Schedule of Activities (SoA), Table 2	Moved the physical examination assessment at 60 hours to 48 hours.	Rationale as provided above for the removal of the time point at 60 hours.
1.3 Schedule of Activities (SoA), Table 1 and Table 2 8.9 Immunogenicity Assessments 9.4.3.3 Immunogenicity Analysis	Addition of testing for antibodies to asfotase alfa in participants who have previously received asfotase alfa (STRENSIQ®).	To assess immunogenicity relating to asfotase alfa in participants who have previously received asfotase alfa.
5.3.1 Meals and Dietary Restrictions	Removal of the restriction on outside food or drink at the inpatient facility.	To enable participants to order food from onsite restaurants at the facility, if they choose, rather than being restricted to food provided by the facility.
5.3.2 Caffeine, Alcohol, and Tobacco	Removal of the restriction on ingesting caffeine- or xanthine-containing products.	A restriction on caffeine- and xanthine-containing products is not required in this study.

Abbreviations: ERT = enzyme replacement therapy; FDA = Food and Drug Administration; HPP = hypophosphatasia; SRC = Safety Review Committee

Amendment 3 (14 May 2021)

This amendment was considered to be substantial according to 21 CFR part 312.30(b) and any applicable local regulations.

Overall Rationale for the Amendment

This protocol was amended to clarify assessment time points and samples that are required during the study, following discussion with the study site.

In addition, minor changes for clarification, consistency, and accuracy were made.

Changes to the protocol in Amendment 3 are detailed below.

Section	Description of Change	Brief Rationale and/or Clarification
Section 1.2 Schedule of Activities, Figure 1	Footnote on home healthcare visits revised to include remote locations and to state that telemedicine visits will be performed by study site staff.	To provide options for remote visits and to clarify that study site staff will perform telemedicine visits.
	Sampling days revised to reflect that Day 3 time point has been added back (which was removed in protocol amendment 2). Subsequent days corrected for first participant from 18, 25, and 42 to 17, 24, and 31 and for subsequent participants from	It was realized that removing Day 3 impacted on the 48-hour time point, which will need to take place on Day 3.

Section	Description of Change	Brief Rationale and/or Clarification
	11, 18, and 25 to 10, 17, and 24 (as per protocol amendment 1).	
Section 1.3 Schedule of Activities, Table 1 & Table 2 Section 8.2.1 Physical Examinations Section 8.2.3 Electrocardiograms Section 8.5 Pharmacokinetics	Removed references to a Study Operations Manual throughout the protocol.	A Study Operations Manual will not be created for this study.
Section 1.3 Schedule of Activities, Table 1	Note revised to state that ophthalmological assessments are only needed at Screening (to be completed before predose Day 1) and ED/EoS	To clarify when ophthalmological assessments are required.
	Note on renal ultrasound revised to state that it is only assessed at Screening (must be completed on or before predose Day 1) and at the ED/EoS visit for all participants during the study.	To clarify when renal ultrasound is required
	Addition of note clarifying that chemistry laboratory tests at screening must include alkaline phosphatase and PLP	To clarify that alkaline phosphatase and PLP must be assessed at screening.
	Removal of PK sample at screening	PK sample is not required at screening
	Removal of immunogenicity testing for ALXN1850 ADA and NAb at Screening.	Immunogenicity testing for ALXN1850 ADA and NAb will be performed at predose.
	Revised the note to state that a CRIM for assay only needs to be collected on Day 1.	To avoid misreading the assessments as also being needed at unnecessary time points.
	Footnote added describing permitting windows for assessments, and that ECG and vital signs must be done in conjunction with each other, within 30 minutes, and before PK/PD sample collection.	To clarify the permitted assessment window and order of assessments, in conjunction with the removal of references to a Study Operations Manual throughout the protocol.
Section 1.3 Schedule of Activities, Table 2	Day 3 time point (which was removed in protocol amendment 2) added back. Subsequent days corrected for first participant from 18, 25, and 42 to 17, 24, and 31 and for subsequent participants from 11, 18, and 25 to 10, 17, and 24 (as per protocol amendment 1).	It was realized that removing Day 3 impacted on the 48-hour time point, which will need to take place on Day 3.
	Deleted the 36-hour timepoint column.	There are no assessments at the 36-hour timepoint, so this column is unnecessary.
	Note revised to state that ophthalmological assessments can occur at screening or Day -1 but must be completed by predose on Day 1.	To clarify when ophthalmological assessments are required.
	Note on renal ultrasound revised to state that it is only assessed at screening (must be	To clarify when renal ultrasound is required.

Section	Description of Change	Brief Rationale and/or Clarification
	completed on or before predose Day 1) and at the ED/EoS visit for all participants during the study.	
	Note added that PTH, ionized calcium magnesium, and phosphorus are also required at Day 29 for subsequent participants. Blood for PTH, ionized calcium, magnesium, and phosphorus on dosing days (Days 1, 8/15, 15/22, 22/29), and on the days after dosing (Days 2, 9/16, 16/23, 23/30) removed.	To clarify when these assessments are required and to remove time points at which these assessments are not required.
Section 5.1 Inclusion Criteria	Removed the word "central" before "laboratory" in inclusion criterion 2a.	This study will not use a central laboratory for genetic testing.
Section 8.5 Pharmacokinetics Section 8.6 Pharmacodynamics	Note added that PK and PD samples collected +/-30 minutes of the scheduled time, whichever is less, will not be considered a protocol deviation.	To clarify the permitted assessment window and order of assessments.
Section 9.5 Interim Analyses	Text has been added noting that interim analyses may be needed.	To make provision for interim analyses, if needed.
All	Minor edits to text.	For consistency and accuracy.

Abbreviations: CRIM = cross-reactive immunological material; ERT = enzyme replacement therapy; FDA = Food and Drug Administration; HPP = hypophosphatasia; SRC = Safety Review Committee

Amendment 4 (27 Oct 2021)

This amendment was considered substantial according to 21 CFR part 312.30(b) and any applicable local regulations.

Overall Rationale for the Amendment

The protocol was amended to address the recommendation from the FDA to add a PK sample collection timepoint at the end of infusion for IV doses. Additional changes to assist recruitment/reduce participant burden were made, and the SoA tables were revised to ease readability. The clarifications in the IRB-approved Administrative Change Letters were incorporated. Additional minor changes were made in the amendment for clarification, consistency, and accuracy.

Changes to the protocol in Amendment 4 are detailed below.

Section	Description of Change	Brief Rationale and/or Clarification
Section 1.1 Synopsis Section 1.2 Study Schema Section 1.3 Schedule of Activities Section 7.2 Participant Discontinuation/Withdrawal from the Study Section 9.2 Sample Size Determination	Designated Day 65 (1st participant)/ Day 57 (subsequent participants) as the End-of-Treatment Visit, which will now be considered the end of the Treatment Period (added to all except Sections 7.2 and 9.2) Added to all except Section 1.2 that participants who withdraw/are withdrawn from the study following completion of end-of-treatment	Alexion decided the End-of-Treatment Visit should be the last critical PK/PD timepoint (5.5 half-lives for study drug) that is also sufficient for safety follow-up

Section	Description of Change	Brief Rationale and/or Clarification
	procedures will be considered "completed" if they completed all prior PK/PD sampling within window and received all doses per the SoA. "Completed" participants do not need to be replaced.	
Section 1.1 Synopsis Section 1.3 Schedule of Activities	Permitted visit windows for the last 3 study visits were expanded from ± 1 day to ± 3 days (Day 51 [1st participant]/Day 43 [subsequent participants]), -3/+ 7 (EoT), -7/+14 days (EoS) Recalculated the planned study duration, including the period lengths comprising duration, due to these window changes	Expanding these windows is not expected to impact PK, PD, or safety assessments, and should reduce participant burden and drop-out tendency towards the end of this study
Section 1.1 Synopsis	Changed "Four participants will be assigned to each of the 3 cohorts (Cohorts 1, 2, and 3)" to "Five participants will be assigned to each of the 3 cohorts (Cohorts 1, 2, and 3)"	Four participants per cohort does not accommodate for potential dropouts. Total numbers have not changed (15 participants must be enrolled to complete at least 9)
Section 1.1 Synopsis and Section 4.1 Overall Design Section 6.6 Dose Modification	Changed "remaining 3 participants in each cohort" to "remaining 4 participants…"	
Section 1.1 Synopsis Section 3 Objectives and Endpoints	Moved the exploratory objective "Explore the immunogenicity potential of ALXN1850" to a secondary objective and changed "Explore" to "Assess"	Per the advice of Alexion's Immunologist, in alignment with ALXN1850 current anticipated Risk Profile (detailed in Section 2.3.1 Risk Assessment)

Section	Description of Change	Brief Rationale and/or Clarification
Section 1.1 Synopsis and Section 6.6.1 Dose Escalation	Changed “all participants” to “at least 3 participants” in Cohort 1 Changed “subsequent” to “2nd and 3rd” in bullets 3 and 5 (Section 6.6.1only)	To describe more accurately the SRC review and dose escalation process
Section 1.1 Synopsis and Section 6.3 Measures to Minimize Bias: Randomization and Blinding	Changed “at least 12” to “at least 9 participants (3 per cohort)”	9 “completed” participants (3 per cohort) were determined sufficient for PK, PD, and safety analyses
Section 1.2 Study Schema	Removed mention of home healthcare visits from the Notes Revised the Schema and its remaining Notes to align with the other changes described in this summary of changes	Home healthcare visits will not be conducted in this study For clarity/consistency
Section 1.3 Schedule of Activities	The 2 SoAs with assessment notes in the last column were reformatted into 3 SoAs with footnotes at the bottom of each table.	To ease readability and add clarity
	Notes specifying days were deleted as unnecessary	All Inpatient and Outpatient Visit days are now shown separately instead of grouped together
	Permit some Inpatient Visits to be changed to Outpatient Visits at the Investigator’s discretion	To ease participant burden and take holidays into account. This permission, at the Investigator's discretion, will not present any change in the safety assessments or pose any additional risk for the participants
Section 1.3 Schedule of Activities (cont.)	Permitted windows for applicable visits are now shown in a header row as some changed while others should not (in PA3, all Outpatient Visits were permitted a ± 1 day window)	For clarity because Inpatient Visits changed to Outpatient should not have the ± 1 day window of an Outpatient Visit. Also, the windows for last 3 study visits were increased to reduce potential participant dropout towards the end of this long study. It was determined these window changes will not significantly impact PK/PD and safety follow-up
	For all participants, removed 3 scheduled visits: 48 and 96 hrs after the 3rd dose, and at 96 hrs after the 4th dose	Alexion PK/PD and Medical/Safety determined that these time points are not necessary to assess the study endpoints, which will reduce participant burden
	The following assessments previously scheduled at the last study visit (End-of-Study) are now performed at the End-of-Treatment Visit: ECG, ophthalmological examination, renal ultrasound, hematology/chemistry/ coagulation labs, and urinalysis	Completion of the end-of-treatment assessments is now when a participant will be considered “completed”, so having all key assessments at this timepoint is more critical than performing them at EoS. Participants discontinued prior to the end-of-

Section	Description of Change	Brief Rationale and/or Clarification
Section 1.3 Schedule of Activities (cont.)		treatment visit should also have the assessments for that visit performed, if possible, which is noted under the SoAs
	Added a PK/PD sample collection at the end of infusion (for IV doses only) in (new) Table 3	Following the FDA's recommendation received after Protocol Amendment 3 submission, Alexion decided this timepoint would allow a better assessment of the ALXN1850 IV PK/PD parameters
	Added a footnote in the SoAs that a positive drug test result for a non-prescribed substance received at any visit will lead to participant discontinuation	For clarity and alignment within the protocol
	Removed "24-hour Holter ECG" from the SoA and added an "X" in the "12-lead ECG (triplicate)" assessment row at the Screening timepoint	24-hour Holter ECG was determined by Safety and Medical to be unnecessary as a 12-lead ECG at Screening is sufficient, which will reduce participant/site burden
	For the assessment row "Urine for calcium, phosphorus, calcium, PEA, and creatinine" Removed the duplicate "calcium" Removed the associated note "Morning spot urine vs. 24-hour urine." Clarified that a Baseline sample is collected only on Day -1	Typo Participants may now be admitted to the site on the dosing day (if day prior is approved Outpatient), which would burden them with collecting morning urine at home prior to coming to the site. 24-hour urine was determined sufficient. To appropriately assess the significance of any changes in these parameters, a Baseline urine sample is needed predose on the same day as the blood sample for clinical chemistry
	Added predose Day 1 assessment for bone biomarkers (sCTX, P1NP, osteocalcin)	To clarify that this assessment is needed predose on Day 1 for all participants (not just the first participant)
	Included clarifications regarding the following assessments: Chemistry tests: ionized calcium, phosphorus, and magnesium Blood PTH	Blood for PTH was listed in the same assessment row as ionized calcium, phosphorous, and magnesium; however, the latter should instead be included in the chemistry assessment (already listed in Table 7, previously Table 6)
	Removed timepoints for urine drug screen on Days 51, 65, and 85 Added a footnote that a negative PCP result at Screening is required for participant enrollment; however, drug screens collected on the days prior to each dose are not required to confirm a negative PCP result prior to dosing. Once the PCS result is received, the participant will be discontinued from the study if positive	These timepoints were determined unnecessary by Alexion as no further dosing will be performed during these last 3 study visits (ie, potential drug interaction is no longer a concern). Participants are already made aware that they must refrain from illicit drug use throughout the study For clarity because PCP results will not be received until 3-5 days after sampling
	Added a timepoint at EoT/ED (Day 65 [1st participant]/Day 57 [subsequent	These timepoints should have been added as part of the EoS/ED safety

Section	Description of Change	Brief Rationale and/or Clarification
	participants]) for hematology (except HbA1c), chemistry, urinalysis, and coagulation laboratory tests	assessments in previous protocol versions. Now that most EoS assessments will be done at EoT
	Reduced the number of glycated hemoglobin (HbA1c) collection timepoints (now only required at Screening). For clarity, HbA1c was separated from hematology in the SoAs	Clinically significant changes in HbA1c between the visits are not expected, and this will reduce participant/site burden
	Expanded the permitted time window for the ophthalmological and renal examinations from 40 days to ≤ 6 months prior to enrollment for rescreening only	As it is not expected to impact participant safety and should ease participant burden
	Added injection/infusion site evaluation timepoints to indicate every 15 minutes for the 1st hour and at 2, 8, and 12 hours postdose (all relative to start-of- infusion [IV dose]/time of injection [SC doses]),	Greater frequency for this assessment will increase participants' safety monitoring while not increasing their burden
	Added permitted assessment windows in the footnotes regarding the ECG and PK timepoints at T_{max} (EoI)	For consistency because all other ECG and PK timepoints have permitted windows indicated
	Modified when samples should be collected following a suspected hypersensitivity reaction from "2 hours and 24 hours postdose" to "as soon as possible (within 1 hour of the reaction) and again at 2 and 8 hours (+ 1 hour window each) after the 1st sample."	Based on similar past studies and immunologist advice, it is expected that modifying these timepoints will capture more accurate suspected hypersensitivity reaction test results
	Added a note to each SoA that all postdose assessment timepoints are relative to the start of infusion (IV dose) or time of SC injection except the end-of-infusion vital signs, PK/PD sample, and infusion site evaluation (IV dose only)	For clarity
	For all participants on each dosing day (now Table 3), combined the 4- and 8-hr postdose assessments (same for both) into a new 6-hr postdose column and removed the 4- and 8-hr postdose columns from the table	It was determined that a PK/PD sample collection at 6-hr postdose would be more appropriate, and with this timepoint added, the 4- and 8-hr postdose samples are no longer needed. This change is not expected to affect the assessment of safety/tolerability

Section	Description of Change	Brief Rationale and/or Clarification
Section 1.3 Schedule of Activities Section 8.2.1 Physical Examinations	Separated full and brief PEs in the SoAs and Section 8.2.1 Removed "(including fundoscopy)" within the 1st bullet of Section 8.2.1	To decrease participant and site burden, a full PE at all visits indicated in PA3 was deemed unnecessary. Alexion Safety and Medical determined which study visits should include a full or brief PE. Fundoscopy is already listed in Section 8.2.8 (Ophthalmological Examination) and does not need to be performed during PEs
Section 1.3 Schedule of Activities Section 8.2.3 Electrocardiograms	Added that all ECG assessments should not be performed after any major meal Clarified that the order should read ECGs performed first, then vitals, then PK/PD collection at any ECG timepoint where 1 or both of the latter assessments are also scheduled (instead of PA3's wording that ECGs in conjunction with vitals should be assessed before PK/PD sampling)	To avoid overlapped effects in QTc baseline due to a heavy meal For clarity as ECGs must be performed first and the site can not assess ECG and vitals simultaneously, anyway
Section 5.1 Inclusion Criteria	Added "or a variants of unknown significance" within 2a	Will likely assist participant enrollment without impacting data (PD/biomarkers) associated with VUS, and often VUS change to likely pathogenic
	Removed the following from 2b "AND a plasma PLP level greater than the ULN at Screening"	Participants considered for enrollment will have mild HPP and may not manifest elevation in PLP because levels of PLP, in general, are highly variable in this population Diagnosis of HPP for inclusion criteria will be based on genetic testing, low ALP and clinical history, which will more adequately characterize the population that is intended to be enrolled Removal of this criteria will not present any change in the safety assessments or pose any additional participant risk
Section 5.2 Exclusion Criteria	Removed exclusion criteria #5, #20, and #22	These criteria further complicate a study that is a Phase 1B study and not a study in healthy volunteers. Investigator discretion should be able to address conditions that may disqualify the candidate, and no impact on participant safety is expected from this change considering ALXN1850's current risk profile.
	Removed "predose on Day 1" from exclusion #7	These exclusion criteria should apply to Screening only
	In exclusion criteria #6 (now #5), replaced "the mean of the 3 values will	Safety and medical agreed that if the 1st ECG measurements are out-of-range,

Section	Description of Change	Brief Rationale and/or Clarification
	be calculated to determine participant inclusion" with wording that at least 1 of the 3 readings must be inside the noted ECG eligibility ranges	then 2 replicate measures should be performed; however, what determines eligibility is that at least 1 of the 3 measures, not their mean, is in the inclusion range
	Slightly revised exclusion criterion #6 to say that participants with a PR value of less than 120 ms or greater than 240 ms will not qualify (instead of "120 ms > PR > 240 ms", which can be misread)	To clarify this ECG exclusion criterion
	Removed (former smokers may be permitted to enroll at the Investigator's discretion) exclusion criterion #23	Text is unnecessary/possibly confusing as this criterion states that current smokers may be enrolled if they agree to abstain during the inpatient stays
	For exclusion criterion #28: removed "Day -1" added "for non-prescribed substances"	drug screen results for PCP take 3-5 days to obtain, so Day -1 results will not be available before enrolling participants ALXN1850 is unlikely to affect the PK of co-administered small molecules and vice versa
	Changed BMI from ≥ 35 kg/m^2 to > 40 kg/m^2 in exclusion criterion #29	Change will assist participant enrollment without significantly impacting ALXN1850 safety or PK/PD
Section 5.2 Exclusion Criteria Section 6.5.2 Disallowed Medicine and Therapy	Removed exclusion criterion #14 about denosumab Removed the sentence about denosumab	Consideration of denosumab is unnecessary for ALXN1850
Section 5.3 Lifestyle Considerations	Changed "24 hours" to "48 hours" and "admission" to "each dose" in the 1st and 2nd bullets	Align with the change noted above regarding admission to the research site being permitted either the day prior to dosing or predose on the dosing day at the Investigator's discretion
Section 5.3.3 Activity	Added "(strenuous, beyond the participant's routine physical activities)"	To clarify what is meant by vigorous activity
Section 6.5.1 Allowed Medicine and Therapy Section 6.5.2 Disallowed Medicine and Therapy	Added "Prescription medications will be permitted during the study at the Investigator's discretion and recorded in the eCRFs" from Section 6.5.1 and removed "Use of nonprescription/over-the-counter medications, including herbal remedies and supplements, must be discontinued within 7 days before Day 1, except with prior approval from Alexion" from Section 6.5.2	ALXN1850 is unlikely to affect the PK of co-administered small molecules and vice versa, so permitting prescription medication at the Investigator's discretion should assist participant recruitment and retention. Also, these Sections had different wording regarding the use of herbal preparations and supplements in PA3, so they were combined in Section 6.5.1 of PA4
Section 7.2 Participant Discontinuation/Withdrawal from the Study	Added the following: bullets for a positive drug (except prescription medications) or pregnancy tests during the study	For clarity and consistency within the protocol Site requested and Alexion approved For clarity and alignment within the protocol

Section	Description of Change	Brief Rationale and/or Clarification
	wording to the pre-existing bullet regarding a COVID-19 diagnosis that these participants will be evaluated for potential discontinuation from treatment and/or study according to the research site's COVID-19 protocol participants who miss a dosing visit or completes it out-of-window do not need to be withdrawn or discontinued from treatment but won't be considered "completed"	
Section 8.2.3 Electrocardiograms	Added "(all 3 should be performed sequentially within a 15-minute period)" after "The triplicates will be performed at approximately 1-minute intervals"	For clarity
Section 8.5 Pharmacokinetics Section 8.6 Pharmacodynamics	Replaced specific collection windows with a statement to refer to the SoAs	To the reduce redundancy and the SoA is better designed to convey the nuances of this information
Section 10.2 Clinical Laboratory Tests	Changed "central" to "local" in the 1st bullet and deleted the 2nd bullet	A local laboratory is used for safety laboratory tests
	Modified the 6th (now 5th) bullet in Section 10.2 to match the SoA note (serum pregnancy test at Screening and urine pregnancy tests at subsequent timepoints)	For clarity, because the information in these 2 sections slightly conflicted in Protocol Amendment 3
Section 10.2 Clinical Laboratory Tests, Table 6	Removed free hemoglobin, erythrocytes, corpuscular hemoglobin content, mean platelet volume, segmented (after neutrophils), urea, and PLP Removed tetrahydrocannabinol (cannabinoids) Added a footnote for glycated hemoglobin (HbA1c) to indicate that it only needs to be collected at Screening Added a footnote that clinical chemistry must be fasting only at Screening	These tests were determined redundant as the information they provide may be obtained from other laboratory tests already scheduled Recreational use of cannabis use is now legal in several US states and decriminalized/permitted for medicinal use in other states and countries (medicinal use of cannabis may relieve some symptoms of HPP). No drug interactions are anticipated with ALXN1850, given experience with asfotase alfa and its mechanism of action Clinically significant changes in HbA1c between the visits are not expected, and this will reduce participant/site burden For clarity
10.4.2.1 Guidance for Female Participants	Modified the first sentence to indicate that a negative serum pregnancy test is required at Screening instead of within 1 day before the first dose	To align with the SoA and the clarification noted above for Section 10.2

Abbreviations: BMI = body mass index; ECG = electrocardiogram; eCRFs = electronic case report forms; ED = early discontinuationa; EoS = end-of-study; EoT = end-of-treatment; FDA = Food and Drug Administration; HPP = hypophosphatasia; P1NP = propeptide of type I procollagen PD = pharmacodynamics;

PK = pharmacokinetics; PLP = pyridoxal-5'-phosphate; sCTX = serum C-terminal Telopeptide of Type 1 Collagen; SoA = Schedule of Assessments; SRC = Safety Review Committee; ULN = upper limit of normal; VUS = variants of unknown significance

11. REFERENCES

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ALEXION AstraZeneca Rare Disease	Form – Source Copy

Clinical Note to File, Form for ALXN-SOP-0005179

Document Number	Version	Status	Effective Date
ALXN-FRM-0007589	2.0	Effective	03 Sep 2021

CLINICAL NOTE TO FILE

Protocol Number:	ALXN1850-HPP-101	
Site Number:	NA	**Subject Number:** NA
Re:	**Protocol Administrative Change Letter #5 – Incorrect PA version date**	

FILE
(Check at least one)

Sponsor Trial Master File: ■	Investigator Site File: ☐	Other: ☐ Please specify:

Note to File:

This Note to file is to correct the date of the finalised Protocol Amendment #5 in the Administrative Clarification Letter#5.

Current:

Protocol Version:

Amendment 5	~~**11 Feb**~~ **2022**

Corrected:

Protocol Version:

Amendment 5	**10 Mar 2022**

ALEXION AstraZeneca Rare Disease	Form – Source Copy

Clinical Note to File, Form for ALXN-SOP-0005179

Document Number	Version	Status	Effective Date
ALXN-FRM-0007589	2.0	Effective	03 Sep 2021

Prepared by:	[redacted]
Title:	[redacted]
Signature:	[redacted]
Date: *(dd/mmm/yyyy)*	[redacted] 14-Jul-2022 | 08:46:56 EDT

Protocol: ALXN1850-HPP-101

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

Protocol Version:

Amendment 5	**10 Mar 2022**

Protocol Administrative Change Letter #6

Subject of the Administrative Change Letter: Clarification needed regarding the following:

- Postdose timepoints evaluation
- Injection/infusion site evaluation
- Hypersensitivity Reaction Labs

To the sites participating in the above named and numbered clinical study, this letter serves to inform you about the following administrative change to the above referenced protocol version.

- **Clarifications in Section 1.3 Schedule of Activities, Table 1, 2 and 3: Postdose timepoints evaluation**

This document provides clarification that all postdose timepoints are relative to the START of the IV infusion/injection (time 0) EXCEPT for ECG and PK/PD samples, performed/collected at EoI.

- **Clarifications in Section 1.3 Schedule of Activities, Table 1, 2 and 3: Injection/infusion site evaluation**

This document provides clarification on the timeframes for injection/infusion site evaluation. Injection/infusion site evaluations have to be performed from Time 0h and every 15 minutes (+ 5 minutes) until the 1st hr after the start of the injection/infusion. The rest of the timepoints have a window of ± 15minutes.

- **Clarifications in Section 1.3 Schedule of Activities, Table 1, 2 and 3: Hypersensitivity Reaction Labs**

The Hypersensitivity Reaction labs have been clarified to reconcile the information from Table 1 and Table 2 with Table 3.

- If a hypersensitivity reaction is suspected, in general study overview for 1st and subsequent participants (table 1 and 2): hypersensitivity reaction labs (tryptase, IgE, C5b-9) as well as chemistry, hematology, and urinalysis samples should be collected as soon as possible (within 1 hour of the reaction) and again at 2 and 8 hours (+ 1 hour window each) after the 1st sample. The Day 1 predose samples will only be analyzed for participants with a reported suspected hypersensitivity reaction at any time following the first dose. If the participant is not in the clinic, these samples do not need to be collected and suspected hypersensitivity reaction will be reported as an AE only. If the suspected hypersensitivity reaction persists beyond 8 hours, the CRU should contact the MM for guidance.
- If a hypersensitivity reaction is suspected, the day of the dosing (table 3): hypersensitivity reaction labs (tryptase, IgE, C5b-9) as well as chemistry, hematology, and urinalysis samples should be collected as soon as possible (within 1 hour of the reaction) and again at 2 and 8 hours (+ 1 hour window each) after the 1st sample. The Day 1 predose samples will only be analyzed for participants with a reported suspected hypersensitivity reaction at any time following the first dose.

Please file this letter and any IRB/EC correspondence with all copies of the protocol in the Investigator Site File and in all pertinent repositories in which the protocol is maintained. If there are any questions concerning these changes, please contact us. Applicable changes will also be captured in any future protocol amendment.

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Cc: eTMF
[redacted]

Table 1: Schedule of Activities - Study Overview for the First Participant in Each Cohort

Assessments	Screening		Treatment Period																			EoT/ED Assessment	FU/ EoS Assessment
Inpatient (I) or Outpatient (O)[a]	**O**	**I/O**	**I**	**I**	**I/O**	**O**	**O**	**I/O**	**I**	**I**	**I/O**	**O**	**I/O**	**I**	**I**	**I/O**	**I**	**I**	**I/O**	**O**	**O**	**O**	**O**
Study Day	**-56 to -2**	**-1**	**1**	**2**	**3**	**5**	**8**	**14**	**15**	**16**	**17**	**19**	**21**	**22**	**23**	**28**	**29**	**30**	**31**	**36**	**51**	**65**	**85**
Hours postdose[b]				**24**	**48**	**96**	**168**			**24**	**48**	**96**			**24**			**24**	**48**	**168**			
Injection/ infusion site evaluation[c]				X	X		X			X	X				X			X	X	X			
Hypersensitivity rxn labs (tryptase, IgE, C5b-9)[d]			← ~~See footnote [m]~~ X^n →																				
Chemistry, hematology, and urinalysis labs			← X^n→																				

[b] All postdose timepoints are relative to the start of the IV infusion/time of the SC injection (ie, ~~T~~time 0) except the ECG~~vital signs measurements,~~ and PK/~~ and~~ PD sample~~s, and infusion site evaluation~~ performed/collected at the EoI (see Table 3).

Error! Reference source not found. Injection/infusion site evaluations will be performed ~~within 15 minutes (± 5 minutes) after injection/EoI and ± 15 minutes of the rest of the timepoints.~~ from Time 0h and every 15minutes (+ 5 minutes) until the 1st hr after the start of the injection/infusion. The rest of the timepoints have a window of ± 15 minutes (see Table 3).

[d] ~~If the participant is in the clinic, collect the first sample ASAP (preferred) or within 1 hour of the suspected hypersensitivity reaction. The 2 subsequent samples also have a permitted + 1 hour window.~~ If a hypersensitivity reaction is suspected, hypersensitivity reaction labs (tryptase, IgE, C5b-9) as well as chemistry, hematology, and urinalysis samples should be collected as soon as possible (within 1 hour of the reaction) and again at 2 and 8 hours (+ 1 hour window each) after the 1st sample. The Hypersensitivity rxn labs Day 1 predose samples will only be analyzed for participants with a reported suspected hypersensitivity reaction at any time following the first dose. If the participant is not in the clinic, these samples do not need to be collected and suspected hypersensitivity reaction will be reported as an AE only. If the suspected hypersensitivity reaction persists beyond 8 hours, the CRU should contact the MM for guidance.

Table 2: Schedule of Activities - Study Overview for Subsequent Participants in Each Cohort

Assessments	Screening		Treatment Period																		EoT Assessments	FU/ EoS Assessments
Inpatient (I) or Outpatient (O)[a]	O	I/O	I	I	I/O	O	I/O	I	I	I/O	O	I/O	I	I	I/O	I	I	I/O	O	O	O	O
Study Day	-56 to -2	-1	1	2	3	5	7	8	9	10	12	14	15	16	21	22	23	24	29	43	57	78
Hours postdose[b]				24	48	96			24	48	96			24			24	48	168			
Injection/infusion site evaluation[c]				X	X				X	X				X			X	X	X			
Hypersensitivity rxn labs (tryptase, IgE, C5b-9)[d]			~~← See footnote[d]~~ X^n →																			
Chemistry, hematology, and urinalysis labs			← X^n→																			

[b] All postdose timepoints are relative to the start of the IV infusion/time of the SC injection (ie, ~~T~~time 0) except the ECG~~vital signs measurements,~~ and PK/ PD sample~~s, and infusion site evaluation~~ performed/collected at the EoI (see Table 3).

[c]Injection/infusion site evaluations will be performed ~~within 15 minutes (± 5 minutes) after injection/EoI and ± 15 minutes of the rest of the timepoints.~~ from Time/0h and every 15minutes (+ 5 minutes) until the 1st hr after the start of the injection/infusion. The rest of the timepoints have a window of ± 15 minutes (see Table 3).

[d] ~~If the participant is in the clinic, collect the first sample ASAP (preferred) or within 1 hour of the suspected hypersensitivity reaction. The 2 subsequent samples also have a permitted + 1 hour window.~~ If a hypersensitivity reaction is suspected, hypersensitivity reaction labs (tryptase, IgE, C5b-9) as well as chemistry, hematology, and urinalysis samples should be collected as soon as possible (within 1 hour of the reaction) and again at 2 and 8 hours (+ 1 hour window each) after the 1st sample. The Hypersensitivity rxn labs Day 1 predose samples will only be analyzed for participants with a reported suspected hypersensitivity reaction at any time following the first dose. If the participant is not in the clinic, these samples do not need to be collected and suspected hypersensitivity reaction will be reported as an AE only. If the suspected hypersensitivity reaction persists beyond 8 hours, the CRU should contact the MM for guidance.

Table 3: Schedule of Activities – Each Dosing Day for All Participants

Assessments	**Each Dosing Day (Inpatient Visits)**								
Study Day (First Participant)	**Days 1, 15, 22, 29**								
Study Day for (Subsequent Participants)	**Days 1, 8, 15, 22**								
Day/Time	**Day 1 Only**	**Each Dosing Day**							
		Predose		**Dose**	**Postdose[a]**				
	Predose	**Per Window (if specified)**	**-0.5 hr**	**0 hr**	**EoI (IV Dose Only)**	**Every 15 min for 1st hr**	**2**	**6**	**12**
Injection/infusion site evaluation[g]				X	~~X~~	X	X	X	X
Hypersensitivity reaction labs (tryptase, IgE, C5b-9~~, chemistry, hematology, and urinalysis~~)	X			← X[i]→					
Chemistry, hematology, and urinalysis labs				← X[i]→					

[a] All postdose timepoints are relative to the start of the IV infusion/time of the SC injection (ie, time 0 hr) except the ECG and PK/PD samples~~, and infusion site evaluation~~ performed/collected at the EoI (see footnote d).

[g] Injection/infusion site evaluations will be performed ~~during the infusion, after I/EoI, and then within 15 minutes~~ from Time/0h and every 15minutes (+ 5 minutes) until the 1st hr after the start of the injection/infusion. The rest of the timepoints have a window of ± 15 minutes.

[i] If a hypersensitivity reaction is suspected, hypersensitivity reaction labs (tryptase, IgE, C5b-9 as well as chemistry, hematology, and urinalysis samples should be collected as soon as possible (within 1 hour of the reaction) and again at 2 and 8 hours (+ 1 hour window each) after the 1st sample. The Hypersensitivity rxn labs Day 1 predose samples will only be analyzed for participants with a reported suspected hypersensitivity reaction at any time following the first dose.