TITLE PAGE

Protocol Title:

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

Protocol Number: ALXN1830-HV-108

Amendment Number:4

Replaces Amendment 3 (08 Feb 2021)

Compound: ALXN1830

Study Phase: Phase 1

Short Title: Safety, Pharmacokinetic and Pharmacodynamic Study of Subcutaneous ALXN1830 in Healthy Adult Participants

Sponsor Name: Alexion Pharmaceuticals, Inc.

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Regulatory Agency Identifier Number(s)

EudraCT: 2020-001081-11

Approval Date: 25 Jun 2021

Sponsor Signatory:

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Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 25-Jun-2021 | 16:10:18 EDT
7459D191B639408EAE6FAD9DF1F36576

[redacted]

Date

Medical Monitor Contact Information will be provided separately.

INVESTIGATOR'S AGREEMENT

I have read the study protocol amendment and agree to conduct the study in accordance with this protocol amendment, all applicable government regulations, the principles of the ICH E6 Guidelines 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 amendment.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 4 (25 Jun 2021)

Replaces Amendment 3 (08 Feb 2021)

Overall Rationale for the Amendment:

This amendment has been prepared to add pregnancy follow-up testing for female participants of childbearing potential approximately monthly for 3 months after the last dose of study drug to be consistent with the Investigator's Brochure. In addition, changes made in Administrative Letters 2, 3, and 4 have been incorporated into this amendment. Minor editorial updates were made for clarification and consistency.

Section # and Name	Description of Change	Brief Rationale
Throughout the protocol	Updated amendment number and approval date.	Administrative change.
Section 1.3 Schedule of Activities, Tables 2, 4, 5, 6, 7, 8, 10, and 11	Added footnote to clarify that the timing for postdose evaluations at the 2-, 4-, 12-, and 24-hour timepoints (as applicable) is relative to the start of infusion time, and to clarify the order of study activities when multiple procedures are scheduled to occur at the same time.	To clarify that the timing for post-dose samples through the 24-hour timepoint is based on the start of infusion time.
Section 1.3 Schedule of Activities, Tables 2, 4, 5, 6, 7, 8, 9, 10, 11, and 12	Added footnote to indicate that visit windows specified in hours are not applicable for urinalysis.	To allow flexibility in the timing of urine sample collection for urinalysis.
Section 1.3 Schedule of Activities, Table 3 (Cohorts 1 and 2)	Added footnote to clarify that the pregnancy test at Day 64/ET for the SAD cohorts may be either serum or urine, and to specify that urine pregnancy test kits should be dispensed for monthly pregnancy testing post Day 64/ET.	To clarify that either serum or urine pregnancy tests may be performed at Day 64/ET for the SAD cohorts and to ensure urine pregnancy test kits are dispensed as needed.
Section 1.3 Schedule of Activities, Table 3 (Cohorts 1 and 2)	For SAD cohorts, added a Day 92 Follow-up Phone Call to capture the collection of pregnancy test results, along with AEs and concomitant medications, at Day 92 or for 3 months after the last dose; revised the footnote to clarify collection of these results.	To add the process for collection of follow-up pregnancy test results.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities, Table 9 (Cohort 3)	Added a footnote to specify that at Day 141/ET, urine pregnancy test kits should be dispensed for monthly pregnancy testing post Day 141/ET.	To ensure that urine pregnancy test kits are dispensed as needed for follow-up pregnancy testing.
Section 1.3 Schedule of Activities, Table 9 (Cohort 3)	Added a Day 169 Follow-up Phone Call to capture the collection of pregnancy test results, along with AEs and concomitant medications, at Day 169 or for 3 months after the last dose; added a footnote to clarify collection of these results.	To add the process for collection of follow-up pregnancy test results.
Section 1.3 Schedule of Activities, Table 12 (Cohorts 4 to 6)	Added pregnancy test at Day 50; added footnote to specify that urine pregnancy test kits should be dispensed for monthly pregnancy testing post Day 85/ET.	To perform pregnancy testing approximately every 28 days; to ensure urine pregnancy test kits are dispensed as needed.
Section 1.3 Schedule of Activities, Table 12 (Cohorts 4 to 6)	Added a Day 113 Follow-up Phone Call to capture the collection of pregnancy test results, along with AEs and concomitant medications, at Day 113 or for 3 months after the last dose.	To add the process for collection of follow-up pregnancy test results.
Section 5.1 Inclusion Criteria	Revised inclusion criterion 5 to allow participants with IgA or IgM levels above the lower limit of normal to enter the study.	Based on available data, IgA or IgM reduction is not expected with ALXN1830 administration; therefore, participants with IgA or IgM above the lower limit of normal may be enrolled.
Section 6.1 Study Interventions Administered	Revised description of the use of different compositions.	To clarify that different compositions of ALXN1830 may be used for the SAD and MAD cohorts.
Section 6.2 Preparation/Handling/Storage/Accountability	Changed "The Investigator must confirm appropriate temperature conditions…study drug" to "The Investigator or designee must confirm appropriate temperature conditions…study drug."	To enhance clarity.

Section # and Name	Description of Change	Brief Rationale
Section 7.2.1 Immunoglobulin Stopping Rules	Added text to specify that a participant for whom IgA or IgM falls below the normal limit and is associated with clinical signs and symptoms will be discontinued from further dosing.	To clarify that participants with IgA or IgM below the normal range and clinical signs and symptoms will be discontinued from dosing.
Throughout the document	Minor grammatical, editorial, and document formatting revisions.	To enhance clarity.

Abbreviations: AE = adverse event; ET = early termination; FcRn occupancy = neonatal crystallizable fragment receptor; Ig = immunoglobulin; MAD = multiple ascending dose; SAD = single-ascending dose

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1. PROTOCOL SUMMARY

1.1. Synopsis

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

Short Title: Safety, Pharmacokinetic and Pharmacodynamic Study of Subcutaneous ALXN1830 in Healthy Adult Participants

Rationale:

ALXN1830, an anti-neonatal crystallizable fragment receptor (FcRn) monoclonal antibody (mAb), has the potential to reduce the level of pathogenic immunoglobulin G (IgG) involved in certain autoimmune disorders. The purpose of this Phase 1 study in healthy adult participants is to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of single ascending doses (SAD) and multiple ascending doses (MAD) of ALXN1830 administered subcutaneously (SC) and to compare safety, tolerability, PK, PD, and immunogenicity of ALXN1830 in Japanese participants with non-Japanese participants. Data from this study are anticipated to help design future studies in patients with IgG-mediated diseases.

Objectives and Endpoints

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

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

Overall Design

This is a Phase 1 study in up to 48 healthy adult participants (36 on active treatment, 12 on placebo [PBO]). The study will consist of 2 SAD (Cohorts 1 and 2) and 4 MAD cohorts (Cohorts 3 to 6). Cohort 6 will enroll only Japanese[1] participants). Eight participants will be randomly assigned in a 6:2 ratio to each of the 6 cohorts to receive either single or multiple doses of ALXN1830 SC (n = 6 per cohort) or single or multiple doses of PBO (n = 2 per cohort).

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

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

Disclosure Statement: This is a sequential treatment study with 6 cohorts that is participant and Investigator blinded.

Number of Participants:

A maximum of 48 participants will be randomized such that approximately 8 evaluable participants per each of 6 cohorts complete the study. The number of participants was chosen based on feasibility and was considered adequate to meet the study objectives.

Study Cohorts and Study Duration:

Participants will be randomly assigned in a 6:2 ratio to each of the 6 cohorts to receive either single or multiple doses of ALXN1830 SC (n = 6 per cohort) or single or multiple doses of PBO (n = 2 per cohort). The planned dose and dose regimens are shown in Table 1. The planned study duration is approximately 124 days for Cohorts 1 and 2: up to 60 days for screening and

[1]Japanese descent is defined as:

- First generation (born to 2 Japanese parents and 4 Japanese grandparents)
- Participant must have been born in Japan, and not have lived outside Japan for greater than 10 years
- Lifestyle, including diet, must not have significantly changed since leaving Japan

approximately 64 days for dosing and follow-up; 201 days for Cohort 3: up to 60 days for screening and approximately 141 days for dosing and follow-up; and 148 days for Cohorts 4 to 6: 60 days for screening and approximately 88 days for dosing and follow-up. Participants will be admitted to an inpatient facility during the dosing and follow-up period as shown in the schedule of activities (SoA). The study schematic is presented in Figure 1.

Table 1: Planned Dose and Dose Regimens in Healthy Participants

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

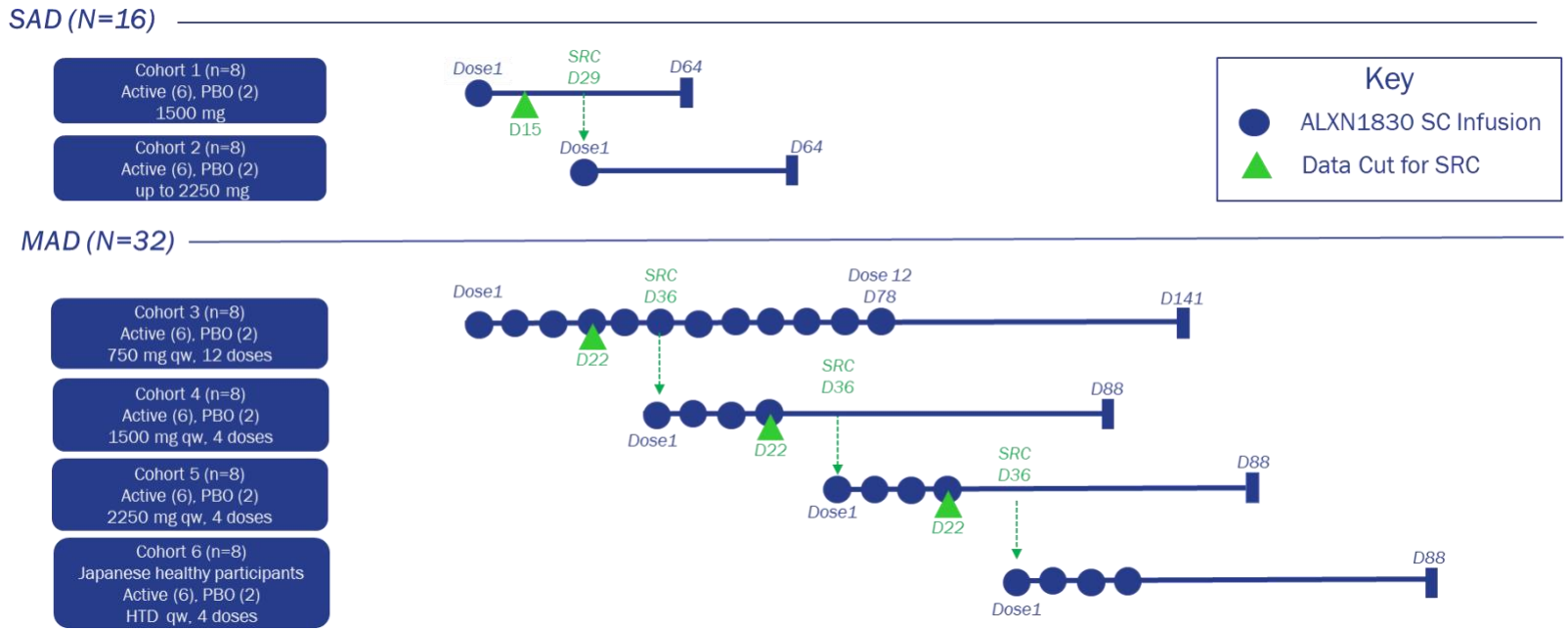
[a] Healthy, Japanese participants enrolled in Cohort 6 will be dosed according to the HTD established in the non-Japanese cohorts.

Abbreviations: qw = weekly; SC = subcutaneous; HTD = highest tolerated dose.

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

1.2. Schema

Figure 1 Study Schematic Diagram



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

1.3. Schedule of Activities (SoA)

The SoA for SAD Cohorts 1 and 2 (Table 2 and Table 3), MAD Cohort 3 (Table 4, Table 5, Table 6, Table 7, Table 8, and Table 9), and MAD Cohorts 4 to 6 (Table 10, Table 11, and Table 12) are presented below.

Note: When multiple procedures are scheduled to occur at the same time, the following order of events should be strictly adhered to whenever possible: ECG, vital signs, blood sampling, study intervention administration.

Table 2: SoA – Screening Through Day 8 for Single-Dose Cohorts 1 and 2

Study Day	**Screening**	**Day -1**	**---------- Day 1 (Dosing Day)----------**					**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8[a]**
Assessments	**Day –60 to Day –2**	**Admit**	**Predose**	**EOI**	**2 h[b]**	**4 h[b]**	**12 h[b]**	**24 h[b]**	**48 h**	**72 h**	**96 h**	**120 h**	**144 h**	**168 h**
Window (hours)			**NA**	**+0.25**	**±0.25**	**±0.5**	**±0.5**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**
Status (OP or CRU)	**OP**	**Admit**	**CRU**											
Informed consent	X													
Inclusion/exclusion criteria	X	X												
Serum pregnancy test (WOCBP)	X	X												
FSH test (postmenopausal women)	X													
Alcohol breath test	X	X												
Urine drug screen	X	X												
Hepatitis B and C screen	X													
Evidence of vaccination[c]	X	X												
HIV (types 1 and 2) screen	X													
Medical history and demographics	X	X												
Physical examination[d]	X		X							X				X
Height, weight, and BMI[e]	X		X											
Randomization			X											
Study drug administration			X											
PK blood sampling			X	X	X	X	X	X	X	X	X	X	X	X
PD blood sampling - IgA, IgM, IgG	X		X	X	X	X	X	X	X	X	X	X	X	X
PD blood sampling - IgG subtypes 1-4			X	X	X	X	X	X	X	X	X	X	X	X
PD blood sampling – CIC			X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity blood sampling - ADA			X											
FcRn occupancy			X	X	X		X	X	X	X		X		X
Biochemistry[f], hematology, coagulation	X	X						X		X				X
Exploratory biomarker sample		X						X		X				X
Urinalysis[g]	X	X						X		X				X
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG (triplicate)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Infusion site evaluation[i]				X	X	X	X	X[j]						
Concomitant medications		←Monitor continuously (after ICF is signed at Screening)→												
Adverse events		←Monitor continuously (after ICF is signed at Screening)→												

[a] Participant will be discharged from the CRU after completing all Day 8 assessments.

[b] Postdose evaluations at the 2-hour, 4-hour, 12-hour, and 24-hour timepoints are to be completed based on the start of infusion time. When multiple procedures are scheduled to occur at the same time, the following order of events should be strictly adhered to whenever possible: ECG, vital signs, blood sampling, and study intervention administration.
[c] All participants must be vaccinated as described in Section 6.5.3.
[d] Full PE at screening and symptom directed PE thereafter.
[e] Height and BMI at Screening only.
[f] Fasting, due to lipid panel. Note: lipid panel is not performed at Screening.
[g] Visit window (hours) is not applicable for urinalysis.
[h] Including temperature, respiratory rate, and pulse oximetry.
[i] In the event of an IRR, it is recommended to collect a blood sample for assessment of tryptase, histamine, CRP, cytokines, and complement as soon as the IRR is observed (prior to administering any IRR medication), and 2 hours, 24 hours, and 7 days (prior to the next dose of study drug) after onset of the IRR; a blood sample for PK/PD and ADAs may be collected if there is no predefined sample collection on the same day.
[j] IRR evaluation will continue until the reaction is fully resolved.

Abbreviations: ADA = antidrug antibodies; BMI = body mass index; CIC = circulating immune complexes; CRP = C-reactive protein; CRU = Clinical Research Unit; ECG = electrocardiogram; EOI = end of infusion; FcRn = neonatal crystallizable fragment receptor; HIV = human immunodeficiency virus; ICF = informed consent form; Ig = immunoglobulin; IRR = infusion related reaction; NA = not applicable; OP = outpatient; PD = pharmacodynamic(s); PE = physical examination; PK = pharmacokinetic(s); WOCBP = women of childbearing potential.

Table 3: SoA – Day 12 Through Day 64/ET for Single-Dose Cohorts 1 and 2

Assessments/ Study Day	Day 12	Day 15	Day 22	Day 29	Day 36	Day 43	Day 50	Day 57	Day 64/ET	Day 92 Follow-up Phone Call
Window (days)	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±3**
Status (OP or CRU)	**OP**									
Pregnancy test				X[a]					X[b]	X[c]
Physical examination[d]				X					X	
PK blood sampling	X	X	X	X	X	X	X	X	X	
PD blood sampling - IgA, IgM, IgG	X	X	X	X	X	X	X	X	X	
PD blood sampling - IgG subtypes 1-4	X	X	X	X	X	X	X	X	X	
PD blood sampling – CIC	X	X	X	X	X	X	X	X	X	
Immunogenicity blood sampling - ADA		X		X		X			X[e]	
FcRn occupancy	X	X	X							
Biochemistry[f], hematology, coagulation		X		X		X			X	
Exploratory biomarker sample		X		X		X			X	
Urinalysis		X		X		X			X	
Vital signs[g]	X	X	X	X	X	X	X	X	X	
12-lead ECG (triplicate)		X		X		X			X	
Concomitant medications	←Monitor continuously (after ICF is signed at Screening)→									
Adverse events	←Monitor continuously (after ICF is signed at Screening)→									

[a] Serum pregnancy test.
[b] May be serum or urine pregnancy test. For the Day 64 Visit, dispense a urine pregnancy test kit for the Day 92 Follow-up Phone Call. For an ET Visit, dispense urine pregnancy test kit to allow monthly testing for 3 months after the last dose.
[c] Participants will be requested to take a urine pregnancy test at home at approximately Day 92, or, if ET, monthly for 3 months after the last dose; the site will solicit pregnancy test results, along with adverse events and concomitant medications, via phone call.
[d] Symptom directed PE.
[e] Participants who are ADA positive at Day 64/ET will be followed for up to 1 year (from the study drug administration) or until ADA titers return to baseline levels (whichever occurs first, see Section 8.9 for more details).
[f] Fasting, due to lipid panel. Note: lipid panel is not performed at Screening.
[g] Including temperature, respiratory rate, and pulse oximetry.
Abbreviations: ADA = antidrug antibodies; CIC = circulating immune complexes; CRU = Clinical Research Unit; ECG = electrocardiogram; ET = early termination; FcRn = neonatal crystallizable fragment receptor; ICF = informed consent form; Ig = immunoglobulin; OP = outpatient; PD = pharmacodynamic(s); PE = physical examination; PK = pharmacokinetic(s); WOCBP = women of childbearing potential.

Table 4: SoA – Screening Through Day 9 for Multiple-Dose Cohort 3

Study Day	**Screen-ing**	**-1**	**1**					**2**	**3**	**4**	**5**	**6**	**7**	**8**			**9**[a]
Assessments	**Day -60 to Day -2**	**Admit**	**Pre-dose**	**EOI**	**2 h**[b]	**4 h**[b]	**12 h**[b]	**24 h**[b]	**48 h**	**72 h**	**96 h**	**120 h**	**144 h**	**Pre-dose**	**EOI**	**2 h**[b]	**24 h**[b]
Window (hours)			**NA**	**+0.25**	**±0.25**	**±0.5**	**±0.5**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**NA**	**+0.25**	**±0.25**	**±1**
Status (OP or CRU)	**OP**	**CRU**															
Informed consent	X																
Inclusion/exclusion criteria	X	X[c]															
Pregnancy test (WOCBP)[d]	X	X															
FSH test (postmenopausal women)	X																
Alcohol breath test	X	X															
Urine drug screen	X	X															
Hepatitis B and C screen	X																
Evidence of vaccination[e]	X	X[c]															
HIV (types 1 and 2) screen	X																
Medical history and demographics	X	X[c]															
Physical examination[f]	X		X							X				X			
Height, weight, and BMI[g]	X		X														
Randomization			X														
Study drug administration			X											X			
PK blood sampling			X		X	X	X	X	X	X	X	X	X	X			
PD blood sampling - IgA, IgM, IgG	X		X		X	X	X	X	X	X	X	X	X	X			
PD blood sampling - IgG subtypes 1-4			X		X	X	X	X	X	X	X	X	X	X			
PD blood sampling – CIC			X		X	X	X	X	X	X	X	X	X	X			
Immunogenicity blood sampling - ADA			X														
FcRn occupancy			X		X		X	X	X	X		X		X			
Biochemistry[h]	X	X								X				X			
Coagulation	X	X								X							
Hematology	X	X						X		X				X			
Exploratory biomarker sample		X								X							
Urinalysis[i]	X	X						X		X							
Vital signs[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 4: SoA – Screening Through Day 9 for Multiple-Dose Cohort 3

Study Day	**Screen-ing**	**-1**	**1**					**2**	**3**	**4**	**5**	**6**	**7**	**8**			**9**[a]
Assessments	**Day -60 to Day -2**	**Admit**	**Pre-dose**	**EOI**	**2 h**[b]	**4 h**[b]	**12 h**[b]	**24 h**[b]	**48 h**	**72 h**	**96 h**	**120 h**	**144 h**	**Pre-dose**	**EOI**	**2 h**[b]	**24 h**[b]
Window (hours)			**NA**	**+0.25**	**±0.25**	**±0.5**	**±0.5**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**NA**	**+0.25**	**±0.25**	**±1**
Status (OP or CRU)	**OP**	**CRU**															
12-lead ECG (triplicate)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Infusion site evaluation[k]				X	X	X	X	X[l]							X	X	X[l]
Concomitant medications	←Monitor continuously (after ICF is signed at Screening)→																
Adverse events	←Monitor continuously (after ICF is signed at Screening)→																

[a] Participant will be discharged from the CRU after completing all Day 9, 16, 30, 37, 44, 51, 58, 65, 72, and 85 assessments.
[b] Postdose evaluations at the 2-hour, 4-hour, 12-hour, and 24-hour timepoints are to be completed based on the start of infusion time. When multiple procedures are scheduled to occur at the same time, the following order of events should be strictly adhered to whenever possible: ECG, vital signs, blood sampling, and study intervention administration.
[c] Activities will be performed on Day -1 only.
[d] Serum pregnancy test at Screening and Day -1 and urine pregnancy test for all other timepoints in CRU.
[e] All participants must be vaccinated as described in Section 6.5.3.
[f] Full PE at screening and symptom directed PE thereafter.
[g] Height and BMI at Screening only.
[h] Fasting, due to lipid panel. Note: lipid panel is not performed at Screening.
[i] Visit window (hours) is not applicable for urinalysis.
[j] Including temperature, respiratory rate, and pulse oximetry.
[k] In the event of an IRR, it is recommended to collect a blood sample for assessment of tryptase, histamine, CRP, cytokines, and complement as soon as the IRR is observed (prior to administering any IRR medication), and 2 hours, 24 hours, and 7 days (prior to the next dose of study drug) after onset of the IRR; a sample for PK/PD and ADAs may be collected if there is no predefined sample collection on the same day.
[l] IRR evaluation will continue until the reaction is fully resolved.

Abbreviations: ADA = antidrug antibodies; BMI = body mass index; CIC = circulating immune complexes; CRP = C-reactive protein; CRU = Clinical Research Unit; ECG = electrocardiogram; EOI = end of infusion; FcRn = neonatal crystallizable fragment receptor; HIV = human immunodeficiency virus; ICF = informed consent form; Ig = immunoglobulin; IRR = infusion related reaction; NA = not applicable; OP = outpatient; PD = pharmacodynamic(s); PE = physical examination; PK = pharmacokinetic(s); WOCBP = women of childbearing potential.

Table 5: SoA – Day 14 through 28 for Multiple-Dose Cohort 3

Study Day	**14**	**15**			**16[a]**	**21**	**22**					**23**	**24**	**25**	**26**	**27**	**28**
Assessments	**Admit**	**Pre-dose**	**EOI**	**2 h[b]**	**24 h[b]**	**Admit**	**Pre-dose**	**EOI**	**2 h[b]**	**4 h[b]**	**12 h[b]**	**24 h[b]**	**48 h**	**72 h**	**96 h**	**120 h**	**144 h**
Window (hours)		**NA**	**+0.25**	**±0.25**	**±1**		**NA**	**+0.25**	**±0.25**	**±0.5**	**±0.5**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**
Status (OP or CRU)	**CRU**																
Pregnancy test (WOCBP)[c]	X					X											
Alcohol breath test	X					X											
Urine drug screen	X					X											
Physical examination[d]		X					X							X			
Weight		X					X										
Study drug administration		X					X										
PK blood sampling		X					X		X	X	X	X	X	X	X	X	X
PD blood sampling - IgA, IgM, IgG		X					X		X	X	X	X	X	X	X	X	X
PD blood sampling - IgG subtypes 1-4		X					X		X	X	X	X	X	X	X	X	X
PD blood sampling – CIC		X					X		X	X	X	X	X	X	X	X	X
Immunogenicity blood sampling - ADA		X															
FcRn occupancy		X					X		X		X	X	X	X		X	
Biochemistry[e,f]	X					X								X			
Hematology[e]	X					X						X		X			
Exploratory biomarker sample														X			
Urinalysis[g]	X					X						X		X			
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG (triplicate)		X					X		X	X	X	X	X	X	X	X	X
Infusion site evaluation[i]			X	X[g]	X			X	X	X	X	X[j]					
Concomitant medications	←Monitor continuously (after ICF is signed at Screening)→																
Adverse events	←Monitor continuously (after ICF is signed at Screening)→																

[a] Participant will be discharged from the CRU after completing all Day 9, 16, 30, 37, 44, 51, 58, 65, 72, and 85 assessments.
[b] Postdose evaluations at the 2-hour, 4-hour, 12-hour, and 24-hour timepoints are to be completed based on the start of infusion time. When multiple procedures are scheduled to occur at the same time, the following order of events should be strictly adhered to whenever possible: ECG, vital signs, blood sampling, and study intervention administration.
[c] Serum pregnancy test at Screening and Day -1 and urine pregnancy test for all other timepoints in CRU.
[d] Full PE at screening and symptom directed PE thereafter.
[e] May be done on the day prior to dosing.
[f] Fasting, due to lipid panel. Note: lipid panel is not performed at Screening.
[g] Visit window (hours) is not applicable for urinalysis.
[h] Including temperature, respiratory rate, and pulse oximetry.
[i] In the event of an IRR, it is recommended to collect a blood sample for assessment of tryptase, histamine, CRP, cytokines, and complement as soon as the IRR is observed (prior to administering any IRR medication), and 2 hours, 24 hours, and 7 days (prior to the next dose of study drug) after onset of the IRR; a sample for PK/PD and ADAs may be collected if there is no predefined sample collection on the same day.
[j] IRR evaluation will continue until the reaction is fully resolved.

Abbreviations: ADA = antidrug antibodies; CIC = circulating immune complexes; CRP = C-reactive protein; CRU = Clinical Research Unit; ECG = electrocardiogram; EOI = end of infusion; FcRn = neonatal crystallizable fragment receptor; ICF = informed consent form; Ig = immunoglobulin; IRR = infusion related reaction; NA = not applicable; OP = outpatient; PD = pharmacodynamic(s); PE = physical examination; PK = pharmacokinetic(s); WOCBP = women of childbearing potential.

Table 6: SoA – Day 29 Through Day 44 for Multiple-Dose Cohort 3

Study Day	**29**			**30**[a]	**35**	**36**			**37**[a]	**42**	**43**			**44**[a]
Assessments	**Pre-dose**	**EOI**	**2 h**[b]	**24 h**[b]	**Admit**	**Pre-dose**	**EOI**	**2 h**[b]	**24 h**[b]	**Admit**	**Pre-dose**	**EOI**	**2 h**[b]	**24 h**[b]
Window (hours)	**NA**	**+0.25**	**±0.25**	**±1**		**NA**	**+0.25**	**±0.25**	**±1**		**NA**	**+0.25**	**±0.25**	**±1**
Status (OP or CRU)	**CRU**													
Pregnancy test (WOCBP)[c]					X					X				
Alcohol breath test					X					X				
Urine drug screen					X					X				
Physical examination[d]	X					X					X			
Weight	X					X					X			
Study drug administration	X					X					X			
PK blood sampling	X					X					X			
PD blood sampling - IgA, IgM, IgG	X					X					X			
PD blood sampling - IgG subtypes 1-4	X					X					X			
PD blood sampling – CIC	X					X					X			
Immunogenicity blood sampling - ADA	X										X			
FcRn occupancy	X					X					X			
Biochemistry[e,f]					X					X				
Hematology[e]	X				X					X				
Exploratory biomarker sample										X				
Urinalysis[g]					X					X				
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG (triplicate)	X					X					X			
Infusion site evaluation[i]		X	X[j]	X			X	X[j]	X			X	X[j]	X
Concomitant medications	←Monitor continuously (after ICF is signed at Screening)→													
Adverse events	←Monitor continuously (after ICF is signed at Screening)→													

[a] Participant will be discharged from the CRU after completing all Day 9, 16, 30, 37, 44, 51, 58, 65, 72, and 85 assessments.

[b] Postdose evaluations at the 2-hour and 24-hour timepoints are to be completed based on the start of infusion time. When multiple procedures are scheduled to occur at the same time, the following order of events should be strictly adhered to whenever possible: ECG, vital signs, blood sampling, and study intervention administration.

[c] Serum pregnancy test at Screening and Day -1 and urine pregnancy test for all other timepoints in CRU.

[d] Full PE at screening and symptom directed PE thereafter.

[e] May be done on the day prior to dosing.

[f] Fasting, due to lipid panel. Note: lipid panel is not performed at Screening.

[g] Visit window (hours) is not applicable for urinalysis.
[h] Including temperature, respiratory rate, and pulse oximetry.
[i] In the event of an IRR, it is recommended to collect a blood sample for assessment of tryptase, histamine, CRP, cytokines, and complement as soon as the IRR is observed (prior to administering any IRR medication), and 2 hours, 24 hours, and 7 days (prior to the next dose of study drug) after onset of the IRR; a sample for PK/PD and ADAs may be collected if there is no predefined sample collection on the same day.
[j] IRR evaluation will continue until the reaction is fully resolved.

Abbreviations: ADA = antidrug antibodies; CIC = circulating immune complexes; CRP = C-reactive protein; CRU = Clinical Research Unit; ECG = electrocardiogram; EOI = end of infusion; FcRn = neonatal crystallizable fragment receptor; ICF = informed consent form; Ig = immunoglobulin; IRR = infusion related reaction; NA = not applicable; OP = outpatient; PD = pharmacodynamic(s); PE = physical examination; PK = pharmacokinetic(s); WOCBP = women of childbearing potential.

Table 7: SoA – Day 49 Through Day 65 for Multiple-Dose Cohort 3

Study Day	**49**	**50**			**51**[a]	**56**	**57**			**58**[a]	**63**	**64**			**65**[a]
Assessments	**Admit**	**Pre-dose**	**EOI**	**2 h**[b]	**24 h**[b]	**Admit**	**Pre-dose**	**EOI**	**2 h**[b]	**24 h**[b]	**Admit**	**Pre-dose**	**EOI**	**2 h**[b]	**24 h**[b]
Window (hours)		**NA**	**+0.25**	**±0.25**	**±1**		**NA**	**+0.25**	**±0.25**	**±1**		**NA**	**+0.25**	**±0.25**	**±1**
Status (OP or CRU)	**CRU**														
Pregnancy test (WOCBP)[c]	X					X					X				
Alcohol breath test	X					X					X				
Urine drug screen	X					X					X				
Physical examination[d]		X					X					X			
Weight		X					X					X			
Study drug administration		X					X					X			
PK blood sampling		X					X					X			
PD blood sampling - IgA, IgM, IgG		X					X					X			
PD blood sampling - IgG subtypes 1-4		X					X					X			
PD blood sampling – CIC		X					X					X			
Immunogenicity blood sampling - ADA		X					X					X			
FcRn occupancy							X								
Biochemistry[e,f]	X					X					X				
Hematology[e]	X					X					X				
Exploratory biomarker sample	X					X					X				
Urinalysis[g]	X					X					X				
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG (triplicate)		X					X					X			
Infusion site evaluation[i]			X	Xj	X			X	Xj	X			X	Xj	X
Concomitant medications	←Monitor continuously (after ICF is signed at Screening)→														
Adverse events	←Monitor continuously (after ICF is signed at Screening)→														

[a] Participant will be discharged from the CRU after completing all Day 9, 16, 30, 37, 44, 51, 58, 65, 72, and 85 assessments.
[b] Postdose evaluations at the 2-hour and 24-hour timepoints are to be completed based on the start of infusion time. When multiple procedures are scheduled to occur at the same time, the following order of events should be strictly adhered to whenever possible: ECG, vital signs, blood sampling, and study intervention administration.
[c] Serum pregnancy test at Screening and Day -1 and urine pregnancy test for all other timepoints in CRU.
[d] Full PE at screening and symptom directed PE thereafter.
[e] May be done on the day prior to dosing.
[f] Fasting, due to lipid panel. Note: lipid panel is not performed at Screening.
[g] Visit window (hours) is not applicable for urinalysis.
[h] Including temperature, respiratory rate, and pulse oximetry.

[i] In the event of an IRR, it is recommended to collect a blood sample for assessment of tryptase, histamine, CRP, cytokines, and complement as soon as the IRR is observed (prior to administering any IRR medication), and 2 hours, 24 hours, and 7 days (prior to the next dose of study drug) after onset of the IRR; a sample for PK/PD and ADAs may be collected if there is no predefined sample collection on the same day.

[j] IRR evaluation will continue until the reaction is fully resolved.

Abbreviations: ADA = antidrug antibodies; CIC = circulating immune complexes; CRP = C-reactive protein; CRU = Clinical Research Unit; ECG = electrocardiogram; EOI = end of infusion; FcRn = neonatal crystallizable fragment receptor; ICF = informed consent form; Ig = immunoglobulin; IRR = infusion related reaction; NA = not applicable; OP = outpatient; PD = pharmacodynamic(s); PE = physical examination; PK = pharmacokinetic(s); WOCBP = women of childbearing potential.

Table 8: SoA – Day 70 Through Day 79 for Multiple-Dose Cohort 3

Study Day	**70**	**71**			**72**[a]	**77**	**78**					**79**
Assessments	**Admit**	**Pre-dose**	**EOI**	**2 h**[b]	**24 h**[b]	**Admit**	**Pre-dose**	**EOI**	**2 h**[b]	**4 h**[b]	**12 h**[b]	**24 h**[b]
Window (hours)		**NA**	**+0.25**	**±0.25**	**±1**		**NA**	**+0.25**	**±0.25**	**±0.5**	**±0.5**	**±1**
Status (OP or CRU)	**CRU**											
Pregnancy test (WOCBP)[c]	X					X						
Alcohol breath test	X					X						
Urine drug screen	X					X						
Physical examination[d]		X					X					
Weight		X					X					
Study drug administration		X					X					
PK blood sampling		X					X		X	X	X	X
PD blood sampling - IgA, IgM, IgG		X					X		X	X	X	X
PD blood sampling - IgG subtypes 1-4		X					X		X	X	X	X
PD blood sampling – CIC		X					X		X	X	X	X
Immunogenicity blood sampling - ADA		X										
FcRn occupancy		X					X		X		X	X
Biochemistry[e]	X					X						
Hematology	X					X						X
Urinalysis[f]	X					X						X
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG (triplicate)		X					X		X	X	X	X
Infusion site evaluation[h]			X	X	X[i]			X	X	X	X	X[i]
Concomitant medications	←Monitor continuously (after ICF is signed at Screening)→											
Adverse events	←Monitor continuously (after ICF is signed at Screening)→											

[a] Participant will be discharged from the CRU after completing all Day 9, 16, 30, 37, 44, 51, 58, 65, 72, and 85 assessments.

[b] Postdose evaluations at the 2-hour, 4-hour, 12-hour, and 24-hour timepoints are to be completed based on the start of infusion time. When multiple procedures are scheduled to occur at the same time, the following order of events should be strictly adhered to whenever possible: ECG, vital signs, blood sampling, and study intervention administration.

[c] Serum pregnancy test at Screening and Day -1 and urine pregnancy test for all other timepoints in CRU.

[d] Full PE at screening and symptom directed PE thereafter.

[e] Fasting, due to lipid panel. Note: lipid panel is not performed at Screening.

[f] Visit window (hours) is not applicable for urinalysis.

[g] Including temperature, respiratory rate, and pulse oximetry.

[h] In the event of an IRR, it is recommended to collect a blood sample for assessment of tryptase, histamine, CRP, cytokines, and complement as soon as the IRR is observed (prior to administering any IRR medication), and 2 hours, 24 hours, and 7 days (prior to the next dose of study drug) after onset of the IRR; a sample for PK/PD and ADAs may be collected if there is no predefined sample collection on the same day.

[i] IRR evaluation will continue until the reaction is fully resolved.

Abbreviations: ADA = antidrug antibodies; CIC = circulating immune complexes; CRP = C-reactive protein; CRU = Clinical Research Unit; ECG = electrocardiogram; EOI = end of infusion; FcRn = neonatal crystallizable fragment receptor; ICF = informed consent form; Ig = immunoglobulin; IRR = infusion related reaction; NA = not applicable; OP = outpatient; PD = pharmacodynamic(s); PE = physical examination; PK = pharmacokinetic(s); WOCBP = women of childbearing potential.

Table 9: SoA – Day 80 Through Day 141 for Multiple-Dose Cohort 3

Study Day	**80**	**81**	**82**	**83**	**84**	**85**[a]	**99**	**113**	**120**	**134**	**141/ET**	**Day 169 Follow-up Phone Call**
Assessments	**48 h**	**72 h**	**96 h**	**120 h**	**144 h**	**168 h**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**
Window (CRU = hours; OP = days)	**±1 h**	**±1 h**	**±1 h**	**±1 h**	**±1 h**	**±1 h**	**±1 day**	**±1 day**	**±1 day**	**±1 day**	**±1 day**	**±3 days**
Status (OP or CRU)	**CRU**						**OP**					
Pregnancy test (WOCBP)[b]							X		X		X[c]	X[d]
Physical examination[e]						X					X	
Weight						X					X	
PK blood sampling	X	X	X	X	X	X	X	X	X	X	X	
PD blood sampling - IgA, IgM, IgG	X	X	X	X	X	X	X	X	X	X	X	
PD blood sampling - IgG subtypes 1-4	X	X	X	X	X	X	X	X	X	X	X	
PD blood sampling – CIC	X	X	X	X	X	X	X	X	X	X	X	
Immunogenicity blood sampling - ADA						X	X		X		X	
FcRn occupancy		X		X		X	X		X			
Biochemistry[f]		X				X		X			X	
Coagulation						X					X	
Hematology		X				X		X			X	
Exploratory biomarker sample		X				X					X	
Urinalysis[g]		X				X						
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG (triplicate)	X	X	X	X	X	X					X	
Concomitant medications	←Monitor continuously (after ICF is signed at Screening)→											
Adverse events	←Monitor continuously (after ICF is signed at Screening)→											

[a] Participant will be discharged from the CRU after completing all Day 9, 16, 30, 37, 44, 51, 58, 65, 72, and 85 assessments.

[b] Serum pregnancy test at Screening and Day -1 and urine pregnancy test for all other timepoints in CRU and OP.

[c] For the Day 141 Visit, dispense a urine pregnancy test kit for the Day 169 Follow-up Phone Call. For an ET Visit, dispense urine pregnancy test kits to allow monthly testing for 3 months after the last dose.

[d] Participants will be requested to take a urine pregnancy test at home at approximately Day 169, or if ET, monthly for 3 months after the last dose; the site will solicit pregnancy test results, along with adverse events and concomitant medications, via phone call.

[e] Full PE at screening and symptom directed PE thereafter.

[f] Fasting, due to lipid panel. Note: lipid panel is not performed at Screening.

[g] Visit window (hours) is not applicable for urinalysis.

[h] Including temperature, respiratory rate, and pulse oximetry.

Abbreviations: ADA = antidrug antibodies; CIC = circulating immune complexes; CRU = Clinical Research Unit; ECG = electrocardiogram; EOI = end of infusion; ET = early termination; FcRn = neonatal crystallizable fragment receptor; h = hours; ICF = informed consent form; Ig = immunoglobulin; NA = not applicable; OP = outpatient; PD = pharmacodynamic(s); PE = physical examination; PK = pharmacokinetic(s); WOCBP = women of childbearing potential.

Table 10: SoA – Screening Through Day 7 for Multiple-Dose Cohorts 4 to 6

Study Day	**Screening**	**-1**	**1**					**2**	**3**	**4**	**5**	**6**	**7**
Assessments	**Day –60 to Day -2**	**Admit**	**Pre-dose**	**EOI**	**2 h[a]**	**4 h[a]**	**12 h[a]**	**24 h[a]**	**48 h**	**72 h**	**96 h**	**120 h**	**144 h**
Window (hours)			**NA**	**+0.25**	**±0.25**	**±0.5**	**±0.5**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**
Status (CRU or OP)	**OP**	**CRU**											
Informed consent	X												
Inclusion/exclusion criteria	X	X[b]											
Pregnancy test (WOCBP)[c]	X	X											
FSH test (postmenopausal women)	X												
Alcohol breath test	X	X											
Urine drug screen	X	X											
Hepatitis B and C screen	X												
Evidence of vaccination[d]	X	X[b]											
HIV (types 1 and 2) screen	X												
Medical history and demographics	X	X[b]											
Physical examination[e]	X		X										
Height, weight, and BMI[f]	X		X										
Randomization			X										
Study drug administration			X										
PK blood sampling			X		X	X	X	X	X	X	X	X	X
PD blood sampling - IgA, IgM, IgG	X		X		X	X	X	X	X	X	X	X	X
PD blood sampling - IgG subtypes 1-4			X		X	X	X	X	X	X	X	X	X
PD blood sampling – CIC			X		X	X	X	X	X	X	X	X	X
Immunogenicity blood sampling - ADA			X										
FcRn occupancy			X		X		X	X	X	X		X	
Biochemistry[g]	X	X						X					
Coagulation	X	X						X					
Hematology	X	X						X		X			
Exploratory biomarker sample		X								X			
Urinalysis[h]	X	X						X		X			
Vital signs[i]	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG (triplicate)	X	X	X	X	X	X	X	X	X	X	X	X	X
Infusion site evaluation[j]				X	X	X	X	X[k]					
Concomitant medications	←Monitor continuously (after ICF is signed at Screening)→												
Adverse events	←Monitor continuously (after ICF is signed at Screening)→												

[a] Postdose evaluations at the 2-hour, 4-hour, 12-hour, and 24-hour timepoints are to be completed based on the start of infusion time. When multiple procedures are scheduled to occur at the same time, the following order of events should be strictly adhered to whenever possible: ECG, vital signs, blood sampling, and study intervention administration.
[b] Activities will be performed on Day -1 only.
[c] Serum pregnancy test at Screening and Day -1 and urine pregnancy test for all other timepoints in CRU.
[d] All participants must be vaccinated as described in Section 6.5.3.
[e] Full PE at screening and symptom directed PE thereafter.
[f] Height and BMI at Screening only.
[g] Fasting, due to lipid panel. Note: lipid panel is not performed at Screening.
[h] Visit window (hours) is not applicable for urinalysis.
[i] Including temperature, respiratory rate, and pulse oximetry.
[j] In the event of an IRR, it is recommended to collect a blood sample for assessment of tryptase, histamine, CRP, cytokines, and complement as soon as the IRR is observed (prior to administering any IRR medication), and 2 hours, 24 hours and 7 days (prior to the next dose of study drug) after onset of the IRR; a blood sample for PK/PD and ADAs may be collected if there is no predefined sample collection on the same day.
[k] IRR evaluation will continue until the reaction is fully resolved.

Abbreviations: ADA = antidrug antibodies; BMI = body mass index; CIC = circulating immune complexes; CRP = C-reactive protein; CRU = Clinical Research Unit; ECG = electrocardiogram; EOI = end of infusion; FcRn = neonatal crystallizable fragment receptor; FSH = follicle stimulating hormone; h = hours; HIV = human immunodeficiency virus; ICF = informed consent form; Ig = immunoglobulin; IRR = infusion related reaction; NA = not applicable; OP = outpatient; PD = pharmacodynamic(s); PE = physical examination; PK = pharmacokinetic(s); WOCBP = women of childbearing potential.

Table 11: SoA – Day 8 Through Day 23 for Multiple-Dose Cohorts 4 to 6

Study Day	**8**			**9[a]**	**14**	**15**			**16[a]**	**21**	**22**					**23**
Assessments	**Pre-dose**	**EOI**	**2 h[b]**	**24 h[b]**	**Admit**	**Pre-dose**	**EOI**	**2 h[b]**	**24 h[b]**	**Admit**	**Pre-dose**	**EOI**	**2 h[b]**	**4 h[b]**	**12 h[b]**	**24 h[b]**
Window (hours)	**NA**	**+0.25**	**±0.25**	**±1**		**NA**	**+0.25**	**±0.25**	**±1**		**NA**	**+0.25**	**±0.25**	**±0.5**	**±0.5**	**±1**
Status (OP or CRU)	**CRU**															
Pregnancy test (WOCBP)[c]					X					X						
Alcohol breath test					X					X						
Urine drug screen					X					X						
Physical examination[d]	X					X					X					
Weight	X					X					X					
Study drug administration	X					X					X					
PK blood sampling	X					X					X	X	X	X	X	X
PD blood sampling - IgA, IgM, IgG	X					X					X	X	X	X	X	X
PD blood sampling - IgG subtypes 1-4	X					X					X	X	X	X	X	X
PD blood sampling – CIC	X					X					X	X	X	X	X	X
Immunogenicity blood sampling - ADA						X										
FcRn occupancy	X					X					X	X	X		X	X
Biochemistry[e]					X					X						
Hematology				X	X				X	X						X
Urinalysis[f]					X					X						
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG (triplicate)	X					X					X	X	X	X	X	X
Infusion site evaluation[h]		X	X[i]	X			X	X[i]	X			X	X	X	X	X[i]
Concomitant medications	←Monitor continuously (after ICF is signed at Screening)→															
Adverse events	←Monitor continuously (after ICF is signed at Screening)→															

[a] Participant will be discharged from the CRU after completing all Day 9, 16, and 29 assessments.

[b] Postdose evaluations at the 2-hour, 4-hour, 12-hour, and 24-hour timepoints are to be completed based on the start of infusion time. When multiple procedures are scheduled to occur at the same time, the following order of events should be strictly adhered to whenever possible: ECG, vital signs, blood sampling, and study intervention administration.

[c] Serum pregnancy test at Screening and Day -1 and urine pregnancy test for all other timepoints in CRU.

[d] Full PE at screening and symptom directed PE thereafter.

[e] Fasting, due to lipid panel. Note: lipid panel is not performed at Screening.

[f] Visit window (hours) is not applicable for urinalysis.

[g] Including temperature, respiratory rate, and pulse oximetry.

[h] In the event of an IRR, it is recommended to collect a blood sample for assessment of tryptase, histamine, CRP, cytokines, and complement as soon as the IRR is observed (prior to administering any IRR medication), and 2 hours, 24 hours and 7 days (prior to the next dose of study drug) after onset of the IRR; a blood sample for PK/PD and ADAs may be collected if there is no predefined sample collection on the same day.

[i] IRR evaluation will continue until the reaction is fully resolved.

Abbreviations: ADA = antidrug antibodies; BMI = body mass index; CIC = circulating immune complexes; CRP = C-reactive protein; CRU = Clinical Research Unit; ECG = electrocardiogram; EOI = end of infusion; FcRn = neonatal crystallizable fragment receptor; h = hours; ICF = informed consent form; Ig = immunoglobulin; IRR = infusion related reaction; NA = not applicable; OP = outpatient; PD = pharmacodynamic(s); PE = physical examination; PK = pharmacokinetic(s); WOCBP = women of childbearing potential.

Table 12: SoA – Day 24 Through Day 85 for Multiple-Dose Cohorts 4 to 6

Study Day	**24**	**25**	**26**	**27**	**28**	**29[a]**	**36**	**50**	**64**	**78**	**85/ET**	**Day 113 Follow-up Phone Call**
Assessments	**48 h**	**72 h**	**96 h**	**120 h**	**144 h**	**168 h**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**
Window (CRU = hours; OP = days)	**±1 h**	**±1 h**	**±1 h**	**±1 h**	**±1 h**	**±1 h**	**±1 day**	**±1 day**	**±1 day**	**±1 day**	**±1 day**	**±3 days**
Status (OP or CRU)	**CRU**						**OP**					
Pregnancy test (WOCBP)[b]								X			X[c]	X[d]
Physical examination[e]		X				X					X	
Weight		X				X					X	
PK blood sampling	X	X	X	X	X	X	X	X	X	X	X	
PD blood sampling - IgA, IgM, IgG	X	X	X	X	X	X	X	X	X	X	X	
PD blood sampling - IgG subtypes 1-4	X	X	X	X	X	X	X	X	X	X	X	
PD blood sampling – CIC	X	X	X	X	X	X	X	X	X	X	X	
Immunogenicity blood sampling - ADA						X		X	X		X	
FcRn occupancy	X	X		X			X	X				
Biochemistry[f]		X						X			X	
Coagulation		X									X	
Hematology		X						X	X		X	
Exploratory biomarker sample		X									X	
Urinalysis		X[g]							X		X	
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG (triplicate)	X	X	X	X	X	X					X	
Concomitant medications	←Monitor continuously (after ICF is signed at Screening)→											
Adverse events	←Monitor continuously (after ICF is signed at Screening)→											

[a] Participant will be discharged from the CRU after completing all Day 9, 16, and 29 assessments.
[b] Serum pregnancy test at Screening and Day -1 and urine pregnancy test for all other timepoints in CRU and OP.
[c] For the Day 85 Visit, dispense a urine pregnancy test kit for the Day 113 Follow-up Phone Call. For an ET Visit, dispense urine pregnancy test kits to allow monthly testing for 3 months after the last dose.
[d] Participants will be requested to take a urine pregnancy test at home at approximately Day 113, or, if ET, monthly for 3 months after the last dose; the site will solicit results, along with adverse events and concomitant medications, via phone call.
[e] Full PE at screening and symptom directed PE thereafter.
[f] Fasting, due to lipid panel. Note: lipid panel is not performed at Screening.
[g] Visit window (hours) is not applicable for urinalysis.
[h] Including temperature, respiratory rate, and pulse oximetry.

Abbreviations: ADA = antidrug antibodies; BMI = body mass index; CIC = circulating immune complexes; CRU = Clinical Research Unit; ECG = electrocardiogram; ET = early termination; FcRn = neonatal crystallizable fragment receptor; h = hours; ICF = informed consent form; Ig = immunoglobulin; NA = not applicable; OP = outpatient; PD = pharmacodynamic(s); PE = physical examination; PK = pharmacokinetic(s); WOCBP = women of childbearing potential.

2. INTRODUCTION

ALXN1830 is a humanized, affinity-matured IgG4 kappa mAb that binds to the FcRn and blocks FcRn-mediated recycling of IgG and IgG immune complexes (ICs), thereby lowering total IgG (including pathogenic autoantibodies) and ICs in circulation. As FcRn is also involved in albumin recycling, ALXN1830 was designed to specifically block the IgG-binding site but not the albumin-binding site on FcRn. Studies in both nonhuman primates and humans have demonstrated that ALXN1830 treatment leads to decreases in endogenous IgG levels without affecting serum albumin levels (Mezo, 2008; Nixon, 2015).

Immunoglobulin G can indirectly cause disease activity through the formation of ICs, which induce the production of inflammatory cytokines or promote antigen presentation and the pathogenic activity of T cells, which also provide help to B cells resulting in the production of additional pathogenic IgG antibodies (Blumberg and Lencer, 2005). The FcRn contributes to such immunopathology by both maintaining the levels of pathogenic IgG antibodies and orchestrating the inflammatory activities of IgG-ICs (Baker, 2009; Pyzik, 2015; Roopenian and Akilesh 2007).

There has been increasing recognition that FcRn blockade is a novel, reversible, and potentially effective means to treat a large number of autoimmune diseases in humans. The potential efficacy of FcRn blockade was originally supported by preclinical studies in experimental autoimmune myasthenia gravis (MG) in rats, wherein such FcRn blockade can impede both passive MG induced by administration of an anti-acetylcholine receptor antibody, or in active MG in rats that were immunized against the acetylcholine receptor (Liu, 2007). More recently, clinical studies in patients with MG and other IgG-mediated autoimmune diseases have demonstrated improvement in disease endpoints following treatment with anti-FcRn therapeutics.

While current treatments for certain autoimmune disorders, including chronic steroids, immunosuppressants, intravenous immunoglobulin (IVIG), plasmapheresis, and anti-CD20 mAbs (such as rituximab), can be effective, they are associated with significant adverse effects, and delayed or non-durable responses particularly in an elderly population. There remains a clear unmet medical need for the treatment of IgG-mediated diseases. Administration of ALXN1830, leading to a significant decrease in total IgG, pathogenic IgG autoantibodies, and the circulating immune complexes (CICs) of which these IgG are constituents, should lead to a decrease in the clinical manifestations of diseases of this type. Moreover, the ability of ALXN1830 to reduce CICs and the innate and adaptive immune responses triggered by CICs may result in sustained disease modification.

The purpose of this Phase 1 study in healthy adult participants is to evaluate the safety, tolerability, PK, PD, and immunogenicity of single ascending and once weekly (qw) multiple ascending SC doses of ALXN1830.

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

2.1. Study Rationale

ALXN1830 has been studied in 4 completed clinical studies using the IV route of administration. It was initially tested in an IV SAD study in healthy participants, Study SYNT001-101. The highest IV dose tested in the SAD study, 30 mg/kg, was well tolerated. ALXN1830 was then studied in 2 Phase 1b/2a studies in autoimmune patients: Study SYNT001-102 in warm autoimmune hemolytic anemia (WAIHA) patients, and Study SYNT001-103 in pemphigus vulgaris (PV) patients. In both studies, the participants received 5 qw doses of 10 mg/kg, a dose and regimen which was well tolerated.

Subsequently, a MAD study in healthy participants, Study SYNT001-104, was initiated to investigate the safety, tolerability, PK, PD, and immunogenicity of ALXN1830 IV. The dose level of the first cohort in the MAD study was 20 mg/kg IV, with 3 doses given qw (3 × qw) followed by 3 doses given every 2 weeks (3 × q2w). A second cohort was initiated using a dose level of 30 mg/kg, but the study was paused after 4 participants in Cohort 2 each received only a single dose due to the observation of acute infusion related reactions (IRRs) in the 20 mg/kg cohort.

SYNT001-102 and SYNT001-103 were also paused at that time for a Good Manufacturing Practice (GMP) investigation of the study drug batches. Although there was no conclusive clinical or safety link between the findings of the GMP investigation and the IRRs, and the drug product lots used had met all of the approved release specifications, the investigation did identify potential impurities in the drug product that could have possibly confounded the safety profile. Alexion has implemented changes to the manufacturing process for future batches to enhance the control and detection of impurities.

Another Phase 1 study in healthy participants using the SC route of administration, Study ALXN1830-HV-105, was initiated at a single site in the United Kingdom to investigate the safety, tolerability, PK, PD, and immunogenicity of single and multiple SC doses of ALXN1830. A total of 12 participants received a single SC dose of 750 mg (n = 6) or 1,250 mg (n = 3) or placebo (PBO; n = 3) before the study was terminated due to the coronavirus disease 2019 (COVID-19) pandemic. The highest SC single dose tested in this study, 1250 mg, was well tolerated.

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

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

2.2. Background

A detailed description of the chemistry, pharmacology, efficacy, safety, and toxicology data available for ALXN1830 is provided in the Investigator's Brochure (IB).

Nonclinical studies have assessed both the potential toxicity and primary PD effects associated with ALXN1830 antagonism of IgG binding to FcRn and IgG recycling mediated by FcRn. The administration of ALXN1830 to cynomolgus monkeys by qw IV infusion at doses from 5 to 100 mg/kg for 2 to 27 weeks was well tolerated, with the exception of immunogenicity related effects of this humanized mAb in monkeys, and produced dose-dependent, specific, and reversible reductions in circulating IgG levels. No effects on IgA, IgM, or albumin levels were observed.

ALXN1830 has been evaluated in 4 completed clinical studies: SYNT001-101 (healthy participants, single dose study), SYNT001-102 (WAIHA patients, 5 × 10 mg/kg qw), SYNT001-103 (PV patients, 5 × 10 mg/kg qw), and SYNT001-104 (healthy participants, 3 × 20 mg/kg qw, then 3 × 20 mg/kg q2w), and 1 clinical study ALXN1830-HV-105, in healthy participants, was paused[2] after completing the first cohort and part of the second cohort (single SC doses of 750 mg and 1,250 mg). In all the clinical studies, ALXN1830 was shown to increase the catabolism of IgG, as manifested by decreased total IgG in serum in a dose-dependent manner up to 64% decrease from baseline, with no effects on IgA, IgM, or albumin. ALXN1830 also decreased the level of circulating IgG IC. This predicts that ALXN1830 will also accelerate degradation of endogenous circulating IgG autoantibodies and IgG IC specifically involved in the pathogenesis of autoimmunity.

2.3. Benefit/Risk Assessment

This is a healthy participant study, and there is no direct benefit to study participants. However, the PK/PD data together with safety profiles without being confounded by underlying disease or concomitant medications, may benefit future human studies in general. Detailed risk assessment is listed in Table 13, as well as in the IB. In addition, a discussion of theoretical risks associated with the reduction of IgG is provided in Section 10.7.1.

[2] A temporary halt was implemented to allow assessment of the extent of SARS-CoV2 exposure in the UK.

2.3.1. Risk Assessment

Table 13: Risk Assessment for ALXN1830

Identified and Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Drug (s) ALXN1830		
Infusion-Related Reaction	A total of 6 IRRs in clinical studies have been observed. The safety data may have been confounded by Chemistry and Manufacturing Control findings.	See Section 10.4 for IRR management.
Immunogenicity	Treatment with any therapeutic protein may induce an immune response. Occasionally, this immune response is clinically meaningful. The consequences of an immune reaction to a therapeutic protein range from transient appearance of antibodies, without any clinical consequence, to severe, life-threatening conditions. Potential clinical consequences also may include severe hypersensitivity-type reactions, decrease in efficacy, and induction of autoimmunity.	See SoA (Section 1.3 and Section 10.4 for IRR (including ADA associated IRR) management.

Abbreviations: ADA = antidrug antibody; IRR = infusion-related reaction.

2.3.2. Benefit Assessment

As this is a study in healthy participants, only societal benefit is expected. Initial testing in healthy participants is warranted, as studies in patients, especially those with rare autoimmune diseases, may take years to accrue and complete. Healthy participant studies however may be completed more rapidly and without the multiple confounding variables of the underlying disease and concomitant medications. Also, for studies in healthy participants, the study duration is limited to the protocol-defined dosing regimen. Therefore, the total exposure is considerably less than what is likely to be required for patients who may require chronic dosing. Most adverse events (AEs) reported in previous studies with ALXN1830 were nonserious and resolved with discontinuation of study drug. While the potential of serious AEs or unexpected AEs exists, this healthy participant study will provide meaningful scientific information which will continue to play an important role in future development of this drug.

2.3.3. Overall Benefit: Risk Conclusion

ALXN1830 was well tolerated after single doses up to 30 mg/kg IV and 1250 mg SC (the highest single doses tested in SAD studies) in healthy adults. Also, ALXN1830 was well tolerated after multiple IV doses at 10 mg/kg × 5 doses in autoimmune patients. However, at multiple IV doses of 20 mg/kg in healthy participants, the development of potentially immune mediated IRRs that resulted in immediate and permanent discontinuation of study drug, together with 100% incidence rate of headache, suggested that close safety monitoring and implementation of risk mitigation measures are warranted for future studies in the clinical development program (Section 10.6). Of note, these IRRs were mild and moderate in severity and all resolved after cessation of the study drug, without treatment. Similarly, all AEs of headache were mild to moderate and were resolved.

As described in Section 2.1, potential impurities in the drug product could possibly have confounded the safety profile. Alexion has implemented changes to the manufacturing process for the current and future batches to enhance the control and detection of impurities.

The proposed safety measures in this study include documentation of pneumococcal and current seasonal flu vaccination; staggered dosing; stopping rules; close participant monitoring through 60 days after the last dose; close safety and PD monitoring with an unblinded medical monitor; avoidance of participants with a high risk of infections; antibiotics to manage infection as needed; rescue measures such as IVIG replacement in an extremely unlikely event of profoundly low IgG; as well as use of an SRC for safety monitoring and dose selections.

Considering the measures taken to minimize risk to participants in this study, the risks associated with ALXN1830 are justified by the anticipated benefits that may be afforded to patients with autoimmune disease.

3. OBJECTIVES AND ENDPOINTS

Objectives and Endpoints:

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

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

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1 study in up to a maximum of 48 healthy adult participants (36 on active treatment, 12 on PBO). The study will consist of 2 SAD (Cohorts 1 and 2) and 4 MAD cohorts (Cohorts 3 to 6). Cohort 6 will enroll Japanese[1] participants. Eight participants will be randomly assigned in a 6:2 ratio in each of the 6 cohorts to receive either single or multiple SC doses of ALXN1830 (n = 6 per cohort) or single or multiple doses of PBO (n = 2 per cohort). The planned study duration is approximately 124 days for Cohorts 1 and 2: up to 60 days for screening and approximately 64 days for dosing and follow-up; 201 days for Cohort 3: up to 60 days for screening and approximately 141 days for dosing and follow-up; and 148 days for Cohorts 4 to 6: 60 days for screening and approximately 88 days for dosing and follow-up. Participants will be admitted to an inpatient facility during the dosing and follow-up period as shown in Section 1.3.

Initially, the first 4 participants randomized to each cohort will be dosed with 3 participants on active treatment and 1 participant on PBO. The dosing will be staggered, with an interval of at least 3 days for the SAD cohorts and at least 7 days for the MAD cohorts, before dosing the rest of the participants in the cohort. The shorter interval of staggered dosing for the SAD cohorts compared to the MAD cohorts is considered appropriate as the expected PK exposure of the ALXN1830 SC doses will be a fraction of that of the IV dose demonstrated to be safe and well tolerated in previous IV studies. The reduction of IgG after a single SC dose will be similar to the observed IgG reduction in previous IV studies; and in general, there will be low risk of immunogenicity and IRRs after a single dose. See Section 4.3 for details regarding expected PK exposures and IgG reduction. All participants will be observed during the drug administration and for 2 hours after dosing for safety and participants will be encouraged to report any discomfort immediately, especially within 24 hours post dosing. At no time will more than 4 participants per cohort be dosed on a given day.

An SRC, consisting of the Investigator, and Alexion Safety Physician, 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 (see SRC charter for description of membership, schedule of meetings, data required for each safety review, and requirements for documenting meeting discussions and outcome). Relevant safety data from any other studies ongoing with ALXN1830 will be made available to the SRC. At Alexion's discretion, and after consultation with the SRC, additional participants may be enrolled as replacement participants only if a participant discontinues within 3 weeks of the last dose for reasons other than drug-related AEs.

The timing and dependencies of the dosing cohorts are described in Table 14 and Table 15.

Table 14: Planned Dose and Dose Regimens of ALXN1830 in Healthy Participants

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

[a] Healthy, Japanese participants enrolled in Cohort 6 will be dosed according to the HTD established in the non-Japanese cohorts.

Abbreviations: qw = weekly; SC = subcutaneous; HTD = highest tolerated dose.

Table 15: Minimum Data Requirements for Dose Escalation

Decision-making Time Point:	Dosing Regimen	Person or Body Making the Decision:	Minimum Data to be Looked at (in Accordance With the CSP):	Method of Documentation of Decision and/or Communication to Alexion (if Applicable):
Continuation from any sub-cohort to the next sub-cohort, within any cohort	As per relevant cohort	PI	A minimum of 3 days (SAD) / 7 days (MAD) post-dose safety and tolerability data from the first sub-cohort.	The Investigator will document the decision in an email to Alexion. The email does not require Alexion's response, unless there is disagreement with the Investigator's decision.
Cohort 1	1500 mg, single dose SC	N/A	N/A	N/A
Cohort 2	2250 mg, single dose SC	SRC	Review all available safety data and IgA, IgG, and IgM data through Day 15 from Cohort 1, from a minimum of 6 participants.	The SRC will document the decision on the escalation/progression approval form.
Cohort 3	750 mg, 12 doses SC, once weekly	SRC	N/A This cohort may start in parallel to Cohort 1.	N/A
Cohort 4	1500 mg, 4 doses SC, once weekly	SRC	Review all available safety data and IgA, IgG, and IgM data through Day 22 from Cohort 3, from a minimum of 6 participants.	The SRC will document the decision on the escalation/progression approval form.
Cohort 5	2250 mg, 4 doses SC, once weekly	SRC	Review all available safety data and IgA, IgG, and IgM data through Day 22 from Cohort 4, from a minimum of 6 participants.	The SRC will document the decision on the escalation/progression approval form.
Cohort 6[a]	HTD, 4 doses SC, once weekly	SRC	Review all available safety data and IgA, IgG, and IgM data through Day 22 from Cohort 5.	The SRC will document the decision on the escalation/progression approval form.

[a] Healthy, Japanese participants enrolled in Cohort 6 will be dosed according to the HTD established in the non-Japanese cohorts.

Abbreviations: CSP = Clinical Study Protocol; HTD = highest tolerated dose; Ig = immunoglobulin; MAD = multiple ascending dose; N/A = not applicable; PI = Principal Investigator; PK = pharmacokinetics; SAD = single ascending dose; SC = subcutaneous; SRC = Safety Review Committee.

4.2. Scientific Rationale for Study Design

ALXN1830 has been studied in 5 clinical studies, 4 studies using the IV route of administration and one SC administration. Refer to Section 2.2 for background on clinical studies conducted with ALXN1830 to date.

This randomized, double-blind, PBO-controlled, SAD/MAD design was chosen for assessment of the safety, tolerability, PK/PD, and immunogenicity of single- and multiple ascending doses of ALXN1830 administered SC.

Healthy participants are the appropriate population for this study, enabling the effects of ALXN1830 to be evaluated without the potential confounding effects of other disease activities, comorbidities, or medications.

A staggered dosing paradigm is being used for participant protection. A PBO control is implemented in each cohort. Due to the difficulty of providing a matching PBO, participants randomized to PBO will receive an equivalent volume of saline at the same SC infusion rate as the active treatment.

ALXN1830 is an anti-FcRn mAb that blocks recycling of IgG antibodies, reducing the total IgG in circulation, including potentially pathogenic IgG autoantibodies associated with multiple autoimmune diseases. Thus, reduction in IgG level is used to measure the anti-FcRn PD activity of ALXN1830.

This study uses a comprehensive approach to minimize the potential risk of infection in the healthy participants due to the theoretical concerns associated with reducing total IgG (discussed in greater detail in Section 10.6). The following criteria will be observed as part of the enrollment criteria (Section 5.1), monitoring, and specified response to certain signs, symptoms, or laboratory results:

- Inclusion criteria of heathy participants with:
  - Immunoglobulin G levels of ≥ 1,000 mg/dL
  - No history of acute and chronic infections, ie, enrolled healthy participants will be immunocompetent
  - Absence of any immunologic deficiencies, as per the Investigator's discretion
  - Pneumococcus and seasonal influenza vaccination
- To ensure a timely and adequate intervention if needed, IgG levels will be continuously and closely monitored during this study.
- Stopping rules (Section 7.2) for individuals and cohorts will be based on reduction of IgG level to ≤ 300 mg/dL (justification for IgG level to ≤ 300 mg/dL is provided in Section 10.6).
  - Dosing will be permanently stopped in any individual if the IgG level is reduced to ≤ 300 mg/dL.
  - If 2 or more participants in a cohort exhibit an IgG reduction to ≤ 300 mg/dL, dosing in that cohort will stop and no further dose escalation will occur.

- Although unlikely to occur, in the unexpected instance of an IgG reduction falling into the severe category (ie, less than 100 mg/dL) or if there is any suggestion, signs, or symptoms of infection, antibiotics and/or IVIG will be considered.

4.3. Justification for Dose

Single and multiple IV doses of ALXN1830 have been administered in healthy participants, and in patients with WAIHA and PV. In healthy participants, single IV doses were given at 1, 3, 10 and 30 mg/kg (Study SYNT001-101), and multiple IV doses were given at 20 mg/kg qw for 3 doses and then q2w for 3 doses (Study SYNT001-104). In WAIHA (Study SYNT001-102) and PV (Study SYNT001-103) patients, IV doses of 10 mg/kg qw for 5 doses were given. Also, single SC doses of 750 mg and 1250 mg ALXN1830 have been administered in a limited number of healthy participants (Study ALXN1830-HV-105).

A physiologically based PK/PD model for IV dosing was established and was fitted to the IV PK/PD data from healthy participants. Due to the lack of robust SC data in humans, an SC PK/PD model is not yet available. However, the following has been observed:

1. The bioavailability (F) of ALXN1830 after SC administration is likely low:
    a. Based on the preliminary results from the 5-week SC monkey toxicity study (Study 2455024), F after a single dose of 30 mg/kg SC in monkeys is around 21.5%.
2. The maximum reduction of IgG for ALXN1830 is likely similar between IV and SC at the same mg/kg dose:
    a. At 100 mg/kg IV or SC in the 5-week Good Laboratory Practice (GLP) toxicology studies (Studies 2455-002 and 2455-024), the maximum IgG reduction was 68% after IV and 69% after SC.
    b. At 750 mg SC or 10 mg/kg IV, similar IgG reduction was observed in a clinical study in healthy participants (Studies ALXN1830-HV-105, SYNT001-01).
3. ALXN1830 bioavailability after SC administration is 20%.

Based on these observations, ALXN1830 exposure, safety margin, and IgG reduction after SC administration was predicted (see Table 16). The following assumptions have been used:

ALXN1830 clearance (CL) and body weight have the following relationship:

$$CL = (\text{Median CL}) \times (\text{body weight}/\text{median body weight})^{0.75}$$

Table 16: Predicted ALXN1830 Exposure, Safety Margin, and Immunoglobulin G Reduction after Subcutaneous Administration

Cohort	Dose (mg)	Body Weight (kg) [a]	Weekly Dose in mg/kg [a,b]	F	AUC of SC Dosing (h*µg/mL) [a,c]	Margin Based on NOAEL of Monkey Toxicology Studies [a,d]	Margin Based on 5-week Monkey SC Toxicology Study [a,e]	Margin Based on 27-week Monkey IV Toxicology Study [a,f]	Expected Maximum IgG Reduction (%) [g]
1	1500, single dose	75 (50 - 90)	20 (16.7 - 30)	0.2	1451 (1265 - 2664)	5 (3.3 - 6)	4 (2 - 5)	24 (13 - 28)	-45
2	2250, single dose	75 (50 - 90)	30 (25 - 45)	0.2	2948 (2571 - 3996)	3.3 (2.2 - 4)	2.2 (1.6 - 2.5)	12 (9 - 14)	-48
3	750 qw × 12	75 (50 - 90)	10 (8.3 - 15)	0.2	675 (589 - 983)	10 (7 - 12)	10 (7 - 11)	52 (35 - 59)	-68
4	1500 qw × 4	75 (50 - 90)	20 (16.7 - 30)	0.2	1451 (1265 - 2664)	5 (3 - 6)	4 (2 - 5)	24 (13 - 28)	-69
5	2250 qw × 4	75 (50 - 90)	30 (25 - 45)	0.2	2948 (2571 - 3996)	3 (2 - 4)	2.2 (1.6 - 2.5)	12 (9 - 14)	-72

[a] Values are median (min - max).
[b] Weekly dose in mg/kg = (dose in mg) / (body weight in kg).
[c] AUCSC = (Dose/CLIV) * F, where CLIV is scaled as CLIV = (Median CLIV) × (body weight/median body weight)$^{0.75}$. Median CLIV at 10 mg/kg = 239 mL/h with a median body weight of 82.7 kg (SYNT001-101); Median CLIV at 20mg/kg = 215 mL/h with a median body weight of 79 kg (SYNT001-104); Median CLIV at 30 mg/kg = 154 mL/h with a median body weight of 75.8 kg (SYNT001-101). Where median CLIV is not available at certain dose levels (eg 15 mg/kg), doses (mg/kg) are round up to obtain a conservative estimate. Median CLIV for 45 mg/kg is set to equal to median AUCIV at 30 mg/kg (2.03 mL/h/kg). The AUC represents $AUC_{0\text{-}inf}$ and AUC_{ss} for single and multiple doses respectively.
[d] Safety margin = (Monkey NOAEL in mg/kg) / (Human dose in mg/kg). Monkey NOAEL for weekly dosing is 100 mg/kg (Studies 2455-024 and 2455-016).
[e] Safety margin = (Monkey $AUC_{0\text{-}120h}$ at NOAEL) / (Predicted human AUCSC). Day 29 $AUC_{0\text{-}120h}$ = 6420 h*µg/mL at 100 mg/kg weekly SC (Study 2455-024).
[f] Safety margin = (Monkey $AUC_{0\text{-}Tlast}$ at NOAEL) / (Predicted human AUCSC). Day 92 $AUC_{0\text{-}Tlast}$ = 34800 h*µg/mL at 100 mg/kg weekly IV (Study 2455-016).
[g] IgG reduction is based on predicted IgG reduction at equivalent IV dose in mg/kg. IgG reduction at median body weight is presented.
Abbreviations: AUC = area under the concentration-time curve; $AUC_{0\text{-}120h}$ = area under the concentration-time curve from time 0 (dosing) to 120 hours post-dose; $AUC_{0\text{-}inf}$ = area under the concentration-time curve from time 0 to infinity; $AUC_{0\text{-}Tlast}$ = area under the concentration-time curve from time 0 to the last quantifiable concentration; AUC_{ss} = area under the concentration-time curve from time 0 to steady state; CL = total body clearance of drug from the plasma; F = absolute bioavailability; IgG = immunoglobulin G; IV = intravenous; min = minimum; max = maximum; NOAEL = no observed adverse effect level; qw = weekly; SC = subcutaneous.

Study ALXN1830-HV-108 will include 2 SAD cohorts and up to 4 MAD cohorts in healthy adult participants (Figure 1). The starting dose of the SAD portion of the SC study will be 1500 mg, equivalent to 20 mg/kg in a 75-kg participant, or 25 mg/kg in a 60-kg participant. Previously, 30 mg/kg has been shown to be well tolerated when administered as a single dose by IV infusion in healthy participants (Study SYNT001-101). Compared to the no observed adverse effect level (NOAEL) in the GLP IV (100 mg/kg/week IV, Study 2455-002 and Study 2455-016) or SC (100 mg/kg/week SC, Study 2455-024) toxicology studies in monkeys, the SC starting dose of 1500 mg will have a safety margin of approximately 2-fold (for a 50-kg participant) or 4-fold (for a 75-kg participant) on a mg/kg dose basis. Assuming a human bioavailability of 20% the expected area under the concentration-time curve (AUC) at 1500 mg SC will have a safety margin of 2-fold (for a 50-kg participant) or 4-fold (for a 75-kg participant) based on the NOAEL exposure from the 5-week SC monkey toxicity study, and 13-fold (for a 50-kg

participant) or 24-fold (for a 75-kg participant) based on the NOAEL exposure from the 27-week IV monkey toxicity study. More importantly, a 30 mg/kg IV single dose has been tested in healthy participants and this starting dose of 1500 mg SC is expected to be roughly one-fifth to one-eighth of the exposure at 30 mg/kg IV, based on the low bioavailability observed in monkeys for ALXN1830 and in healthy participants from other anti-FcRn compounds. Based on these observations, the expected maximum IgG reduction at 1500 mg SC would be around -45% from baseline.

In the SAD portion, the SC dose will be escalated 1.5-fold from 1500 mg (Cohort 1) to 2250 mg (Cohort 2). An SRC review of safety, tolerability, and IgG data will be conducted before each dose escalation. Staggered dosing and pre-specified stopping rules based on safety and IgG reduction will be implemented in all cohorts.

As shown in Table 16 the first MAD cohort will be administered 750 mg SC qw for 12 weeks (Cohort 3). On a mg/kg basis, the 750 mg SC qw dose represents at least a 7 to 35-fold safety margin when compared to the NOAEL exposures of the 5-week SC and 27-week IV monkey GLP studies. The first MAD cohort (750 mg, qw, Cohort 3) may start at the same time as the single-dose Cohort 1 (1500 mg) while the rest of the MAD cohorts will start after SRC review of the previous MAD cohorts. While all the MAD cohorts have a treatment duration of 4 weeks, Cohort 3 (750 mg SC qw for 12 weeks) is of an extended duration to enable the evaluation of immunogenicity and safety after long term administration of ALXN1830.

The SC multiple doses will be escalated 2-fold from 750 mg qw to 1500 mg qw (Cohort 4), and then 1.5-fold to 2250 mg qw (Cohort 5) after SRC review. At these dose levels, the expected maximum IgG reduction after 4 qw doses is expected to be around 69% and 72%, respectively, which is similar to that observed with 20 mg/kg IV in Study SYNT001-104 (after the 3 qw loading doses).

As shown in Table 15, Cohort 6 will assess the safety, tolerability, PK, PD, safety, and immunogenicity of ALXN1830 in Japanese participants at the highest tolerable dose established in the non-Japanese participants (ie, either up to 1500 mg or up to 2250 mg SC qw for 4 doses). The exact dose and time of dosing will be determined after SRC review of all safety data through Day 36 from Cohort 5 as well as from all prior cohorts. Japanese participants are expected to have a lower mean body weight than non-Japanese participants. This and other differences (eg, genetics) may impact PK/PD in Japanese participants. Although Japanese participants may potentially have slightly higher exposure based on the lower mean body weight, the overall exposure in Japanese participants is predicted not to exceed established safety margins.

4.4. End of Study Definition

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

The end of the study is defined as the date of the last participant follow-up visit in the study, as specified in the SoA.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

Male and female participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participants must be between the ages of 18 and 55 years, inclusive, at the time of signing the informed consent.

Type of Participant

2. Participants who are healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.
3. Participant agrees to not donate blood for 4 months after completion of their last study visit.
4. Baseline IgG concentrations ≥ 1,000 mg/dL at Screening.
5. Baseline IgA and IgM[3] above the lower limit of normal at Screening.
6. Participants must have had vaccination against pneumococcus (Pneumovax 23 [PPSV23]) at least 28 days, and maximally 4 years prior to Day 1.
7. Participants must have had seasonal influenza vaccination for the current season at least 28 days prior to Day 1.
8. Participants of Japanese descent (Cohort 6) are defined as:
   a. First generation (born to 2 Japanese parents and 4 Japanese grandparents).
   b. Participant must have been born in Japan, and not have lived outside Japan for greater than 10 years.
   c. Lifestyle, including diet, must not have significantly changed since leaving Japan.

Weight

9. Body weight within 60 to 90 kg, inclusive, and body mass index (BMI) within the range of 18 to 30 kg/m^2, inclusive.

[3]IgM levels are expected to be above the upper level of normal per local laboratory reference range if the participant has recently received Pneumovax 23 vaccination. Therefore, participants are eligible if they have been recently vaccinated with Pneumovax 23 per vaccination criteria described in Section 6.5.3 and the IgM level corresponds with the post-vaccination normal limits, per the Investigator's discretion.

Contraception

10. Female participants of childbearing potential and male participants with female partners of childbearing potential must be willing to follow protocol-specified contraception guidance during the study and for 3 months after last dose of study drug (see Section 10.5 for more contraceptive guidance).

Informed Consent

11. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and the protocol.

5.2. Exclusion Criteria

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

Medical Conditions

1. History or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrinological, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study drug; or interfering with the interpretation of data.
2. Abnormal blood pressure (BP) as determined by the Investigator (resting BP should be between 140/80 mmHg and 90/60 mmHg) at Screening.
3. Participants who have any clinically significant history of allergy or hypersensitivity.
4. History of unexplained, recurrent infection, or infection requiring treatment with systemic antibiotics within 90 days prior to dosing on Day 1.
5. Participants with a history of frequent and/or chronic headaches, including migraine disorder, cluster headache disorder, and tension headache disorder.
6. Previous history of cancer, except for adequately treated basal cell or squamous cell carcinoma of the skin.
7. Clinically significant abnormalities and laboratory test results.
8. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
9. Corrected QT (QTc) > 450 msec for male participants or > 470 msec for female participants.
   NOTE: The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF). It is either machine-read or manually over-read.
10. Female participants who are pregnant or breastfeeding.

Prior/Concomitant Therapy

11. Past or intended use of over-the-counter or prescription medication including herbal medications within 14 days (or longer in case of a specific herbal medication) prior to dosing.

12. Known exposure to investigational or marketed therapeutic proteins, such as mAbs, fusion proteins, bispecific molecules, or antibody drug conjugates, within 60 days or 5 half-lives (whichever is longer) prior to dosing.
13. Participants who have prior exposure to ALXN1830.
14. Any vaccination within 2 weeks of screening other than those required for this study.
15. Any live virus vaccination within 6 months of screening.

Prior/Concurrent Clinical Study Experience

16. Exposure to more than 4 new (small molecule) investigational compounds within 12 months prior to dosing.
17. Current enrollment or past participation within the last 90 days before signing of consent in this or any other interventional clinical study.

Diagnostic Assessments

18. Presence of hepatitis B surface antigen (HBsAg) at Screening.
19. Positive hepatitis C antibody test result at Screening.
20. Positive pre-study drug/alcohol screen at Screening.
21. Positive human immunodeficiency virus (HIV) antibody test at Screening.

Other Exclusions

22. History of illicit drug abuse and/or history of significant alcohol abuse within 1 year prior to the Screening Visit or clinical evidence of substance and/or alcohol dependence within the 2 years before screening.
23. Use of tobacco in any form (eg, smoking or chewing) or other nicotine-containing products in any form (eg, gum, patch, electronic cigarettes) within 24 hours prior to the planned first day of dosing.
24. Has a tattoo or body piercing which might interfere with infusion site examination throughout the duration of the study.
25. Individuals who are either immunocompromised or have one of the following underlying medical conditions: anatomic or functional asplenia (including sickle cell disease); primary antibody deficiencies; or HIV.
26. Professional healthcare workers exposed to environments of greater risk for infectious disease.
27. Research, industrial, and clinical laboratory personnel routinely exposed to infectious agents (bacterial or viral).
28. Students living on a college or university campus.
29. Daycare center workers
30. Individuals who are in prolonged contact (defined as providing personal care for or living under the same roof) with:
    a. Children who attend daycare

b. Students living on a college or university campus

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

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

5.3.2. Caffeine, Alcohol, and Tobacco

Participants will be required to abstain from:

- Ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) 24 hours before admission through discharge from the inpatient facility, and 24 hours before each study follow-up visit.
- Ingesting alcohol 24 hours before admission through discharge from the inpatient facility, and 24 hours before each study follow-up visit.
- Smoking tobacco products from 24 hours before admission through discharge from the inpatient facility, and 24 hours before each study follow-up visit.

5.3.3. Activity

Participants will be required to abstain from strenuous physical activity within 48 hours prior to blood draws for clinical safety laboratory testing.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study drug. 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 (CONSORT) publishing requirements (Schulz, 2010) and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details (eg, failed eligibility criteria), and any serious adverse event (SAE) occurring during the screening period.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

Any study-related testing performed at Screening may be repeated within the screening visit window per the Investigator's discretion for the purpose of further determining eligibility.

6. STUDY INTERVENTION

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

6.1. Study Interventions Administered

The doses and formulations to be administered in this study are presented in Table 17. The SAD and MAD cohorts may use study drug that has been manufactured with different compositions which can be considered comparable based on analytical and characterization data. Refer to the IB for the compositions of ALXN1830. Placebo will be commercially available normal saline.

Table 17: Study Drug

Drug name	ALXN1830	Placebo
Type	Biologic	Diluent
Dose formulation	Sterile liquid	Sterile liquid
Unit dose strength(s)	ALXN1830 is formulated at 150 mg/mL, and supplied as a 1500 mg/10 mL vial	Placebo
Dosage level(s)	Refer to Table 14	Not applicable
Route of administration	SC infusion	SC infusion
Use	Investigational Product	Placebo
IMP and NIMP	IMP	IMP
Sourcing	Provided by Alexion	Provided by study site
Packaging and labeling	Study drug will be provided in a 10 mL vial. Each vial will be labeled as required per country requirement	Placebo (normal saline) will be provided in country-specific commercially available form

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

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 drug received and any discrepancies are reported and resolved before use of the study drug.
2. Only participants enrolled in the study may receive study drug and only authorized site staff may supply or administer 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 site's pharmacy staff is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
    a. This responsibility includes the reporting of any product complaints to [redacted] within 1 business day. A product complaint is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, usability, safety, effectiveness, or performance of a product or clinical trial material and/or its packaging components after it is has been released for distribution to an end customer that affects the performance of such product.
4. Further guidance regarding preparation, handling, storage, and accountability and information for the final disposition of unused study drug is provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

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

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

Participants will be randomly assigned in a 6:2 ratio to receive either single or multiple doses of ALXN1830 or PBO (Table 14). The Investigator will remain blinded to each participant's assigned study drug throughout the course of the study. In order to maintain this blind, site's pharmacy staff will be responsible for the reconstitution and dispensation of all study drug.

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

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

6.4. Study Intervention Compliance

Participants will receive study drug directly from the Investigator, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study drug and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study drug.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, or other specific categories of interest) 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

Concomitant treatment that is medically indicated for any AEs the participant experiences during the study is permitted.

If concomitant medication is needed during the study, this medication must be recorded on the eCRF, stating its generic name, time of administration, dose, route and duration, as well as the reason for administration.

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

6.5.1. Hydration

It is recommended that study participants drink **approximately 2 L (women)/2.5 L (men) of water every da**y during the 3 days preceding and following an infusion treatment (further information on hydration prior to dosing is provided in Section 10.7.2).

6.5.2. Supportive/Symptomatic Care

The use of supportive therapy/symptomatic treatment is allowable at any time during the study to treat AEs. The date and time of administration of supportive therapy/symptomatic treatment as well as the name and dosage regimen of any medication must be recorded. Details are provided in the study manual.

Supportive/symptomatic care such as histamine H1 and H2 receptor blockers, eg, diphenhydramine and famotidine are recommended for any manifesting allergic reactions and associated gastrointestinal symptoms; ondansetron for persistent nausea; bronchodilators for potential dyspnea, eg, salbutamol or pirbuterol; analgesics/antipyretics for headache, pyrexia and myalgia, eg, acetaminophen; and fluids or normal saline in case of hypotension.

Adhere to infectious disease preventive measures per World Health Organization (WHO) and local guidance. If a participant develops any signs or symptoms suggestive of infection (any), they should be treated as per the relevant local guidelines.

6.5.3. Vaccinations

To mitigate the potential of sinopulmonary infections associated with anti-FcRN targeted IgG reduction therapy, all participants in this study must have been adequately vaccinated against the following:

1. Pneumococcus
2. Seasonal influenza

6.5.4. Antibiotics Use

Antibiotics may be administered as needed to manage infection.

6.5.5. Disallowed Medication

During the study, participants are not allowed to use any kind of prescribed medication, including mAbs other than the study drug, any investigational drug or device, and vaccinations within 2 weeks of screening (other than those to be administered as part of this study; refer to Section 6.5.3) and for the duration of the study.

The use of over-the-counter medication is not allowed from 14 days prior to the first administration of study drug until the end of study (EOS) except the medications described above.

6.6. Dose Modification

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

6.7. Intervention After the End of the Study

This is a healthy participant study and no follow-up study drug administration is planned.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study drug. Unless a participant fully withdraws their consent, they will continue their enrollment without study drug administration but will be required to complete a follow up visit for safety purposes. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study drug and follow-up and for any further evaluations that need to be completed.

7.2. Stopping Criteria

7.2.1. Immunoglobulin Stopping Rules

It is proposed that the lower limit of IgG will be set at ≤ 300 mg/dL as an individual stopping rule for the healthy participant study. More specifically, if any predose measurements show a reduction of IgG level to ≤ 300 mg/dL, the individual stopping rule will be met. Repeat testing to confirm the consistency of the result is permitted. Healthy participants can rebound to their baseline IgG level when the drug is discontinued because they are not immunocompromised, as evidenced by existing anti-FcRn studies. Additionally, risk mitigation strategies such as antibiotics or IVIG replacement therapy may be implemented if participants have laboratory evidence of infection and/or are clinically symptomatic.

If 2 or more participants in a cohort exhibit IgG reduction to ≤ 300 mg/dL, dosing in that cohort/dose level will stop and no further dose escalation will occur.

In addition, any participant for whom IgA or IgM falls below the normal limits (according to the reference ranges of the laboratory) and is associated with clinical signs and symptoms will be discontinued from further dosing.

7.2.2. Safety Stopping Rules (Individual, Cohort and Study Level Stopping Rules)

Individual Level:

- Study drug will be discontinued immediately (if applicable) and permanently if any of the following occurs:
  - Development of a 'serious' adverse reaction (AR), or 'severe' (≥ Grade 3) AR.
  - Development of a 'serious' adverse reaction (AR), or 'severe' (≥ Grade 3) IRR.
- If a moderate Grade 2 AR is observed, study drug administration may be continued, delayed, or discontinued in accordance with Investigator's clinical judgment and in consultation with Alexion.

Cohort and Study Level:

- A cohort and other cohort with a dose at an equal or higher level will be stopped or not initiated if any of the following occurs:
  - ≥ 2 participants on study drug in the cohort experience a moderate (Grade 2) AR that does not improve by 14 days after treatment
  - ≥ 2 participants on study drug in the cohort experience an IRR as described earlier (see individual level)
- Study will be discontinued (all dosing [lower, equal, or higher doses]) and continuation of the cohort or study will require a substantial amendment, if any of the following occurs:
  - Two participants on study drug in any cohort experience a severe (Grade 3) AR
  - One participant on study drug in any cohort experiences a serious AR

7.3. Participant Discontinuation/Withdrawal from the Study

- All efforts should be made to ensure participants are willing to comply with study participation prior to conducting the screening procedures. The study staff should notify Alexion and their site monitor of all study withdrawals as soon as possible. The reason for participant discontinuation must be recorded in the source documents and CRF.
- 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. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early termination visit should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study drug and from the study at that time.
- 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.

Not all participants who withdraw will be replaced. At Alexion's discretion, and after consultation with the SRC, additional participants may be enrolled as replacement participants only if a participant discontinues within 3 weeks of the last dose for reasons other than drug-related AEs.

7.4. 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 and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator 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 to have withdrawn from the study.

Discontinuation of specific sites or of the study is handled as part of Section 10.1.9 Study and Site Start and Closure.

The Investigator, competent authority, or Sponsor may terminate the study for reasonable cause. Conditions that warrant termination of the study include, but are not limited to, the following:

- Discovery of an unexpected, serious, or unacceptable risk to participants enrolled in the study.
- Decision on the part of Alexion to suspend or discontinue testing, evaluation, or development of the study drug.
- Failure of the Investigator to comply with the approved protocol, pertinent guidelines, and/or regulations.
- Submission of knowingly false information from the Investigator to Alexion and/or regulatory authorities.

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 drug.
- Adherence to the study design requirements, including those specified in the SoA, 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.

8.1. Efficacy Assessments

No efficacy assessments will be obtained during the study.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

A full physical examination will be performed at Screening. A symptom-driven physical examination will be performed predose and at the EOS visit and may be performed at other times, at the Investigator's discretion.

Each examination will include the following assessments: general appearance; skin; head, ears, eyes, nose, and throat; neck; lymph nodes; chest; heart; abdominal cavity; limbs; central nervous system; and musculoskeletal system.

Height and BMI will be recorded at Screening. Weight will also be recorded predose.

8.2.2. Vital Signs

- Vital signs 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, and pulse oxymetry. The timing of vital sign measurements is described in the SoA (Section 1.3). Out of range BP or pulse measurements will be repeated at the Investigator's discretion. Confirmed, clinically significant vital sign measurements will be recorded as AEs.

- Blood pressure and pulse measurements will be assessed in a semi-supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones). Ideally, the same arm for each participant should be used for measurements.

8.2.3. Electrocardiograms

12-lead electrocardiogram (ECG) will be conducted as outlined in the SoA (see Section 1.3) to obtain heart rate, PR, QRS, QT, and QTc intervals after participant has been in the supine position for at least 5 minutes.

The subjects will avoid postural changes, and clinical staff will ensure that subjects 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 at approximately 1-minute intervals. Each ECG recording (trace) will last 10 seconds. Repeat ECGs will be performed until at least three 10-second ECG records per scheduled time point meet the quality criteria.

8.2.4. Clinical Safety Laboratory Assessments

- See Section 10.2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (CRF). The laboratory reports must be filed with the source documents.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 5 half-lives after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and Alexion notified.
  - All protocol required- laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA.
  - 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 CRF.

8.2.5. Virus Serology

Blood samples collected at Screening will be analyzed for HIV-1, HIV-2, HBsAg, hepatitis B core antibody, and hepatitis C virus antibody titers.

8.2.6. Vaccination

Participants will be adequately vaccinated as described in Section 6.5.3 and Section 5.1.

8.2.7. Drug and Alcohol Screen

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

8.2.8. Pregnancy

- Pregnancy data from female participants and female spouses/partners of male participants will be collected from the first dose of study drug until 3 months after the last dose of study drug. Any female participant who becomes pregnant while participating in the study will be discontinued from the study drug. 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 10.5.
- For all Alexion products, both in development or postapproval, 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 drug or withdraws from the study. The corresponding infant must be followed-up for 3 months postpartum.
- Pregnancy is not considered as an AE (Section 10.5.3) unless there is a suspicion that the study drug 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) (Section 8.3). Elective abortions without complications should not be reported as AEs.

8.2.9. Infusion Site Evaluation

Infusion site evaluations will be performed at the time points specified in the SoA (Section 1.3). Infusion site reactions (eg, induration ≤ 1 cm in size) will not be listed as an AE unless they persist for more than 24 hours.

8.3. Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs and specific reporting requirements can be found in Section 10.3.

All AEs will be reported to the Investigator or qualified designee by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study drug 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 (Appendix 3).

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

All AEs and SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to Alexion or the designee 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 it being available.

Investigators are not obligated to actively seek AEs 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 drug 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 AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

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

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification of an SAE by the Investigator to Alexion is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study drug 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 drug under clinical investigation. Alexion will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and Investigators.
- Suspected unexpected serious adverse reactions (SUSARs) must be reported according to local regulatory requirements and Alexion policy and forwarded to Investigators as necessary.

- 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. Adverse Events of Special Interest

Any nonserious AE of special interest (AESI) is required to be reported by the Investigator to Alexion immediately (≤ 24 hours after learning of the AESI). The AESI will be documented in the safety database and a narrative will be required for each event.

The AESIs for ALXN1830 include the following:

- Any IRR equal to or higher than Grade 3; or any IRR that may jeopardize the participant and requires immediate intervention to prevent it from leading to severe outcomes.
- Potential cases of any delayed hypersensitivity reactions, equal to or higher than Grade 2.

8.3.5.1. Infusion-Related Reaction

Infusion-related reactions to mAbs include both immune mediated and non-immune mediated reactions. Symptoms of IRRs may include flushing, alterations in heart rate and BP, dyspnea, bronchospasm, back pain, fever, urticaria, edema, nausea, and all types of rashes. Anaphylaxis is recognized as a severe, life-threatening, generalized, or systemic reaction. IRRs usually develop during drug infusion, or within hours of infusion, although may be delayed for up to 24 hours. Most IRRs are mild to moderate in severity.

Refer to Section See Section 10.4 for guidance on management of IRRs.

8.3.5.2. Non-acute Hypersensitivity Reaction

Non-acute hypersensitivity (ie, serum sickness) and immune responses secondary to IC formation typically have a subacute presentation (FDA, 2014). Clinical signs may include delayed onset of fever, rash, arthralgia, myalgia, hematuria, proteinuria, and serositis, in the face of an ongoing antibody response to the study drug (Hunley, 2004). Assessment of AE causality will likely require evaluation of CICs and complement activation.

8.4. Treatment of Overdose

An overdose is defined as a significant variation above the recommended/scheduled dosage for a product. The dosing for this study will be conducted in a controlled clinical setting and an overdose is not anticipated. However, in the event of an accident, for this study, an overdose of ALXN1830 is considered any dose of ALXN1830 greater than 2250 mg.

Overdoses are medication errors that are not considered AEs unless there is an untoward medical occurrence resulting from the overdose.

In the event of an overdose, the Investigator should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until IgG levels have returned to normal.
- Follow-up until ALXN1830 can no longer be detected systemically or IgG levels have returned to Baseline.
- Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Whole blood samples will be collected for measurement of serum concentrations of ALXN1830 as specified in the SoA. All efforts should be made to obtain the PK samples at the exact nominal time relative to dosing within the specified window. Additional samples may be collected during the study if warranted and agreed upon between the Investigator and Alexion. The total blood volume will not exceed the blood volume limit for healthy participants (Section 8.2.4).

Instructions for the collection and handling of biological samples will be provided by Alexion. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be analyzed using a validated analytical method in compliance with Alexion standard operating procedures.

8.6. Pharmacodynamics

Venous blood samples will be collected for measurement of IgA, IgM, IgG, and IgG subtypes (1 - 4), FcRn receptor occupancy, and CIC at timepoints described in the SoA (Section 1.3). Blood will be separated into 2 aliquots for Igs; 1 each for Ig and subclass testing. A separate sample will be collected for CIC, and a separate sample will be collected for FcRn receptor occupancy on human monocytes. The actual date and time (24-hour clock time) of each sample will be recorded.

As data become available during the study, the timing of PD sampling may be altered in order to ensure appropriate monitoring of participants. Detailed instructions on the procedure for collecting, processing, storing, and shipping serum samples for PD analysis will be provided in the laboratory manual.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

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

In the event of an IRR, it is recommended to collect a blood sample for assessment of tryptase, histamine, C-reactive protein, complement, and cytokines as soon as the IRR is observed (prior to administering any IRR medication), and 2 hours, 24 hours and 7 days (prior to the next dose of study drug) after onset of the IRR.

8.9. Immunogenicity Assessments

Samples for immunogenicity should be collected at times specified in the SoA (Section 1.3). Assays for the determination of human antidrug (anti-ALXN1830) antibodies (ADA) will be performed. All samples that are positive in a screening assay will be confirmed for antibody specificity and further characterized for titer. All samples that are confirmed positive for ADA will be evaluated for the presence of neutralizing antibodies. Other analyses may be performed to verify the stability of antibodies to ALXN1830 and/or further characterize the immunogenicity of ALXN1830.

In the event of an IRR, a sample for PK/PD and ADAs may be collected if there is no predefined sample collection on the same day.

The detection and characterization of antibodies to ALXN1830 will be performed using a validated assay method by or under the supervision of Alexion.

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

Detailed instructions on the procedure for collecting, processing, storing, and shipping serum samples for immunogenicity analysis will be provided in the laboratory manual.

8.10. Medical Resource Utilization

Medical resource utilization and health economics data, associated with medical encounters, will not be collected as a part of this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

No statistical hypotheses will be tested for this study.

9.2. Sample Size Determination

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

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

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Table 18: Populations for Analyses

Population	Description
Enrolled set	All participants who sign the ICF and pass inclusion/exclusion criteria.
Safety set	All participants who receive at least 1 dose of study drug. Participants will be analyzed according to the study drug they actually received.
PK analysis set	All participants in the Enrolled set who have sufficient serum ALXN1830 concentration data to evaluate PK parameters. Participants will be analyzed according to the study drug they actually received.
PD analysis set	All participants in the Enrolled set who have sufficient serum IgG data to evaluate PD effects. Participants will be analyzed according to the study drug they actually received.

Abbreviations: ICF = informed consent form; IgG = immunoglobulin G; PD = pharmacodynamics; PK = pharmacokinetics.

9.4. Statistical Analyses

The Statistical Analysis Plan (SAP) will be developed and approved before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

All data and all outcomes derived from the data will be presented in detailed data listings or summary tabulations. Graphical displays may also be provided when appropriate. All analyses will be performed using SAS® release, version 9.4 or higher (SAS Institute Inc., Cary, NC, USA) or other validated statistical software. Continuous variables will be summarized using descriptive statistics, including number of observations and mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized by frequency counts and percentage of participants.

All cohorts will be summarized separately along with the overall summaries for SAD and MAD. Within the MAD cohorts, the non-Japanese Cohorts 3, 4, and 5 and the Japanese Cohort 6 will be quantitatively evaluated.

One of the secondary objectives of this study is to compare safety, PK, PD, and immunogenicity of ALXN1830 SC between Japanese and non-Japanese healthy participants. For this, descriptive statistics for safety, PK parameters (maximum observed serum concentration [C_{max}], AUC), PD parameters (percent change in IgG), and immunogenicity (ADA levels) will be summarized in each group separately.

Details will be provided in the SAP.

9.4.1. Safety Analyses

All safety analyses will be performed on the Safety set.

Safety analyses will include an analysis of all treatment-emergent adverse events (TEAEs), SAEs, AESIs, ECGs, clinical laboratory data, physical examinations, and vital sign measurements using descriptive statistics. No inferential statistical analyses are planned on the safety parameters of this study. Clinical AEs will be coded according to MedDRA Version 21.1 or higher; AEs will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 or higher. AEs will be classified as pretreatment or treatment-emergent as follows:

Pretreatment AEs are defined as AEs that were reported or worsened after signing the ICF up to the start of study drug dosing.

Treatment-emergent AEs are defined as AEs that were reported or worsened on or after the start of study drug dosing through the Safety Follow-up Visit.

Only TEAEs will be summarized. The number and percentage of participants experiencing a TEAE will be summarized, by System Organ Class and Preferred Term for each cohort, by relationship to study drug, and by severity of the AE. Serious AEs and TEAEs resulting in study drug discontinuation will be listed. Some rules that will apply to the summarization of AEs are (1) a participant with multiple occurrences of the same AE or a continuing AE will only be counted once; (2) only the maximum severity level will be presented in the severity summary; and (3) only the worst relationship level will be presented in the relationship summary.

All statistical analyses of laboratory values will be performed using SI units. Changes from baseline in vital sign measurements and laboratory assessments (eg, chemistry, hematology, and urinalysis) at each scheduled time point will be summarized by cohort. Laboratory parameter values will be graded according to the CTCAE. Shift tables by cohort will be produced for these laboratory parameters. These tables will summarize the number of participants with each baseline grade relative to the reference ranges and changes to the worst highest grade assessed post-dose during the study.

The ECG 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 by each cohort.

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

- QT, QTcF interval > 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

All concomitant medications will be coded using the current version of the WHO Drug Dictionary, and the frequency and percentage of concomitant medications will be summarized.

9.4.2. Other Analyses

9.4.2.1. Pharmacokinetic Analyses

All PK analyses will be performed on the PK analysis set and will be reported by cohort and study drug within each cohort (ie, ALXN1830 or PBO).

The individual serum concentration data from participants who receive ALXN1830 SC with actual sampling dates and times will be used to derive the PK parameters by noncompartmental analysis methods using Phoenix WinNonlin 6.3 or higher. Pharmacokinetic parameter data will be presented in tabular form and descriptively summarized for all participants by cohort.

The following PK parameters will be derived as appropriate and data permitting:

Parameters	Dose Regimen	Definitions
C_{max}	SD, MD	Maximum observed serum concentration
t_{max}	SD, MD	Time to maximum observed serum concentration
AUC_t	SD, MD	Area under the concentration-time curve from time 0 to the last quantifiable concentration
AUC_{tau}	MD	Area under the concentration-time curve during the dosing interval
$AUC_{0-\infty}$	SD	Area under the concentration-time curve from time 0 (dosing) to time infinity
$t_{½}$	SD, MD	Terminal elimination half-life
λ_z	SD, MD	Terminal-phase elimination rate constant
CL/F	SD	Total body clearance or apparent clearance
V_d/F	SD	Volume of distribution or apparent volume of distribution
R_{ac}	MD	Accumulation ratio

Abbreviations: MD = multiple-dose; SD = single-dose.

Additional details will be provided in the SAP.

9.4.2.2. Pharmacodynamic Analyses

All PD analyses will be performed on the PD analysis set and will be reported by cohort and study drug within each cohort (ie, ALXN1830 or PBO).

The PD effects of single and multiple SC doses of ALXN1830 will be evaluated by assessing changes in serum IgA, IgM, IgG, and IgG subtypes (1 to 4) over time. In addition, changes in CIC and FcRn receptor occupancy on human monocytes will be evaluated.

Biomarker assays may be conducted as an exploratory analysis on collected samples.

Pharmacokinetic, PD, immunogenicity (secondary analyses), and biomarker exploratory analyses will be described in the SAP (or the PK analysis plan, as applicable), and finalized before database lock.

9.5. Interim Analyses

No interim analyses are planned.

9.6. Safety Review Committee (SRC)

An SRC, consisting of the Investigator, and Alexion Safety Physician, 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 (see SRC charter for description of membership, schedule of meetings, data required for each safety review, and requirements for documenting meeting discussions and outcome). Relevant safety data from any other studies ongoing with ALXN1830 will be made available to the SRC.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 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 with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council of Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, 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 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.
  - Notifying the IRB/IEC of deviations from the study protocol or GCP as defined as a serious breach or as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulation (CFR), ICH guidelines, the IRB/IEC, 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 to obtain signed (written or electronic signature) informed consent from all study participants prior to any study-related procedures including screening assessments.
- The Investigator or his/her representative 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 defined according to local and country regulations where the study is taking place will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that signed (written or electronic) informed consent was obtained before the participant was screened in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the signed (written or electronic) ICF(s) 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. 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 are required to sign a new ICF (see Section 5.4).
- The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each participant or their legally authorized representative the objectives of the exploratory research. If sharing exploratory research results with the Investigator is not planned, the ICF should mention it. Participants or their legally authorized representative will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

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 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 by Alexion in accordance with local data protection law. The level of disclosure must also be explained to the participants who will be required to give consent for their data to be used as described in the informed consent
- Participants must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Alexion, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

An SRC, consisting of the Investigator, Alexion 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 (see SRC charter for description of membership, schedule of meetings, data required for each safety review, and requirements for documenting meeting discussions and outcome). Relevant safety data from any other studies ongoing with ALXN1830 will be made available to the SRC. At Alexion's discretion, and after consultation with the SRC, additional participants may be enrolled as replacement participants only if a participant discontinues within 3 weeks of the last dose for reasons other than drug-related AEs.

10.1.6. 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.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRF unless transmitted to Alexion 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 CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Alexion 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 CRF 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.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 2 years after the last marketing application approval, or if not approved, 2 years following the discontinuance of the study drug, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Alexion. No records may be transferred to another location or party without written notification to Alexion.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The Investigator 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 CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available. Source documents are filed at the Investigator's site.

10.1.9. 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 the sole discretion of Alexion. 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 termination visit, all data have been collected and entered into electronic data capture system, all required documents and study supplies have been collected, 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 GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study drug development

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

- Discovery of an unexpected, serious, or unacceptable risk of the study drug to patients enrolled or continuing in the study.
- Sponsor decision to suspend or discontinue testing, evaluation, or development of the study drug.

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.

10.1.10. Publication Policy

The full terms regarding publication of the results of this study are outlined in the applicable Clinical Study Agreement.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 19 will be performed by the central laboratory.

- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 19: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet count RBC count Hemoglobin Hematocrit	RBC indices: Mean corpuscular volume Mean corpuscular hemoglobin % Reticulocytes	WBC count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical chemistry	BUN Chloride Potassium Bicarbonate Sodium Glucose	AST ALT Alkaline phosphatase Gamma glutamyltransferase HbA1C (Screening only) Urea	Total and direct bilirubin Total protein Albumin Cholesterol (total) LDL HDL Triglycerides Creatinine Creatine phosphokinase
Coagulation	International normalized ratio, partial thromboplastin time, prothrombin time		
Routine urinalysis	Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase Microscopic examination (if any leucocytes, more than a trace protein, nitrites, and blood [if not menstruating] are abnormal)		
Other screening tests	• Alcohol breath and urine drug screen (to include at minimum: amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, methamphetamine, 3,4-methylenedioxy-methamphetamine, methadone, and tetrahydrocannabinol [cannabinoids]) • IgG, IgA and IgM concentration • HIV-1 and HIV-2 antibodies, HBsAg, anti-HBC IgG + IgM (if IgG positive), and anti-HCV with confirmation by HCV RNA • Serum hCG pregnancy test (as needed for women of childbearing potential) • FSH (postmenopausal females only)		
IRR	• In the event of an IRR, it is recommended to collect a blood sample for assessment of tryptase, histamine, CRP, cytokines, and complement as soon as the IRR is observed (prior to administering any IRR medication), and 2 hours, 24 hours and 7 days (prior to the next dose of study drug) after onset of the IRR.		
Signs of infection	If a participant shows signs of infection, the following investigations should be included: • Blood cultures (taken prior to start of antibiotics) • Routine profile		

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CRP = C-reactive protein; FSH = follicle stimulating hormone; HbA1c = glycated hemoglobin; HBC = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HDL = high-density lipoprotein; HIV = human immunodeficiency virus; Ig = immunoglobulin; IRR = infusion-related reaction; LDL = low-density lipoprotein; RBC = red blood cells; RNA = ribonucleic acid; WBC = white blood cells.

Investigators must document their review of each laboratory safety report. Laboratory/analyte results that could unblind the study will be reviewed by dedicated unblinded staff at the investigative sites or other blinded personnel until the study has been unblinded.

10.3. Appendix 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 study intervention, whether or not considered related to the study intervention.

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

10.3.2. Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
1. Results in death
2. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it was more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
4. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
5. Is a congenital anomaly/birth defect
6. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

Recording of AE and/or SAE

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

Assessment of Intensity

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

Recording of AE and/or SAE

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 CRF 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.
- 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. 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.
- 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 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 with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to Alexion within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Alexion via Paper Safety Reporting Form

- All SAEs will be recorded and reported to Alexion or designee immediately and within 24 hours of awareness.
- 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: [redacted] or Fax: [redacted]
- Additional follow-up information, if required or available, should be entered into the CRF and sent to Alexion GDS within 24 hours of the Investigator or study site staff becoming aware of this additional information via the reporting process outlined above.
- For all SAEs, the Investigator must provide the following:
  - Appropriate and requested follow-up information in the time frame detailed above
  - Causality of the SAE(s)
  - Treatment of/intervention for the SAE(s)
  - Outcome of the SAE(s)
  - Medical records and laboratory/diagnostic information
- All paper forms and follow-up information submitted to Alexion GDS **must** be accompanied by a cover page signed by the Investigator.
- Paper source documents and/or reports should be kept in the appropriate section of the study file.

10.4. Appendix 4: Guidelines for Grading and Management of Allergic or Infusion-Related Reactions

Infusion-associated reactions are a potential risk with the use of monoclonal antibodies; these reactions can be nonimmune or immune mediated (eg, hypersensitivity reactions). Signs and symptoms may include headache, fever, facial flushing, pruritus, myalgia, nausea, chest tightness, dyspnea, vomiting, erythema, abdominal discomfort, diaphoresis, shivers, hypertension, lightheadedness, hypotension, palpitations, and somnolence. Signs and symptoms of hypersensitivity or allergic reactions may include hives, swollen face, eyelids, lips, or tongue, or trouble with breathing.

All infusion-associated reactions will be reported to the Investigator and qualified designee. The Investigator and qualified designee are responsible for detecting, documenting, and recording events that meet the definition of AE or SAE and remain responsible for following up events that are serious, considered related to the study drug, or study procedures; or that caused the participant to discontinue ALXN1830.

Definitions and procedures for recording, evaluating, follow-up, and reporting AEs and SAEs are outlined in Section 10.3.

Before any infusion is started, the treating physician and other appropriate personnel must make certain that medication (i.e., adrenaline, inhaled beta agonists, antihistamines, corticosteroids) and other equipment to treat anaphylaxis are readily available. The infusion must be stopped immediately if Grade ≥ 2 allergic/hypersensitivity reactions (including drug fever) or Grade ≥ 3 cytokine release syndrome/acute infusion reaction occurs. The Sponsor must be notified within 24 hours of any infusion reaction requiring interruption or discontinuation of study drug or meet the criteria of AESI.

Patients /subject who experience a reaction during the administration of study drug should be treated according to institutional guidelines. For a Grade 1 or Grade 2 infusion reaction, the infusion should be temporarily stopped and treatment with an antihistamine (eg, diphenhydramine 25 to 50 mg orally or equivalent) and acetaminophen (650 mg orally or equivalent) may be considered. If the patient's signs and symptoms have resolved (with or without administration of the above medication), the infusion may be restarted. However, the patients should be infused at a slower rate and be monitored closely for any signs and symptoms of infusion reactions during the remainder of the infusion. Patients experiencing an infusion reaction should be observed in the clinic until resolution of the reaction, or until the Investigator determines the patient is no longer at risk. Patients who experience a severe reaction during administration of study drug resulting in discontinuation of study drug should undergo all scheduled safety, PK, and PD evaluations required by the protocol.

If anaphylaxis occurs according to the criteria listed below, then administration of subcutaneous epinephrine (1/1000, 0.3 mL to 0.5 mL, or equivalent) should be considered. In the case of bronchospasm, treatment with an inhaled beta agonist also should be considered. Patients administered an antihistamine for the treatment or prevention of an infusion reaction should be given appropriate warnings about drowsiness and impairment of driving ability before being discharged from the center.

In the event of an IRR considered to be a hypersensitivity reaction, it is recommended to collect a blood sample for assessment of tryptase, histamine, CRP, and complement as soon as the IRR is observed (prior to administering any IRR medication), 2 hours after onset of the IRR, and 7 days later, prior to the next dose of study drug.

Table 20: Grading and Management of Allergic or Infusion-Related Reactions

Adverse Event	Grade				
	1	2	3	4	5
Infusion-related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, non-steroidal anti-inflammatory drugs [NSAIDs], narcotics, IV fluids): prophylactic medications indicated for ≤ 24 hours	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement, hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention required	Death
Allergic reaction	Transient flushing or rash, drug fever < 38.0°C. Intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids): prophylactic medications indicated for ≤ 24 hours	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement, hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention required	Death
Anaphylaxis	–	–	Symptomatic bronchospasm, with or without urticarial; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention required	Death
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids): prophylactic medications indicated for ≤ 24 hours	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement, hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilator support indicated	Death

Abstracted from NCI CTCAE Version 5.0.
Abbreviations: IV = intravenous; NSAIDs = nonsteroidal anti-inflammatory drugs

10.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

10.5.1. Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal 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 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 1 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.

10.5.2. 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 10.5.3.1). 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.

10.5.2.1. Guidance for Female Participants

Female participants of childbearing potential must have a negative pregnancy test ([urine or serum]) as required by local regulations within 3 months before the first dose of study intervention. Additional requirements for pregnancy testing during and after dosing with study intervention 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 study intervention.

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 study intervention.

1. Intrauterine device in place for at least 6 weeks prior to first dose of study intervention.
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 study intervention.
3. Intrauterine progestogen releasing system for at least 6 weeks prior to first dose of study intervention.
4. Bilateral tubal occlusion for at least 6 weeks prior to first dose of study intervention.
5. Combined (estrogen- and progestogen-containing) hormonal contraception (either oral, intravaginal, or transdermal) for at least 6 weeks prior to first dose of study intervention.
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 study intervention). 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 study intervention.

10.5.2.2. Guidance for Male Participants

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

Male participants who have had a vasectomy > 6 months prior to the first dose of study intervention must use a condom during heterosexual intercourse. Male participants who have had a vasectomy < 6 months prior to the first dose of study intervention must use a condom and spermicide during heterosexual intercourse for at least 3 months after their final dose of study intervention.

10.5.2.2.1. 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 participants' s preferred and usual lifestyle. Abstinent male participants who become heterosexually active must use a condom and 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 the last dose of study intervention.

10.5.3. Collection of Pregnancy Information

Pregnancy data will be collected during this study for all female participants and female spouses/partners of male participants. 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 partner becomes pregnant from the first dose of study intervention up to 3 months after the last dose of study intervention, the Investigator must submit the "Pregnancy/Breastfeeding Reporting and Outcome Form" to Alexion GDS via facsimile or email (Email: [redacted] or Fax: [redacted]). 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 or designee 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.

Any female participant who becomes pregnant while participating in the study will be discontinued from study intervention.

10.5.3.1. 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 study intervention.
- 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 estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.5.3.2. 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 postapproval, 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 post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to Alexion as described in Section 8.3.4. 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 be withdrawn from the study.

10.6. Appendix 6: Biomarkers

- Blood samples will be collected for biomarker analyses and the data will be used for research (eg, exploratory) related to ALXN1830 and related diseases. The samples may also be used to develop tests/assays including diagnostic tests related to ALXN1830 and/or others of this study drug class.
- The samples may be analyzed as part of a multistudy assessment of biomarkers in the response to ALXN1830 to understand study disease or related conditions.
- The results of biomarker analyses may be reported in the CSR or in a separate study summary.
- Alexion or designee will store the samples obtained for biomarker analyses in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on ALXN1830 continues but no longer than allowed per local requirements.

10.7. Appendix 7: Justification for Protective Measures

The proposed safety measures in this study include documentation of pneumococcal and current seasonal flu vaccination; staggered dosing; stopping rules; close participant monitoring through 60 days after the last dose; close safety and PD monitoring with an unblinded medical monitor; avoidance of participants with a high risk of infections; antibiotics to manage infection as needed; rescue measures such as IVIG replacement in an extremely unlikely event of profoundly low IgG; as well as use of an SRC for safety monitoring and dose selections.

10.7.1. IgG Lowering and the Potential Risk of Infection

ALXN1830 is an anti-FcRn mAb that blocks recycling of IgG antibodies, reducing the total IgG in circulation, including potentially pathogenic IgG autoantibodies associated with multiple autoimmune diseases. Thus, reduction in IgG level is used to measure the anti-FcRn PD activity of ALXN1830.

Chronic deficiency of Ig across multiple Ig classes can be associated with an increased risk of infections (eg, in patients with known hypogammaglobulinemia due to primary causes and for secondary reasons due to iatrogenic intervention in patients treated with broadly active therapies, such as rituximab or plasma exchange). For example, rituximab has been documented to widely deplete the B-cell population and affect other Ig classes, while plasma exchange removes all types of serum proteins (Marco, 2014). Likewise, hereditary hypogammaglobulinemia is generally characterized by persistent deficiency of both IgG and other Ig (IgA or IgM) due to inadequate production of gamma globulin. Other immune system disorders, such as common variable immunodeficiency are characterized by lower percentages of memory and isotype switched-memory B cells; increased infection susceptibility; chronic recurrent, persistent infections; and insufficient immune responses to most vaccines, which in turn is also underlined by low levels of IgG and at least 1 other subclass of Ig, such as IgA or IgM documented by laboratory investigations (Filion, 2019).

In contrast to the broadly active agents and immune system disorders discussed above, ALXN1830 is highly specific in reducing IgG in circulation. ALXN1830 has no effect on IgM or IgA levels, and it is also not expected to affect the catabolism of complement, cytokines, or other proteins involved in the immune response, or affect pre-existing cellular immunity (Rath, 2015). Thus, most of the immune system repertoire has been shown to be unaffected by ALXN1830 treatment, maintaining an immunocompetent host. This is supported by prior experience with anti-FcRn therapeutics in healthy participants, which has shown no increase in infection risk despite a significant reduction in tIgG.

The lack of infection risk following anti-FcRn treatment is likely due to both the specificity and transient nature of the IgG reduction, which returns to baseline relatively rapidly after discontinuation of treatment. Specifically, in a single dose and 4-week multiple dose study of the anti-FcRn antibody M281 in healthy participants (n = 50), tIgG was reduced by 85% compared to baseline, and at least 50% of participants experienced a decrease of IgG to < 200 mg/dL over the 2 highest SAD and both MAD cohorts, with no SAEs and few moderate AEs. The incidence of infection-related AEs in this study was similar between the drug-treated groups and PBO, and IgG levels returned to within 20% to 25% of baseline levels within 56 days (Ling, 2019).

Similarly, in a 4-week multiple dose study in healthy participants (n = 62) using the anti-FcRn, efgartigimod, tIgG was decreased on average by approximately 75%, with some individuals showing reductions of up to 85%. There was no increase in infections due to efgartigimod treatment, and IgG levels returned to baseline within 8 weeks after the last dose (Ulrichts, 2018). Also, in a SAD study in healthy participants (n = 48) of the anti-FcRn, rozanolixizumab, IgG levels were reduced by up to 47.6% and returned to baseline within 57 days post dose, with little or no TEAEs reported (Kiessling, 2017). Recently, in a SAD and 4-week MAD study of RVT-1401, total IgG was reduced by up to > 75%, with all AEs being mild to moderate in severity and no participants requiring premature discontinuation due to AEs (Collins, 2019).

Finally, in the previous SAD and MAD studies of ALXN1830 in healthy participants, an IgG lowering of up to 64% was observed (in the 20 mg/kg MAD cohort) with no increased risk of infection, and the IgG levels returned to baseline levels 43 days after the last dose. In total, studies with 5 different anti-FcRn therapeutics (M281, efgartigimod, rozanolixizumab, RVT-1401, and ALXN1830) in well over 200 healthy participants have generally shown no increased risk of infection, and there have been no cases of severe or serious infections reported following anti-FcRn treatment.

In summary, treatment with ALXN1830 is known to lead to a specific reduction of IgG, but not of IgA or IgM, and the IgG lowering is a transient effect with a robust, predictable, and consistent return to baseline in healthy participants. Prior experience with anti-FcRn therapies suggests a low risk of infection even with lowering of IgG to below 200 mg/dL. There have been no cases of severe or serious infections reported following anti-FcRn treatment in healthy participants.

10.7.1.1. IgG Level Stopping Rule

The stopping rule based on IgG level of ≤ 300 mg/dL was chosen based on generally used classifications of IgG lowering and the prior experience with anti-FcRn treatments discussed above. Classification of reduction in IgG levels has been specified as “mild to moderate” (300 to 600 mg/dL), “significant” (100 to 299 g/dL), or “profoundly reduced” (< 100 mg/dL).

Participants with IgG levels of 200 to 400 mg/dL and total Ig level of 400 to 600 mg/dL are considered to have adequate antibody levels to convey humoral immunity, but this is less likely if total Ig levels are less than 400 mg/dL or serum IgG levels are less than 200 mg/dL (Agarwal and Cunningham-Rundles, 2007). Prior experience with anti-FcRn therapeutics in healthy participants showed no increased risk of evidence of infection despite reduction in IgG less than 200 mg/dL. Thus, isolated reduction of IgG to levels as low as 200 mg/dL in the presence of normal IgA and IgM levels and normal cellular elements of immunity (white blood cell [WBC]/differential) would most likely maintain an immunocompetent status. However, to avoid IgG reductions below the mild to moderate range, we will utilize a more conservative level of 300 mg/dL as the threshold for individual and cohort level stopping rules.

To further ensure the IgG nadir would not drop below 300 mg/dL, the inclusion criterion for IgG was set to ≥ 1000 mg/dL, higher than the lower limit of normal. Since the proposed dosing regimens of ALXN1830 are not expected to lower IgG levels more than ~ 70% as predicted by PK/PD modeling, the IgG levels should remain above 300 mg/dL. Furthermore, the IgG nadir is a transient phenomenon, with IgG levels rising back towards baseline in a relatively rapid timeframe.

Finally, IVIG replacement will be considered only if IgG is profoundly low, ie, below 100 mg/dL, and this low nadir is sustained for more than 7 days despite discontinuation of ALXN1830, which again would be an extremely unlikely event as discussed above.

10.7.1.2. Evidence of Immunity/Vaccination

To mitigate the risk of sinopulmonary infections associated with anti-FcRn targeted IgG reduction therapy, healthy participants will have current vaccinations against pneumococcus and seasonal influenza.

10.7.2. Hydration

Adverse events of anti-FcRn agents and other Ig are commonly reported to be associated with headaches (Robak, 2010; Ling, 2019; Kiessling, 2017). Similarly, in ALXN1830 studies, both in patients and healthy participants, headaches (mild to moderate in grade) occurred in both SAD and MAD dose regimens with or without nonprescription analgesics. In the case of Ig, multiple mechanistic factors have been postulated, such as osmolality, volume load, total volume infused, rate of infusion, concentration, and total dose of the Ig infused, which were shown to affect infusion tolerability (Vo, 2006). Hydration was considered to be an important factor for improvement of infusion-induced headaches (Feldmeyer, 2010). To ensure adequate hydration, it is recommended that study participants drink **approximately 2 L (women)/2.5 L (men) of water every day** during the 3 days preceding and following an infusion treatment (National Academies of Sciences, Engineering, and Medicine, 2004).

10.8. Appendix 11: Abbreviations

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

Abbreviation	Explanation
PD	pharmacodynamics
PK	pharmacokinetics
PV	pemphigus vulgaris
q2w	every 2 weeks
QTcF	QT interval corrected for heart rate according to Fridericia's formula
qw	weekly
SAD	single ascending dose
SAE	serious adverse event
SC	subcutaneous
SoA	schedule of activities
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WAIHA	warm autoimmune hemolytic anemia
WBC	white blood cell
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			
Document	**Type of Amendment (Global or Country-specific)**	**Date**	**Summary of Key Changes in the Amendment**
Amendment 4	Not applicable (single site)	25 JUN 2021	Added pregnancy follow-up testing for female participants of childbearing potential approximately monthly for 3 months after the last dose of study drug to be consistent with the Investigator's Brochure; added changes made in Administrative Letters 2, 3, and 4.
Amendment 3	Not applicable (single site)	8 FEB 2021	Extended Screening period from 42 to 60 days; reduced the overall blood volume required to be drawn from participants in the MAD cohorts during the study, added conditions that may warrant termination of the study, and included additional clarifying text and corrections in other sections of the document.
Amendment 2	Not applicable (single site)	20 DEC 2020	Revised lower limit of body weight eligibility from 50 to 60 kg and updated dose justification based on revised body weight criteria; added clarity on prior exposure to which therapeutic proteins excludes participation.
Amendment 1	Not applicable (single site)	09 NOV 2020	Added vital sign measurement (including temperature and pulse oximetry) time points after infusion on dosing day to the SoA (Section 1.3), removed limitations for the type of IUD and hormonal contraception to be considered highly effective methods of contraception (Section 10.5.2), and changed the period for contraception use after last dose of study drug, from "at least 2 months" to "3 months".
Original protocol (not submitted)	Not applicable	28 OCT 2020	Not applicable.

Abbreviations: IUD = intrauterine device; MAD = multiple ascending dose; SOA = schedule of activities.

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