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-105

Version Number:

Version 3

Amendment Number:

Amendment 2

Compound:

ALXN1830

Study Phase:

Phase 1

Short Title:

Safety and Pharmacokinetic Study of Subcutaneous ALXN1830 in Healthy Adult Participants

Sponsor Name:

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Regulatory Agency Identifier Number:

EudraCT number: 2019-003496-18

Approval Date: 24 January 2020

Sp[redacted]

[redacted]

Date

Medical Monitor Name and Contact Information will be provided separately.

INVESTIGATOR'S AGREEMENT

I have read the ALXN1830-HV-105 study protocol and agree to conduct the study in accordance with this protocol, 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.

[redacted]

_____

Printed Name of Investigator

[redacted]

Signature of Investigator

1/24/2020

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	24-Jan-2020
Amendment 1	28-Oct-2019
Original Protocol	23-Sep-2019

Amendment 2 (24 January 2020)

Section # and Name	Description of Change	Brief Rationale
Throughout the document	Editorial and minor grammatical changes	To enhance clarity
Section 1.1 Synopsis	Added: "Progression to the next dosing cohort will be gated by review of initial dosing data by a Safety Review Committee (SRC) consisting of the Investigator, Safety Monitor, Medical Monitor, Study Statistician, and Clinical Pharmacologist."	To summarize in the synopsis how progression to the next dosing cohort is gated, in alignment with criteria presented in Table 11
Section 1.1 Synopsis Section 4.1 Overall Design	Changed duration of Screening period from 28 to 42 days and overall study duration from 169 days to 183 days accordingly	To allocate a sufficient amount of time for vaccination during screening, if required (ie, at least 28 days prior to Day 1)
Section 1.3 Schedule of Activities	Increased start of Screening window from D -28 to D -42	To allocate a sufficient amount of time for vaccination during screening, if required (ie, at least 28 days prior to Day 1)
Section 1.3 Schedule of Activities	Removed ±1-day window for visits that occur at the CRU	Participants are admitted to the CRU for the corresponding activities, therefore a window of time (±1-day) is not relevant
Section 1.3 Schedule of Activities	Changed row header "Evidence of immunity to *Haemophilus influenzae* / Tetanus toxoid / Streptococcus pneumoniae" to "Evidence of Vaccination"	To align with changes to the vaccination requirements in Section 5.1 Inclusion Criteria
Section 1.3 Schedule of Activities	Moved time point for pregnancy test for Cohorts 1,2 and 3 from Day 5 to Day 4	Correction and alignment with other cohorts
Section 1.3 Schedule of Activities	Added row titled "Sample for Pneumovax 23 titer" and marked timepoints with an "X" for sample to be taken	To specify time points for samples to be taken for assessment of Pneumovax 23 titers
Section 1.3 Schedule of Activities	Deleted footnote "Height at Screening only"	A full physical examination is to be performed only at screening, and symptom-driven thereafter
Section 1.3 Schedule of Activities	Added "… (or up to 3 months prior to Day 1)" to footnote regarding Cardiac Holter assessment.	Cardiac health as assessed by Holter monitor does not need to be repeated at Screening if a result is available within the previous 3-months.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Added footnote "Participants must be vaccinated as described in Section 6.5.3.	To enhance utility and readability of the protocol by directing the reader to additional detail
Section 1.3 Schedule of Activities	Updated footnote superscripts as appropriate.	For accuracy as a result of footnotes that were added and / or deleted, described above
Section 2.2 Background	Shortened summary of ALXN1830 background.	To enhance readability by focusing the body of the protocol on procedural elements and consolidating detailed justifications and rationale in the appendix.
Section 2.3 Benefit / risk Assessment	Added cross reference to Section 4.2	To refer the reader to a discussion of theoretical risks associated with the reduction of IgG
Section 4.1 Overall Design	Added geographic location of the single study site (United Kingdom)	For completeness
Section 4.1 Overall Design	Added cross reference to Table 11	To enhance utility and readability of the protocol by directing the reader to additional detail.
Section 4.2 Scientific Rationale for Study Design	Shortened summary of scientific rationale for study design by moving detailed rationale to Section 10.7	To enhance readability by focusing the body of the protocol on procedural elements and consolidating detailed justifications and rationale in the appendix
Section 4.2 Scientific Rationale for Study Design	Revised rationale for the implementation of certain inclusion criteria that were designed to minimize the potential risk of infection in the healthy participants due the theoretical concerns associated with reducing total IgG	Alignment with changes to vaccination requirements (see Section 5.1 and Section 6.5.3)
Section 4.4 End of Study Definition	Deleted the phrase "all phases of the study including…"	This study does not consist of pre-defined phases. A participant is considered to have completed the study if he/she has completed the last scheduled visit shown in the Schedule of Activities (SoA).
Section 5.1 Inclusion Criteria	Updated numbering of inclusion criteria (1-10)	Correction
Section 5.1 Inclusion Criteria	Added footnote to Inclusion Criterion #5 as follows: 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 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.	For inclusion criterion #5 "Baseline IgA and IgM within normal levels at screening," the intent is to include participants with a healthy immune system prior to dosing with ALXN1830. In this trial subjects need to have been vaccinated against pneumococcal infection. A rise IgM level post vaccination is a sign of a healthy immune system and can therefore be interpreted as being "within normal levels" (of someone who has recently been vaccinated).

Section # and Name	Description of Change	Brief Rationale
Section 5.1 Inclusion Criteria	Revised Inclusion Criteria #6 to remove requirement for evidence of current vaccination against tetanus toxoid, Hib, and MMR	To limit potential vaccinations to those recommended for immunosuppression in the Green Book, Chapter 7, "Immunisation of individuals with underlying medical Conditions")
Section 5.1 Inclusion Criteria	Revised Inclusion Criteria #7 to delete "…who undergo study drug administration during the influenza season 2019/2020…"	To enhance clarity as all participants must be vaccinated against seasonal influenza for the current season
Section 5.2 Exclusion Criteria	Revised Exclusion Criterion #5 to include tension headache disorder as follows: Participants with the history of frequent and/or chronic headaches, including migraine disorder, cluster headache disorder, and tension headache disorder.	To specify types of chronic headache disorders, including tension headache
Section 5.2 Exclusion Criteria	Added Exclusion Criterion #11: "Female participants who are pregnant or breastfeeding"	For consistency with Section 8.3.5 which states that pregnant or breastfeeding females are excluded from the study
Section 5.2 Exclusion Criteria	Moved text from Exclusion Criterion #24 regarding exclusion of individuals with children who are first-year college/university students to a separate exclusion criterion (#25)	To enhance clarity
Section 5.2 Exclusion Criteria	Added new Exclusion Criterion (#26) to exclude first-year college/university students	First-year college/university students are considered to have a high risk of acquiring sinopulmonary infections
Section 5.4 Screen Failures	Revised language regarding re-testing to specify that 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	To enhance clarity
Section 6.5.1 Premedication and Hydration	Replaced ranitidine with famotidine	Due to voluntary recall of ranitidine
Section 6.5.1 Premedication and Hydration	Changed units for recommended amounts of water from ounces to liters	For consistency
Section 6.5.1 Premedication and Hydration	Added a cross reference to the detailed justification for recommended hydration in section 10.7.2	To enhance utility and readability of the protocol by directing the reader to additional detail
Section 6.5.2 Supportive / Symptomatic Care	Moved justification for premedication and hydration to the Appendix (Section 10.7.2)	To enhance readability by focusing the body of the protocol on procedural elements and consolidating detailed justifications and rationale in the appendix

Section # and Name	Description of Change	Brief Rationale
Section 6.5.3 Vaccinations	To remove requirement for evidence of current vaccination against tetanus toxoid, Hib, and MMR	To align with changes to Inclusion Criteria (Section 5.1)
Section 6.5.3 Vaccinations	Added requirements for taking blood samples for assessment of Pneumovax titers	To enhance clarity
Section 6.5.4 Antibiotics Prophylaxis	New sub-heading for information regarding prophylactic use of antibiotics. Revised recommendations for when to start antibiotics	To enhance clarity
Section 7.2.1 Immunoglobulin Stopping Rules	Added specific vaccination titers to be assessed (Pneumovax 23)	To enhance clarity
Section 8.2.1 Physical Examinations	Deleted "…and at the beginning of each dosing visit." From the description of when to perform a full physical examination	A full examination is only required at Screening, and symptom directed thereafter
Section 8.2.3 Oxygen Saturation	Added "…which is measured along with vital signs…" and deleted information regarding the brand of device used to measure oxygen saturation	For alignment with the Schedule of Assessments and updated information
Section 8.2.4.3 24-hour Holter ECG	New section "24-hour Holter ECG"	To enhance clarity
Section 8.2.4.4 Real Time Display (ECG Telemetry)	New section "Real time display (ECG Telemetry)"	To enhance clarity
Section 8.2.7 Vaccination	Information replaced with a cross-reference to Section 6.5.3	To reduce redundancy and enhance readability
Section 8.3.6 Infusion-Related Reaction	Deleted section	To reduce redundancy and enhance readability. Information regarding definition and management of IRRs is presented in Section 8.3.6.1 and Section 10.4
Section 8.3.7 Injection/Infusion-associated Reactions	Deleted section	To reduce redundancy and enhance readability. Information regarding definition and management of IRRs is presented in Section 8.3.6.1 and Section 10.4
Section 8.4 Treatment Overdose	Added further information for the definition and recommended action in the case of an overdose of ALXN1830	To enhance clarity
Section 8.8 Biomarkers	Added "Whole blood for assessment of exploratory biomarkers…"	To enhance clarity
Section 9.3 Populations for Analyses	Added definition for "Enrolled Set" and "PD Analysis Set"	To enhance clarity
Section 9.4.2 Other Analyses	Added text to specify analysis sets used for PK and PD analyses	To enhance clarity

Section # and Name	Description of Change	Brief Rationale
Section 10.1.3 Informed Consent Process	Changed statement to require re-screened participants to sign a new ICF	Correction
Section 10.2 Appendix 2: Clinical Laboratory Tests	Added laboratory assessments for signs of infection and Pneumovax 23 titers to Table 14	For alignment with the Schedule of Activities
Section 10.2 Appendix 2: Clinical Laboratory Tests	Revised language regarding laboratory results that may unblind the study site to include review of results that could unblind the study by dedicated unblinded staff at the investigative site	To further ensure participant safety
Section 10.3.6 Reporting of Serious Adverse Events	Deleted information regarding reporting of SAEs via an electronic data collection tool	An EDC is not being used for SAE reporting in this study
Section 10.4 Appendix 4: Infusion Related Reactions – Definitions of Severity Levels and Management Algorithm	Replaced “suspended” with “stopped”	To enhance clarity
Section 10.6 Appendix 6 Contraceptive Guidance and Collection of Pregnancy Information	Deleted “or acceptable contraception”	Female participants of childbearing potential, if heterosexually active, must use only highly effective contraception as defined in the protocol
Section 10.7 Appendix 7: Justification for Protective Measures	Section added “Appendix 7: Justification for Protective Measures”	Detailed rationale/justification for protective measures, including mitigation of the potential risk of infection due to IgG lowering, and hydration recommendations due to the risk of infusion-induced headaches was moved from within the body of the protocol to the appendix for improved clarity/readability

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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 and Pharmacokinetic 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). 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	• ALXN1830 PK profiles and PK parameters • Change in IgG levels • Measurement of ADA levels and NAbs

Abbreviations: ADA = antidrug antibody; AESI = adverse events of special interest; ECG = electrocardiogram; IgG = immunoglobulin G; IV = intravenous; NAb = neutralizing antibody; 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 56 healthy adult participants (42 on active treatment, 14 on placebo [PBO]) conducted at a single site. Eight participants will be randomly assigned in a 6:2 ratio to each of 7 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).

Of these 7 cohorts, 1 cohort is optional; a dose to be determined (based on the safety of the predetermined doses) in the MAD. 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 ALXN 1830 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 well within the observed IgG reduction observed in previous IV studies; and in general, there will be low risk of immunogenicity and infusion related reactions after a single dose. See Section 4.3 for details regarding expected PK exposures and IgG reduction. 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) consisting of the Investigator, Safety Monitor, Medical Monitor, Study Statistician, and Clinical Pharmacologist. At Alexion's discretion, and after consultation with the SRC, additional participants may be enrolled as replacement participants if a participant discontinues within 3 weeks of the last dose for reasons other than drug-related adverse events.

Number of Participants:

A maximum of 56 participants will be randomly assigned to study drug such that approximately 8 evaluable participants per cohort complete the study. The number of participants was chosen based on feasibility and was considered adequate to meet the study objectives.

Study Drug Groups and Duration:

Participants will be randomly assigned in a 6:2 ratio to each of 7 cohorts (Table 1) 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 study duration is approximately 183 days: up to 42 days for screening and approximately 141 days for dosing and follow-up.

Table 1: Dose and Dose Regimen of ALXN1830 in Healthy Participants

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

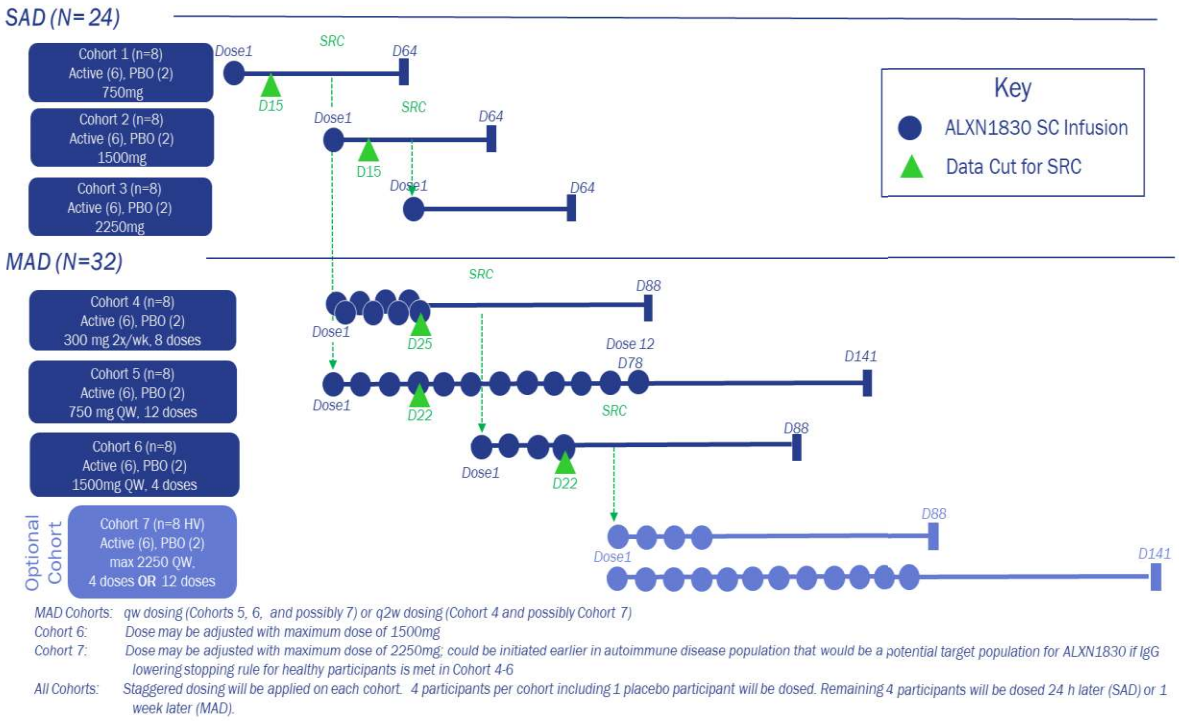
[a] Optional

[b] If Cohort 6 is terminated early due to safety or IgG stopping rules, then Cohort 7 may be dosed at a < 1500 mg lower weekly dose for 4 doses. If Cohort 6 does not reach the expected IgG reduction, and no safety or IgG stopping rules are met, then Cohort 7 may be dosed at higher dose > 1500 mg (but not to exceed 2250 mg) weekly for 4 doses).

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

1.2. Schema

Figure 1: Study Schematic Diagram



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

1.3. Schedule of Activities

The schedule of activities (SoA) for the SAD, MAD Cohort 4, MAD Cohort 5, and MAD Cohort 6 (and the optional MAD Cohort 7) are shown in Table 2, Table 3, Table 4, Table 5, and Table 6, respectively. The schedules of activities during CRU confinement for all SAD and MAD cohorts are shown in Table 7 and Table 8.

Table 2: Schedule of Activities (Single Ascending Dose Cohorts 1, 2 and 3)

Assessments	Screening	D −1	D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 8	D 10	D 12	D 15	D 22	D 29	D 36	D 43	D 50	D 57	D 64/ET
Status (OP or CRU)	**D -42 to D -2**	**CRU**	**CRU**	**CRU**	**CRU**	**CRU**	**CRU**	**CRU**	**CRU**	**CRU**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**
Window (days)		**ADM**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**
Informed consent	X																			
Inclusion/exclusion criteria	X	X																		
Serum pregnancy test	X	X		X		X				X			X		X		X			X
Alcohol breath test	X	X																		
Urine drug screen	X	X																		
Hepatitis B and C screen	X																			
Evidence of vaccination[g]	X	X																		
Sample for Pneumovax 23 titer[g]	X		X[c,d]							X[c,d]										
HIV (types 1 and 2) screen	X																			
Medical history and demographics	X	X																		
Physical examination[a,c]	X	X	X			X				X			X		X		X			X
Height, weight and BMI	X																			
Randomization			X																	
Study drug administration (ALXN1830 or PBO)			X																	
PK blood sampling[b]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PD blood sampling - IgA, IgM, IgG [b,c]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PD blood sampling - IgG subtypes 1-4[b,c]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PD blood sampling – CIC[b,c]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity[d]			X										X		X		X			X
Biochemistry[e]	X	X		X		X				X			X		X		X			X

Table 2: Schedule of Activities (Single Ascending Dose Cohorts 1, 2 and 3) (Continued)

Assessments	Screening	D −1	D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 8	D 10	D 12	D 15	D 22	D 29	D 36	D 43	D 50	D 57	D 64/ET
Status (OP or CRU)		**CRU**	**CRU**	**CRU**	**CRU**	**CRU**	**CRU**	**CRU**	**CRU**	**CRU**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**
Window (days)	**D -42 to D -2**	**ADM**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**
Hematology[c]	X	X		X		X				X			X		X		X			X
Coagulation[c]	X	X		X		X				X			X		X		X			X
Exploratory biomarker sample	X	X		X		X				X			X		X		X			X
Urinalysis[c]	X	X		X		X				X			X		X		X			X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Oxygen saturation[g]			X																	
12-lead ECG (triplicate)	X	X	X	X	X	X	X	X	X	X			X		X		X			X
Cardiac Holter/telemetry[e]	X		X																	
Injection/infusion site evaluation			X	X		X														
Adverse events	X																			
Review potential safety risk of ALXN1830	X																			
Concomitant medications	X																			

[a] Full PE at screening and symptom directed PE thereafter.
[b] Refer to Table 7 and Table 8 for timing.
[c] Could be done on the day prior to dosing.
[d] Predose.
[e] Holter at Screening (or up to 3 months prior to Day1); telemetry at 1-hour predose until 24 hours after start of infusion.
[f] Oxygen saturation measurement on dosing days should be done with vital signs.
[g] Participants must be vaccinated as described in Section 6.5.3.

Abbreviations: ADM = admission; BMI = body mass index; CIC = circulating immune complexes; CRU = Clinical Research Unit; D = day; ECG = electrocardiogram; ET = early termination; HIV = human immunodeficiency virus; Ig = immunoglobulin; NA = not applicable; OP = outpatient; PD = pharmacodynamic(s); PE = physical examination; PK = pharmacokinetic(s).

Table 3: Schedule of Activities (Multiple Ascending Dose Cohort 4)

Assessments	Screening	D -1	D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 8	D 11	D 15	D 18	D 22	D 25	D 32	D 39	D 46	D 53	D 60	D 67	D 74	D 81	D 88/ ET
Status (OP or CRU)		CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	OP	OP	OP	OP	OP	OP	OP	OP	OP
Window (days)	D -42 to D -2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	±1	±1	±1	±1	±1	±1	±1	±1	±1
Informed consent	X																							
Inclusion/ exclusion criteria	X	X																						
Serum pregnancy test	X	X		X		X				X	X	X	X	X	X			X			X			X
Alcohol breath test	X	X																						
Urine drug screen	X	X																						
Hepatitis B and C screen	X																							
Evidence of vaccination[h]	X	X																						
Sample for Pneumovax 23 titer[h]	X		X[c,d]							X[c,d]						X								
HIV (types 1 and 2) screen	X																							
Medical history and demographics	X	X																						
Physical examination[a,c]	X	X				X				X	X	X	X	X	X			X			X			X
Height, weight and BMI	X																							
Randomization			X																					
Study drug administration			X			X				X[g]	X	X	X	X	X									
PK blood sampling[b,c]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PD blood sampling - IgA, IgG, IgM[b,c]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PD blood sampling - IgG subtypes 1-4[b,c]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 3: Schedule of Activities (Multiple Ascending Dose Cohort 4) (Continued)

Assessments	Screening	D -1	D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 8	D 11	D 15	D 18	D 22	D 25	D 32	D 39	D 46	D 53	D 60	D 67	D 74	D 81	D 88/ ET
Status (OP or CRU)		CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	OP	OP	OP	OP	OP	OP	OP	OP	OP
Window (days)	D -42 to D -2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	±1	±1	±1	±1	±1	±1	±1	±1	±1
PD blood sampling – CIC[b,c]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity[d]			X									X				X		X			X			X
Biochemistry[c]	X	X		X		X				X	X	X	X	X	X			X			X			X
Hematology[c]	X	X		X		X				X	X	X	X	X	X			X			X			X
Coagulation[c]	X	X		X		X				X	X	X	X	X	X			X			X			X
Exploratory biomarker sample	X	X		X		X				X	X	X	X	X	X			X			X			X
Urinalysis[c]	X	X		X		X				X	X	X	X	X	X			X			X			X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Oxygen saturation[f]			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	X									
Cardiac Holter/telemetry[e]	X		X							X		X		X	X									
Injection/infusion site evaluation			X	X		X				X	X	X	X	X	X									
Adverse events	X																							
Review potential safety risk of ALXN1830	X																							
Concomitant medications	X																							

[a] Full PE at screening and symptom directed PE thereafter.
[b] Refer to Table 7 and Table 8 for timing.
[c] Could be done on the day prior to dosing.
[d] Predose.
[e] Holter at Screening (or up to 3 months prior to Day 1); telemetry at 1-hour predose until 24 hours after start of infusion.
[f] Oxygen saturation measurement on dosing days should be done with vital signs.
[g] Discharge after all 24-hour procedures are completed.
[h] Participants must be vaccinated as described in Section 6.5.3. Abbreviations: BMI = body mass index; CIC = circulating immune complexes; CRU = Clinical Research Unit; D = day; ECG = electrocardiogram; ET = early termination; HIV = human immunodeficiency virus; Ig = immunoglobulin; NA = not applicable; OP = outpatient; PD = pharmacodynamic(s); PE = physical examination; PK = pharmacokinetic(s).

Table 4: Schedule of Activities (Multiple Ascending Dose Cohort 5; Screening Through Day 36)

Assessments	Screening	D -1	D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 8	D 11	D 15	D 18	D 22	D 25	D 29	D 36
Status (OP or CRU)		**CRU**	**CRU**	**CRU**	**CRU**	**CRU**	**CRU**	**CRU**	**CRU**	**CRU**	**OP**	**CRU**	**OP**	**CRU**	**OP**	**CRU**	**CRU**
Window (days)	**D -42 to D -2**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**±1**	**NA**	**±1**	**NA**	**±1**	**NA**	**NA**
Informed consent	X																
Inclusion/exclusion criteria	X	X															
Serum pregnancy test	X	X		X		X				X		X		X			X
Alcohol breath test	X	X															
Urine drug screen	X	X										X		X			
Hepatitis B and C screen	X																
Evidence of vaccination[g]	X	X															
Sample for Pneumovax 23 titer[g]	X		X[c,d]							X[c,d]							
HIV (types 1 and 2) screen	X																
Medical history and demographics	X																
Physical examination[a,c]	X	X				X				X		X		X	X		
Height, weight and BMI	X																
Randomization			X														
Study drug administration			X							X		X		X		X	X
PK blood sampling[b,c]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PD blood sampling - IgA, IgG, IgM[b,c]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PD blood sampling - IgG subtypes 1-4[b,c]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PD blood sampling – CIC[b,c]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity[d]			X									X				X	
Biochemistry[c]	X	X		X		X				X		X		X			X
Hematology[c]	X	X		X		X				X		X		X			X
Coagulation[c]	X	X		X		X				X		X		X			X
Exploratory biomarker sample	X	X		X		X				X		X		X			
Urinalysis[c]	X	X		X		X	X			X		X		X			
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Oxygen saturation[f]			X							X		X		X		X	X
12-lead ECG (triplicate)	X	X	X	X	X	X	X	X	X	X		X		X			

Table 4: Schedule of Activities (Multiple Ascending Dose Cohort 5; Screening Through Day 36) (Continued)

Assessments	**Screening**	**D -1**	**D 1**	**D 2**	**D 3**	**D 4**	**D 5**	**D 6**	**D 7**	**D 8**	**D 11**	**D 15**	**D 18**	**D 22**	**D 25**	**D 29**	**D 36**
Status (OP or CRU)		**CRU**	**CRU**	**CRU**	**CRU**	**CRU**	**CRU**	**CRU**	**CRU**	**CRU**	**OP**	**CRU**	**OP**	**CRU**	**OP**	**CRU**	**CRU**
Window (days)	**D -42 to D -2**		**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**±1**	**NA**	**±1**	**NA**	**±1**	**NA**	**NA**
Cardiac Holter/telemetry[e]	X		X			X				X		X		X			
Injection/infusion site evaluation			X	X		X				X		X		X			
Adverse events										X							
Review potential safety risk of ALXN1830										X							
Concomitant medications										X							

[a] Full PE at screening and symptom directed PE thereafter.
[b] Refer to Table 7 and Table 8 for timing.
[c] Could be done on the day prior to dosing.
[d] Predose.
[e] Holter at Screening (or up to 3 months prior to Day 1); telemetry at 1-hour predose until 24 hours after start of infusion.
[f] Oxygen saturation measurement on dosing days should be done with vital signs.
[g] Participants must be vaccinated as described in Section 6.5.3.

Abbreviations: BMI = body mass index; CIC = circulating immune complexes; CRU = Clinical Research Unit; D = day; ECG = electrocardiogram; HIV = human immunodeficiency virus; Ig = immunoglobulin; NA = not applicable; OP = outpatient; PD = pharmacodynamic(s); PE = physical examination; PK = pharmacokinetic(s).

Table 5: Schedule of Activities (Multiple Ascending Dose Cohort 5; Day 43 Through Day 141)

Assessments	**D 43**	**D 50**	**D 57**	**D 64**	**D 71**	**D 78**	**D 85**	**D 92**	**D 99**	**D 106**	**D 113**	**D 120**	**D 127**	**D 134**	**D 141/ET**
Status (OP or CRU)	**CRU**	**CRU**	**CRU**	**CRU**	**CRU**	**CRU**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**
Window (days)	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**
Serum pregnancy test	X			X			X		X			X			X
Alcohol breath test															
Urine drug screen	X			X			X		X			X			X
Evidence of vaccination[h]															
Sample for Pneumovax 23 titer[h]							X								
Physical examination[a,b]	X			X			X		X			X			X
Study drug administration	X	X	X	X	X	X									
PK blood sampling[b,c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PD blood sampling - IgA, IgG, IgM[b,c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PD blood sampling - IgG subtypes 1-4[b,c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PD blood sampling – CIC[b,c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity[d]	X			X			X		X			X			X
Biochemistry[e]	X			X			X		X			X			X
Hematology[e]	X			X			X		X			X			X
Coagulation[e]	X			X			X		X			X			X
Exploratory biomarker sample	X			X			X		X			X			X
Urinalysis	X			X			X		X			X			X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Oxygen saturation[f]	X	X	X	X	X	X									
12-lead ECG (triplicate)															
Cardiac Holter / telemetry[e]															
Injection/infusion site evaluation															
Adverse events								X							
Review potential safety risk of ALXN1830								X							

Table 5: Schedule of Activities (Multiple Ascending Dose Cohort 5; Day 43 Through Day 141) (Continued)

Assessments	D 43	D 50	D 57	D 64	D 71	D 78	D 85	D 92	D 99	D 106	D 113	D 120	D 127	D 134	D 141/ET
Status (OP or CRU)	**CRU**	**CRU**	**CRU**	**CRU**	**CRU**	**CRU**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**
Window (days)							**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**
Concomitant medications	X														

[a] Full PE at screening and symptom directed PE thereafter.
[b] Refer to Table 7 and Table 8 for timing.
[c] Could be done on the day prior to dosing.
[d] Predose.
[e] Holter at Screening (or up to 3 months prior to Day 1); telemetry at 1-hour predose until 24 hours after start of infusion.
[f] Oxygen saturation measurement on dosing days should be done with vital signs.
[g] Participants must be vaccinated as described in Section 6.5.3.

Abbreviations: BMI = body mass index; CIC = circulating immune complexes; CRU = Clinical Research Unit; D = day; ECG = electrocardiogram; ET = early termination; HIV = human immunodeficiency virus; Ig = immunoglobulin; NA = not applicable; OP = outpatient; PD = pharmacodynamic(s); PE = physical examination; PK = pharmacokinetic(s).

Table 6: Schedule of Activities (Multiple Ascending Dose Cohort 6 and optional Cohort 7)

Assessments	**Screening**	**D -1**	**D 1**	**D 2**	**D 3**	**D 4**	**D 5**	**D 6**	**D 7**	**D 8**	**D 11**	**D 15**	**D 18**	**D 22**	**D 25**	**D 29**	**D 32**	**D 39**	**D 46**	**D 53**	**D 60**	**D 67**	**D 74**	**D 81**	**D 88/ ET**
Status (OP or CRU)		CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	OP	CRU	OP	CRU	OP	OP	OP	OP	OP	OP	OP	OP	OP	OP	OP
Window (days)	**D -42 to D -2**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**±1**	**NA**	**±1**	**NA**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**
Informed consent	X																								
Inclusion/exclusion criteria	X	X																							
Serum pregnancy test	X	X		X		X				X		X		X		X			X			X			X
Alcohol breath test	X	X																							
Urine drug screen	X	X										X		X					X			X			X
Hepatitis B and C screen	X																								
Evidence of vaccination[g]	X	X																							
Sample for Pneumovax 23 titer[g]	X		X							X						X									
HIV (types 1 and 2) screen	X																								
Medical history and demographics	X	X																							
Physical examination[a]	X	X				X				X		X		X	X				X			X			X
Height, weight and BMI	X																								

Table 6: Schedule of Activities (Multiple Ascending Dose Cohort 6 and optional Cohort 7) (Continued)

Assessments	Screening	D -1	D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 8	D 11	D 15	D 18	D 22	D 25	D 29	D 32	D 39	D 46	D 53	D 60	D 67	D 74	D 81	D 88/ ET
Status (OP or CRU)		CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	OP	CRU	OP	CRU	OP	OP	OP	OP	OP	OP	OP	OP	OP	OP	OP
Window (days)	D -42 to D -2	NA	NA	NA	NA	NA	NA	NA	NA	NA	±1	NA	±1	NA	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1
Randomization			X																						
Study drug administration			X							X		X		X											
PK blood sampling[b,c]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PD blood sampling - IgA, IgG, IgM[b,c]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PD blood sampling - IgG subtypes 1-4[b,c]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PD blood sampling – CIC[b,c]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogen-icity[d]			X									X					X		X			X			X
Biochemistry[e]	X	X		X		X				X		X		X		X			X			X			X
Hematology[e]	X	X		X		X				X		X		X		X			X			X			X
Coagulation[e]	X	X		X		X				X		X		X		X			X			X			X
Exploratory biomarker sample	X	X		X		X				X		X		X					X			X			X
Urinalysis[e]	X	X		X		X	X			X		X		X		X			X			X			X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Oxygen saturation[f]			X							X		X		X											
12-lead ECG (triplicate)	X	X	X	X	X	X	X	X	X	X		X		X											
Cardiac Holter / telemetry[e]	X		X			X				X		X		X											

Table 6: Schedule of Activities (Multiple Ascending Dose Cohort 6 and optional Cohort 7) (Continued)

Assessments	Screening	D -1	D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 8	D 11	D 15	D 18	D 22	D 25	D 29	D 32	D 39	D 46	D 53	D 60	D 67	D 74	D 81	D 88 /ET
Status (OP or CRU)		**CRU**	**CRU**	**CRU**	**CRU**	**CRU**	**CRU**	**CRU**	**CRU**	**CRU**	**OP**	**CRU**	**OP**	**CRU**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**	**OP**
Window (days)	**D -42 to D -2**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**±1**	**NA**	**±1**	**NA**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**
Injection/infusion site evaluation			X	X		X				X		X		X											
Adverse events														X											
Review potential safety risk of ALXN1830														X											
Concomitant medications														X											

[a] Full PE at screening and symptom directed PE thereafter
[b] Refer to Table 7 and Table 8 for timing
[c] Could be done on the day prior to dosing
[d] Predose.
[e] Holter at Screening (or up to 3 months prior to Day 1); telemetry at 1-hour predose until 24 hours after start of infusion
[f] Oxygen saturation measurement on dosing days should be done with vital signs.
[g] Participants must be vaccinated as described in Section 6.5.3.Abbreviations: BMI = body mass index; CIC = circulating immune complexes; CRU = Clinical Research Unit; D = day; ECG = electrocardiogram; ET = early termination; HIV = human immunodeficiency virus; Ig = immunoglobulin; NA = not applicable; OP = outpatient; PD = pharmacodynamic(s); PE = physical examination; PK = pharmacokinetic(s).

Table 7: Schedule of Activities during Clinical Research Unit confinement for Single Ascending Dose / Multiple Ascending Dose

Study Day	Time (h)[a]	Injection/Infusion Site Evaluation	PK[a]/PD Sampling [IgA, IgG, IgM, IgG Subtypes 1-4, CIC]	Vital Signs	Hematology, Chemistry, Urinalysis, and Coagulation	ECG
D1	Predose[b]		X	X		X
	EOI		X	X		X
	0.5	X	X	X		X
	2	X	X	X		X
	4	X	X	X		X
	8	X	X	X		X
	12		X	X		X
D2	24	X	X	X	X	X
D3	48		X	X		X
D4[b]	72		X	X	X	X
D5	96		X	X		X
D6	120		X	X		X
D7	144		X	X		X
D8[c]	168		X	X	X	X

[a] All samples collected from Start of Infusion unless otherwise specified.
[b] Not applicable for Cohort 4.
[c] Activities may be done on the admission day prior to dosing. PK and PD samples must always be taken together.
Abbreviations: CIC = circulating immune complex; D = day; ECG = electrocardiogram; EOI = end of infusion; h = hour; Ig = immunoglobulin; PD = pharmacodynamic(s); PK = pharmacokinetic(s).

Table 8: Schedule of Activities during Clinical Research Unit confinement for Multiple Ascending Dose

Study Day	Time (h)[a]	Injection/Infusion Site Evaluation	PK[a]/PD Sampling [IgA, IgG, IgM, IgG Subtypes 1-4, CIC]	Vital Signs	Hematology, Chemistry, Urinalysis, and Coagulation	ECG
Cohort 4: D4/D8/D11/D15/D18/D22/D25 Cohort 5: D8/D15/D22/D29/D36/D43/D50/D57/D64/D71/D78 Cohort 6 (and optional Cohort 7): D8//D15/D22	Predose[b]		X	X	X	X
	EOI		X	X		X
	0.5	X	X	X		X
	2	X	X	X		X
	4	X	X	X		X
	8	X	X	X		X
	12		X	X		X
Day after dosing - discharge after blood sampling	24	X	X	X		X

[a] Samples collected from start of infusion unless otherwise noted.

[b] Activities may be done on the admission day prior to dosing. PK and PD samples must always be taken together.

Abbreviations: CIC = circulating immune complex; CRU = Clinical Research Unit; D = day; ECG = electrocardiogram; EOI = end of infusion; h = hour; Ig immunoglobulin; PD = pharmacodynamic(s); PK = pharmacokinetic(s).

2. INTRODUCTION

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

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 et al, 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 et al, 2009; Pyzik et al, 2015; Roopenian, 2007).

There has been increasing recognition that FcRn blockade is a desirable, unique, reversible, and potentially effective means to treat a large number of autoimmune diseases in humans. This has led to the development of mAbs that specifically target the IgG, but not albumin binding site on FcRn. This approach 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 et al, 2007). More recently, it has been directly demonstrated that fully human mAbs that block the IgG binding site on FcRn led to similar decreases in endogenous IgG levels in nonhuman primates without affecting serum albumin levels (Mezo et al, 2008; Nixon et al, 2015). Such studies support the approach of mAb therapy directed at disrupting IgG binding to FcRn as a potential means to treat IgG-mediated diseases.

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

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

In the Phase 1 first-in-human study, Study SYNT-101, ALXN1830 was administered as single ascending intravenous (IV) doses in healthy adult participants at doses up to 30 mg/kg and

demonstrated a good safety profile. The purpose of this Phase 1 study in healthy adult participants is to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of single ascending doses and multiple ascending doses of ALXN1830 administered subcutaneously.

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

2.1. Study Rationale

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

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

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

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

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

Healthy participants are the appropriate population for this study because it 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 a 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 monoclonal antibody in monkeys, and produced dose-dependent, IgG isotype-selective and reversible reductions in circulating immunoglobulin (Ig) levels.

ALXN1830 has been evaluated in four clinical studies: SYNT-101 (healthy participants, single dose study), SYNT001-102 (WAIHA patients, 5 × 10 mg/kg qw), SYNT001-103 (pemphigus patients, 5 × 10 mg/kg qw), and SYNT001-104 (healthy participants, 3 × 20 mg/kg qw, then 3 × 20 mg/kg q2w). In all the clinical studies, ALXN1830 was shown to increase the catabolism of IgG, as manifested by decreased total IgG in serum. 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 concomitants medications, may benefit our future human studies in general. Detailed risk assessment is listed in the following table, 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.

2.3.1. Risk Assessment

Table 9: Risk Assessment for ALXN1830

Identified and Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Drug (s) ALXN1830		
Important Potential Risk: 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, including antibodies to the endogenous form of the protein. A total of 6 IRRs have been reported in clinical studies, along with high incidence of ADA (+) have been observed	See Section 10.4 for IRR management stopping rules; staggered dosing; See Section 7.2 for details related to stopping rules

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 trials in patients, especially those with rare autoimmune diseases, may take years to accrue and complete. Healthy participant trials 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 trials with ALXN1830 were nonserious and resolved with discontinuation of investigational therapy. While the potential of serious AEs or unexpected AEs exists, this healthy participant trial 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 at 10 mg/kg x 5 doses in autoimmune patients. However, at multiple 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. 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.

The proposed safety measures in this trial include vaccination/confirmation of 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; prophylaxis for IRRs and headache as needed; avoidance of participants with a high risk of infections; prophylactic infection management when warranted in the healthy participants after iatrogenic immunosuppression; 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	Endpoints
Primary • To assess the safety and tolerability of single and multiple doses of ALXN1830 SC	• Safety assessed by the incidence and relatedness of TEAEs, SAEs, AESIs, physical examination, vital sign measurements, clinical laboratory and ECG results
Secondary • To assess the PK of single and multiple doses of ALXN1830 SC • To explore the PD effects of single and multiple doses of ALXN1830 SC • To assess the immunogenicity of ALXN1830 SC	• ALXN1830 PK profiles and PK parameters • Change in IgG levels • Measurement of ADA levels and NAbs

Abbreviations: ADA = antidrug antibody; AESIs = adverse events of special interest; ECG = electrocardiogram; IgG = immunoglobulin G; NAb = neutralizing antibody; 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 56 healthy adult participants (42 on active treatment, 14 on placebo [PBO]) conducted at a single site in the United Kingdom. Eight participants will be randomly assigned in a 6:2 ratio to each of 7 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; Table 10). Of these 7 cohorts, 1 cohort is optional; a dose to be determined (based on the safety of the predetermined doses) in the MAD. Initially, the first 4 participants randomized to each cohort will be dosed with 3 participants on active treatment and 1 participant on PBO. Initially, the first 4 participants randomized to each cohort will be dosed with 3 participants on ALXN1830 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 ALXN 1830 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 well within the observed IgG reduction observed in previous IV studies; and in general, there will be low risk of immunogenicity and infusion related reactions 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, 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 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 11.

Table 10: ALXN1830-HV-105 Dosing Cohorts

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

[a] Optional.

[b] If Cohort 6 is terminated early due to safety or IgG stopping rules, then Cohort 7 may be dosed at a < 1500 mg lower weekly dose for 4 doses. If Cohort 6 does not reach the expected IgG reduction, and no safety or IgG stopping rules are met, then Cohort 7 may be dosed at higher dose > 1500 mg (but not to exceed 2250 mg) weekly for 4 doses).

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

Table 11: Minimum Data Requirements for Dose Escalation

Decision-making time point:	Dosing regime	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	750 mg, single dose SC	N/A	N/A	N/A
Cohort 2	1500 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 six participants.	The SRC will document the decision on the escalation/progression approval form.
Cohort 3	2250 mg, single dose SC	SRC	Review of all available safety data, IgA, IgG and IgM data and PK data through Day 15 for Cohort 2, from a minimum of six participants.	The SRC will document the decision on the escalation/progression approval form.
Cohort 4	300 mg, 8 doses SC, twice weekly	SRC	Review all available safety data and IgA, IgG and IgM data through Day 15 from Cohort 1, from a minimum of six participants.	The SRC will document the decision on the escalation/progression approval form.
Cohort 5	750 mg, 12 doses SC, once weekly	SRC	Review all available safety data and IgA, IgG and IgM data through Day 15 from Cohort 1, from a minimum of six participants.	The SRC will document the decision on the escalation/progression approval form.
Cohort 6	1500 mg, 4 doses SC, once weekly	SRC	Review all available safety data, IgA, IgG and IgM data and PK data through Day 25 of Cohort 4 and Day 22 from Cohort 5 (whichever occurs later), from a minimum of six participants.	The SRC will document the decision on the escalation/progression approval form.
Cohort 7	2250 mg, 4 doses SC, once weekly	SRC	Review all available safety data and IgA, IgG and IgM data through Day 22 from Cohort 6, from a minimum of six participants.	The SRC will document the decision on the escalation/progression approval form.

Abbreviations: CSP = Clinical Study Protocol; 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

The planned study duration is approximately 183 days: up to 42 days for screening and approximately 141 days for dosing and follow up.

4.2. Scientific Rationale for Study Design

ALXN1830 has been studied in four clinical studies, each using the IV route of 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 initial assessment of the safety, tolerability, PK/PD, and immunogenicity of ALXN1830 administered SC.

Healthy participants are the appropriate population for this study, enabling the effects of ALXN1830 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 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.

A comprehensive approach to minimize the potential risk of infection in the healthy participants due the theoretical concerns associated with reducing total IgG (discussed in greater detail in Section 10.7). The following criteria will be observed as part of the inclusion 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 (above the upper limit of normal [ULN])
  - No history of acute and chronic infections; ie, enrolled healthy participants will be immunocompetent
  - Absence of any immunologic deficiencies; eg, IgM, IgA within normal limits
  - Pneumococcus and seasonal influenza vaccination (see Section 6.5.3 and Section 10.7).
- 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 10.7).
  - 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, prophylactic antibiotics and/or IVIG will be considered as detailed in the protocol (Section 6.5).

4.3. Justification for Dose

Single and multiple IV doses of ALXN1830 have been administered in healthy participants, and in patients with WAIHA and pemphigus vulgaris (PV). In healthy participants, single IV doses were given at 1, 3, 10 and 30 mg/kg (Studies SYNT-101 and SYNT001-104), 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.

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 SC data in human, 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 2455-024), the bioavailability (F) after a single dose of 30 mg/kg SC in monkeys is around 21.5%.
   b. For healthy participants, SC bioavailability of another anti-FcRn mAb was around 11%.
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. Similar IgG reduction was observed at the same mg/kg dose in a clinical trial in healthy participants with another anti-FcRn mAb.

Based on these observations, ALXN1830 exposure, safety margin and IgG reduction after SC administration was predicted (see Table 12). The following assumptions have been used:

1. ALXN1830 bioavailability after SC administration is 20%.
2. 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 12: 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	750	75 (50-90)	10 (8.3-15)	0.2	675 (589-983)	10 (6.7-12)	10 (7-11)	52 (35-59)	-30
2	1500	75 (50-90)	20 (16.7-30)	0.2	1451 (1265-2664)	5 (3.3-6)	4 (2-5)	24 (13-28)	-45
3	2250	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
4	300 twice weekly x 4	75 (50-90)	8 (6.7-12)	0.2	540 (471-732)	13 (8-15)	12 (9-14)	64 (48-74)	-53
5	750 qw x 12	75 (50-90)	10 (8.3-15)	0.2	675 (589-983)	10 (7-12)	10 (7-11)	52 (35-59)	-68
6	1500 qw x 4	75 (50-90)	20 (16.7-30)	0.2	1451 (1265-2664)	5 (3-6)	4 (2-5)	24 (13-28)	-69
7	2250 qw x 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] $AUC_{SC} = AUC_{IV} * F$. Median AUC_{IV} at 10 mg/kg = 2.89 mL/h/kg with a median body weight of 82.7 kg (SYNT-101); Median AUC_{IV} at 20 mg/kg = 215 mL/h with a median body weight of 79 kg (SYNT001-104); Median AUC_{IV} at 30 mg/kg = 2.03 mL/h/kg with a median body weight of 75.8 kg (SYNT-101). Where median AUC_{IV} is not available at certain dose levels (e.g. 15 mg/kg), doses (mg/kg) are round up to obtain a conservative estimate. Median AUC_{IV} for 45 mg/kg is set to equal to median AUC_{IV} at 30 mg/kg (2.03 mL/h/kg).
[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 AUC_{SC}). 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 AUC_{SC}). 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; $AUC_{0\text{-}Tlast}$ = Area under the serum concentration versus time curve from time 0 to the last quantifiable concentration; F = bioavailability; IV = intravenous; q2w = once every two weeks; qw = weekly; SC = subcutaneous.

Study ALXN1830-HV-105 will include 3 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 750 mg, equivalent to 10 mg/kg in a 75 kg participant, or 15 mg/kg in a 50 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 SYNT-101 and Study SYNT001-104). 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 750 mg will have a safety margin of approximately 6.7-fold (for a 50-kg participant) or 10-fold (for a 75-kg participant). Assuming a human bioavailability of 20% the expected AUC at 750 mg SC will have a safety margin of 7-fold (for a 50-kg

participant) or 10-fold (for a 75-kg participant) based on the NOAEL exposure from the 5-week SC monkey toxicity study, and 35-fold (for a 50-kg participant) or 52-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 750 mg SC is expected to be roughly 1/10 to 1/15 of the exposure at 30 mg/kg IV, based on the low bioavailability observed in monkey for ALXN1830 and in healthy participants from other anti-FcRn compounds . Based on these observations, the expected maximum IgG reduction at 750 mg SC would be around -30% from baseline.

In the SAD portion, the SC dose will be escalated 2-fold from 750 mg (Cohort 1) to 1500 mg (Cohort 2), and then 1.5-fold to 2250 mg (Cohort 3). 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 12 the first two MAD cohorts will be administered 300 mg SC biw for 4 weeks (Cohort 4) and 750 mg SC qw for 12 weeks (Cohort 5). On a mg/kg basis, the 300 mg SC biw dose represents at least a 9 to 48-fold safety margin, and 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. Both MAD cohorts will start after SRC review of the first SAD cohort (single dose of 750 mg SC). While most of the MAD cohorts have treatment duration of 4 weeks, Cohort 5 (750 mg SC weekly for 12 weeks) is of an extended duration to enable the evaluation of immunogenicity after long term administration of ALXN1830.

The SC multiple doses will be escalated 2.5-fold from 300 mg twice weekly and 750 mg weekly to 1500 mg once weekly (Cohort 5 and 6, respectively) after SRC review. At this dose level, the expected maximum IgG reduction is expected to be around 69%, which is similar to that observed with 20 mg/kg IV in Study SYNT001-104 (after the three weekly loading doses).

An optional fourth MAD cohort (Cohort 7) may be enrolled under the following scenarios:

3. If Cohort 6 is terminated early due to safety or IgG stopping rules, then Cohort 7 may be dosed at a < 1500 mg weekly dose for 4 doses.
4. If Cohort 6 does not reach the expected IgG reduction, and no safety or IgG stopping rules are met, then Cohort 7 may be dosed at > 1500 mg (but not more than 2250 mg) weekly for 4 doses.

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 Schedule of Activities (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 65 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 ≥ 1000 mg/dL at Screening.
5. Baseline IgA and IgM[1] within normal levels 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.

Weight

8. Body weight within 50 to 90 kg, inclusive, and body mass index (BMI) within the range of 18 to 24.9 kg/m^2, inclusive.

[1] 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

9. 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 up to 3 months after last dose of study drug.

Informed Consent

10. 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 intervention; or interfering with the interpretation of data.
2. Abnormal blood pressure (BP) as determined by the Investigator (resting BP should be between 120/80 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 the history of frequent and/or chronic headaches, including migraine disorder, cluster headache disorder, and tension headache disorder.
6. Lymphoma, leukemia, or any malignancy active within the past 5 years except for locally curable cancers that have been completely removed such as superficial basal cell or squamous epithelial carcinomas of the skin.
7. Alanine transaminase (ALT) > 1.5 × ULN at Screening and Day -1.
8. Bilirubin > 1.5 × ULN (isolated bilirubin > 1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%) at Screening and Day -1.
9. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
10. 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.
11. Female participants who are pregnant or breastfeeding.

Prior/Concomitant Therapy

12. 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.
13. Known exposure to therapeutic proteins, such as mAbs, including marketed drugs prior to dosing.
14. Participants who have prior exposure to ALXN1830.
15. Any vaccination within 2 weeks of screening other than those required for this study. 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, 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. Alcohol abuse is defined as regular weekly intake of more than 14 units (for both males and females) (NHS, 2018).
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 3 months prior to the planned first day of dosing.
24. Individuals who are intimate with or who are in prolonged contact with (defined as living under the same roof or providing personal care to) people younger than 3 years of age or older than 65 years of age, or 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.
25. Individuals with children attending daycare and/or with children who are first-year college/university students.
26. First-year college/university students.
27. Individuals who are one of the following:

- Professionals (eg, healthcare workers) exposed to environments of greater risk for infectious disease.
- Research, industrial and clinical laboratory personnel who are routinely exposed to infectious agents (bacterial or viral).

28. Has a tattoo or body piercing which might interfere with injection site examination throughout the duration of the study.

5.3. Lifestyle Considerations

Table 13: Lifestyle Considerations for Participants in Study ALXN1830-HV-105

Items participants must not consume or do:	When participants must stop:	When participants can re-start:
Tobacco in any form (eg, smoking or chewing) or other nicotine-containing products in any form (eg, gum, patch, electronic cigarettes).	From three months prior to the planned first day of dosing.	After study completion/last visit.
Meals/snacks/water	Whenever participants are confined in the ward, only the drinks and meals provided by the trial personnel will be allowed. Standard meals will be provided at the standard unit times as stated in the study plan, and meals should be completed each time.	Standard meals will be given at regular intervals throughout the in-house stay.
Any other substances known to be potent inhibitors or inducers of CYP P450s. This includes food or drink products containing cranberry, pomegranate, star fruit, grapefruit, pomelos, exotic citrus fruits or Seville oranges (including marmalade and juices made from these fruits).	Within three weeks before the planned first study drug administration.	After study completion/last visit.
Caffeine-containing or Xanthine-containing products.	48 hours before the planned first study drug administration and each out-patient/ follow-up visit.	After study completion/last visit.
Energy drinks or drinks containing taurine, glucuronolactone (eg Red Bull).	48 hours before the planned first study drug administration and each out-patient/ follow-up visit.	After study completion/last visit.
Alcohol.	48 hours before the planned first study drug administration and each out-patient/ follow-up visit.	After study completion/last visit.
Strenuous physical activity.	48 hours before screening, admission and out-patient/follow-up visit.	After study completion/last visit. [Participants should not start new physical training activities during the study until study completion (last visit)]

Table 13: Lifestyle Considerations for Participants in Study ALXN1830-HV-105 (Continued)

Items participants must not consume or do:	When participants must stop:	When participants can re-start:
Any prescription medication. For details, including exceptions see Section 6.5.	14 days before the planned first study drug administration.	After study completion/last visit. Please refer to Section 6.5. N.B: If participants have a medical need to take any medication or have any medications prescribed to them by a doctor, they should follow the medical advice but inform the Investigator as soon as possible afterwards. Participants should be informed not to stop taking any medication that has been prescribed by their GP or other doctor.
Any over-the-counter medication. For details, including exceptions see Section 6.5.	14 days before the planned first study drug administration.	After study completion/last visit.
Any herbal remedy or dietary supplement containing St John's Wort.	Three weeks before the planned first study drug administration.	After study completion/last visit.
Blood and plasma donation.	Sixteen weeks before the planned first study drug administration.	Three months after study completion/last visit.
Contraception: Participants must comply with the appropriate contraceptive requirements as stated in Section 10.6.	Start times for contraceptives vary according to method used - see applicable contraceptive method in in Section 10.6.	Until the end of systemic exposure (for this study, this is until the follow-up visit).

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 et al, 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 DRUG

Study drug 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 Drug Administered

The study drug formulation and doses to be administered in this study are presented in Table 10 and study drug dose preparation is presented below.

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/10mL vial	Placebo
Dosage Level(s)	Refer to Table 10	Not applicable
Route of Administration	SC injection or infusion SC push for 300 mg (2 ml) and SC infusion for 750 mg and above	SC injection or infusion SC push for cohort of 300 mg (2 ml) ALXN1830 and SC infusion for cohorts of 750 mg ALXN1830 and above
Use	Investigational Product	Placebo
IMP and NIMP	IMP	IMP
Sourcing	Provided by Alexion	Provided by trial site
Packaging and Labeling	Study Drug will be provided in a 10mL Vial. Each vial will be labeled as required per country requirement	Study Drug will be provided in country-specific commercially available form

Abbreviations: IMP = investigational medicinal product; 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).
4. Further guidance and information for the final disposition of unused study drugs are 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 7 cohorts of the study, according to the randomization schedule generated prior to the study by the Statistics Department at Alexion (or designee).

Participants will be randomly assigned in a 6:2 ratio to receive ALXN1830 or PBO. 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, etc) 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 Drug Compliance

Participants will receive study drug directly from the Investigator or designee, 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 electronic case report form (eCRF). 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. Premedication and Hydration

Premedication is recommended as shown in the table below.

Table 14: Recommended Premedication

Medication	Dose	Route	When given	Max dosing
Paracetamol	1 g	Oral	30 minutes prior to each dose	Single dose
Chlorpheniramine	4 mg	Oral	30 minutes prior to each dose	Single dose
Famotidine	20 mg	Oral	30 - 60 min before meal on dosing day	Single dose

In addition, 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 (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 H1 and H2 blockers, eg, diphenhydramine and famotidine is 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, fluids of normal saline in case of hypotension.

6.5.3. Vaccinations

To mitigate the risk 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 vaccine (if being dosed during "flu season")

What constitutes "adequately vaccinated"?

Satisfactory documentation must be provided for the stated vaccinations. The following (and only the following) constitutes "adequately vaccinated" based on recommendations from Chapter 7 of the Public Health England Green Book for "Immunisation of Individuals with Underlying Medical Conditions" and its "specific indications for immunisation of other vulnerable groups" (Public Health England, 2016).

1. Pneumococcus:
    a. Has received: pneumococcal polysaccharide vaccine, Pneumovax 23 (PPSV23), at least 28 days, and maximally 4 years prior to dosing of ALXN1830 on Day 1.
        i. One dose must have been given.
2. Seasonal influenza vaccine:
    a. Has received: quadrivalent influenza vaccine for the current season, at least 28 days prior to dosing of ALXN1830 on Day 1. This must be most recent and up-to-date formulation available.
        i. One dose must have been given.

Vaccination titers

Blood samples for assessment of vaccination titers (both prevaccination and postvaccination) will be taken at various time points. Titers will have no consequence on eligibility.

6.5.4. Antibiotics Prophylaxis

3. Prophylactic antibiotic treatment may be utilized as a temporary measure, oral azithromycin 250 mg once daily under following conditions:
    a. When to consider starting*: when IgG level is equal to or falls below 300 mg/dL.
    b. When to stop: when IgG level is ≥ 600mg/dL and no further doses of ALXN1830 are to be given.
    c. At the discretion of the investigator, if they observe a prodromal state or any clinical sign or symptom of infection, which warrants antibiotic treatment.

    *Once started, azithromycin will be given every day, until IgG level is > 600mg/dL and no further doses of study drug are to be given.

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 5.1) 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) with the exception of the medications described above.

6.6. Dose Modification

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

6.7. Drug 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 DRUG AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Drug

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, and the procedure to maintain blinding under these circumstances will be described in the study operations manual (SOM). 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 immunoglobulin (Ig) replacement therapy are implemented if participants have lab 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 individual for whom IgA, IgM, or Pneumovax 23 vaccine titers fall below the normal limits (according to the reference ranges of the laboratory) 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 an IRR:
    a. That has not fully resolved after symptomatic treatment / supportive care;
    b. Manifesting as dyspnea on moderate exertion, which is associated with any other constitutional symptoms.
    c. With evidence of hemodynamic instability (isolated hypotension not requiring intervention is however permitted) that responds to 1 L of fluids, infused rapidly.

- 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

- 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 discontinuation 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.

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 or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, three 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 as a whole is handled as part of Section 10.1.8.

7.5. Criteria for Study Termination

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.

8.1. Efficacy Assessments

No efficacy assessments will be obtained during this study.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

A full physical examination will be performed at Screening. A symptom-driven physical examination will be performed 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 (screening only) and weight will also be measured and recorded at Screening. Body mass index will be calculated and recorded at Screening.

8.2.2. Vital Signs

Vital sign measurements will be taken after the participant has been resting in the supine or semi recumbent position for at least 5 minutes and will include temperature (°C; tympanic or oral), respiratory rate, oxygen saturation (Section 8.2.3), supine BP, and pulse. Orthostatic (standing) BP will only be measured at Screening. 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.

8.2.3. Oxygen Saturation

Functional oxygen saturation (SpO2), which is measured along with vital signs (Section 8.2.2), is the ratio of oxygenated hemoglobin capable of transporting oxygen. The measurement is performed using automated monitors.

8.2.4. Electrocardiograms

8.2.4.1. Recording of 12-Lead ECGs

A triplicate 12-lead electrocardiogram (ECG) will be obtained using a GE Marquette MAC1200® /MAC1200ST® recorder connected via a fixed network connection to the MUSE® Cardiology Information System (hereinafter referred to as MUSE) after the participant has been resting for at least 10 minutes. The 12-lead ECGs will be conducted before PK/PD/biomarker blood sampling if these 2 events occur at the same time. The timing of 12-lead ECGs is described in the SoA (Section 1.3).

The 12-lead ECGs recorded during screening will be stored electronically on the MUSE® information system. Only ECGs recorded electronically will be valid ECGs for any purpose other than safety assessment. ECG printouts may be included in the participant's case report form (CRF) for medical safety reviews.

Each 12-lead ECG recorder will be set up to the required technical specifications and containing the information required to identify the records. Each ECG recording will be clearly identified (Participant ID, visit date, and the actual times of ECG recordings).

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

At each time point, the 12-lead 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 timepoint meet the quality criteria set out in the SOM and the applicable Standard Operating Procedure to enable reading and analyzing at least 5 complexes per derivation.

8.2.4.2. Safety Review of 12-lead ECGs

All recorded 12-lead ECGs will be reviewed by the Investigator, or qualified designee, and the review findings will be documented in the CRF. If a participant shows an abnormal ECG, additional safety recordings (including the use of 5- or 12-lead Holter equipment) may be made and the abnormality be followed to resolution, if required.

8.2.4.3. 24-hour Holter ECG

Holter recording will be performed at Screening, or up to 3 months prior to Day 1, as described in the SoA (Section 1.3). Each electronic Holter ECG file will be downloaded onto the GE Gatemed Holter Analysis system.

8.2.4.4. Real time display (ECG telemetry)

A 12-lead real time ECG will be recorded as described in the SoA (Section 1.3). Electrocardiogram (ECG) telemetry will be monitored by the investigator or qualified member of clinical staff. The system will be managed according to local working practices. The ECG telemetry reports will be archived with study documents.

8.2.5. Clinical Safety Laboratory Assessments

- See Section 10.2 for the list of clinical laboratory tests to be performed and to the SoA (see 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 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.

8.2.6. 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.

8.2.7. Vaccination

Participants will be adequately vaccinated as described in Section 6.5.3.

8.2.8. 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).

8.2.9. Pregnancy Testing

Pregnancy testing will be performed for all female participants of childbearing potential at the time points specified in the SoA (Section 1.3).

If a pregnancy is reported, the Investigator should inform Alexion within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 8.3.5.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

8.2.10. Injection or Infusion Site Evaluation

Injection/infusion site evaluations will be performed at the time points specified in the SoA (Section 1.3). Injection/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 an AE or SAE and specific reporting requirements are located in Section 10.3.

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 (See Section 7).

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All AEs 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 designee within 24 hours of awareness, 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 SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has exited the study, and he/she considers the event to be reasonably related to the study drug, the Investigator must promptly notify Alexion.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

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

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed 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 Serious Adverse Events

- Prompt notification by the Investigator to Alexion of a SAE 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, institutional review boards (IRB)/IEC, and Investigators.
- Alexion must prepare Investigator safety reports for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forward 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 must review and then file it along with the IB and must notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

No studies of ALXN1830 have been conducted in pregnant women. Pregnant or breastfeeding females are excluded from the clinical study. Participants enrolled in the study, and a spouse or partner, will use a highly effective or acceptable method of contraception (Section 10.6).

8.3.5.1. Exposure During Pregnancy and Lactation

Pregnancy data will be collected during this study for all participants. For all Alexion products, both in development or post-approval, exposure during pregnancy must be recorded and followed. Exposure during pregnancy, also called exposure in utero, can be the result of either maternal exposure or transmission of drug product via semen following paternal exposure.

If a female participant participating in this study or a male participant's female partner becomes or is found to be pregnant while being treated or exposed to study drug, the Investigator must submit the "Pregnancy Reporting and Outcome/Breast Feeding Form" to Alexion or designee via the same method as SAE reporting. Female participants who become pregnant will be discontinued from dosing but will continue to be followed for safety where feasible. Male participants may continue in the study if an accidental pregnancy of their female partner occurs despite adequate contraception.

The female participant should be followed until the outcome of the pregnancy is known (spontaneous miscarriage, elective termination, normal birth or congenital abnormality), even if the participant discontinues study drug or discontinues from the study. When the outcome of the pregnancy becomes known, the form should be updated and returned to Alexion or designee. If additional follow-up is required, the Investigator will be requested to provide the information.

Pregnancy in and of itself is not regarded as an AE, unless there is a suspicion that investigational product may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs, and many may meet criteria for an SAE. Complications of pregnancy and abnormal outcomes of pregnancy, such as ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly, would meet the criteria of an SAE and therefore should be reported as an SAE.

Elective abortions without complications should not be handled as an AE. Exposure of an infant to an Alexion product during breastfeeding should also be reported on the "Pregnancy Reporting and Outcome/Breast Feeding Form." Any AEs an infant experiences following breastfeeding are to be reported to Alexion or designee.

8.3.6. Adverse Events of Special Interest

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

The AESIs for ALXN1830 include the following:

- Any IRRs 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.

8.3.6.1. 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 10.4 for guidance on management of IRRs.

8.3.6.2. 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, serositis, etc., in the face of an ongoing antibody response to the study drug (Hunley et al, 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.

In the event of an overdose, the Investigator should:

- Immediately contact the Medical Monitor.
- 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. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Instructions for the collection and handling of biological samples will be provided by Alexion. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of ALXN1830. Each serum sample will be divided into 2 aliquots (1 each for [primary and a back-up]). Samples collected for analyses of study drug (serum) concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained. At visits during which whole blood samples for the determination of PK/PD of ALXN1830 will be taken, one sample of sufficient volume can be used.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.6. Pharmacodynamics

Venous blood samples will be collected for measurement of IgA, IgM, IgG, and IgG subtypes (1-4), 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.

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

Serum samples will be screened for antibodies binding to ALXN1830 and the titer of confirmed positive samples will be reported. 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 antidrug antibodies (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. All samples collected for detection of ADA will also be evaluated for ALXN1830 serum concentration to enable interpretation of the antibody data. All samples that are confirmed positive for ADA will be evaluated for the presence of neutralizing antibodies. Samples may be stored for a maximum of 5 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by Alexion to enable further analysis of immune responses to ALXN1830.

8.10. Medical Resource Utilization and Health Economics

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 hypothesis will be tested for this study.

9.2. Sample Size Determination

Up to 56 participants will be enrolled. Participants will be randomly assigned in a 6:2 ratio to up to 7 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). Of these 7 cohorts, 1 cohort is optional; a dose to be determined (based on the safety of the predetermined doses) in the MAD. 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 are considered adequate to meet the study objectives.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Table 15: Populations for Analyses

Population	Description
Enrolled set	All participants who sign the ICF
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 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 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.

9.4.1. Safety Analyses

All safety analyses will be performed on the Safety Population.

Safety analyses will include an analysis of all TEAEs, 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. The prevalence of TEAEs and SAEs will be summarized, by System Organ Class (SOC) and Preferred Term for each

cohort and overall, by relationship to study drug. Adverse events will also be summarized by cohort and overall, by severity. Serious AEs and TEAEs resulting in study discontinuation will be listed. Participants having multiple TEAEs within a category (eg, overall, SOC, Preferred Term) will be counted once in that category. For severity tables, a participant's most severe event within a category will be counted.

Changes from baseline in vital sign measurements and laboratory assessments (eg, chemistry, cell blood count with differential, and urinalysis) will be summarized by each cohort. Laboratory parameter values will be graded according to the Common Terminology Criteria for Adverse Events (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 corrected 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

All PK analyses will be performed on the PK Population and all PD analyses will be performed on the PD Population. Pharmacokinetic, PD, immunogenicity (secondary analyses), and biomarker exploratory analyses will be described in the statistical analysis plan (or the PK analysis plan, as applicable), and finalized before database lock.

9.5. Interim Analyses

No interim analyses are planned.

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 ICH Good Clinical Practice (GCP) Guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator Brochure, 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 by UK legislation 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 Regulations (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

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative 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 written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF (see Section 5.4).

10.1.4. Data Protection

- Participants will be assigned a unique identifier by Alexion. Any participant records or datasets that are transferred to Alexion will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her 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 participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her 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. 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 European Union website www.clinicaltrialsregister.eu), as appropriate, and in accordance with national, regional, and local regulations.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed CRF or eCRF unless transmitted to Alexion or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the 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 or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the 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 a minimum of 25 years after study completion, 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.

10.1.7. Source Documents

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

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

Alexion or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of Alexion. The study site will be closed upon study

completion. A study site is considered closed when 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 the 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.

If the study is prematurely terminated, 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, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participants and should assure appropriate participant therapy and/or follow-up.

10.1.9. 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 16 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 16: 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 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 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 subject shows signs of infection, the following investigations should be included: • Blood cultures (taken prior to start of antibiotics) • Routine profile		
Pneumovax 23 titer	• Pneumovax 23 vaccine titers (refer to Section 6.5.3)		

Abbreviations: ALT = alanine transaminase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; FSH = follicle stimulating hormone; CRP = C-reactive protein; HBsAg = hepatitis B surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; RNA = ribonucleic acid; gonadotropin; HIV = human immunodeficiency virus; Ig = immunoglobulin; IRR = infusion-related reaction; RBC = red blood cells; 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. Adverse Event Definition

Adverse Event Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study drug, whether or not considered related to the study drug. • 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 drug.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae which may or may not be to a suspected drug-drug interaction.

Events NOT Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • 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.

10.3.2. Adverse Reaction Definition

Adverse Reaction Definition
• An AR is any TEAE that is considered to have a causal relationship to the study drug.

10.3.3. Serious Adverse Event Definition

An SAE is defined as an AE 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 were 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.

An SAE is defined as an AE that, at any dose:
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.

10.3.4. Suspected Unexpected Adverse Reaction Definition

Suspected Unexpected Serious Adverse Reactions Definition
Suspected unexpected serious adverse reactions are serious events that are not listed in the IB and that the Investigator identifies as related to study drug or procedure. The US 21CFR312.32 and EU Clinical Trial Directive 2001/20/EC and the associated detailed guidance documents or national regulatory requirements in participating countries require the reporting of SUSARs. Alexion has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidance documents. Suspected unexpected serious adverse reactions will be reported to the national competent authority and IECs where applicable.

10.3.5. Recording and Follow-Up of Adverse Event and/or Serious Adverse Event

Adverse Event and Serious Adverse Event Recording
• 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 or 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 1 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)

Adverse Event and Serious Adverse Event Recording

- Grade 4: Life-threatening
- Grade 5: Fatal

Changes in the severity of an AE should be documented to allow an assessment of the AE duration at each level of intensity to be evaluated. Adverse events characterized as intermittent require documentation of onset and duration of each episode, if the severity of the intermittent event changes.

Assessment of Causality

- The Investigator is obligated to assess the relationship between the study drug and each occurrence of each AE or SAE. An Investigator causality assessment must be provided for all AEs (both nonserious and serious). This assessment must be recorded in the eCRF and on any additional forms, as appropriate. **The definitions for the causality assessments are as follows:**
  - Not related (unrelated): There is no causal association with study drug
  - Related: There is causal (temporal) association to the study drug. Other conditions (concurrent illness, concurrent medication reaction, or progression/expression of disease state) do not appear to explain the event; the event corresponds with the known pharmaceutical profile; improvement on discontinuation; 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 drug administration will be considered and investigated.
- This protocol will use the current IB as the Reference Safety Document. The expectedness and reporting criteria of an SAE will be determined by Alexion, based on the Reference Safety Document. The Investigator will also consult the IB 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 makes an assessment of causality for every event before the initial transmission of the SAE data to Alexion or designee.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Events and Serious Adverse Events

- 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.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to Alexion within 24 hours of receipt of the information.

10.3.6. Reporting of Serious Adverse Events

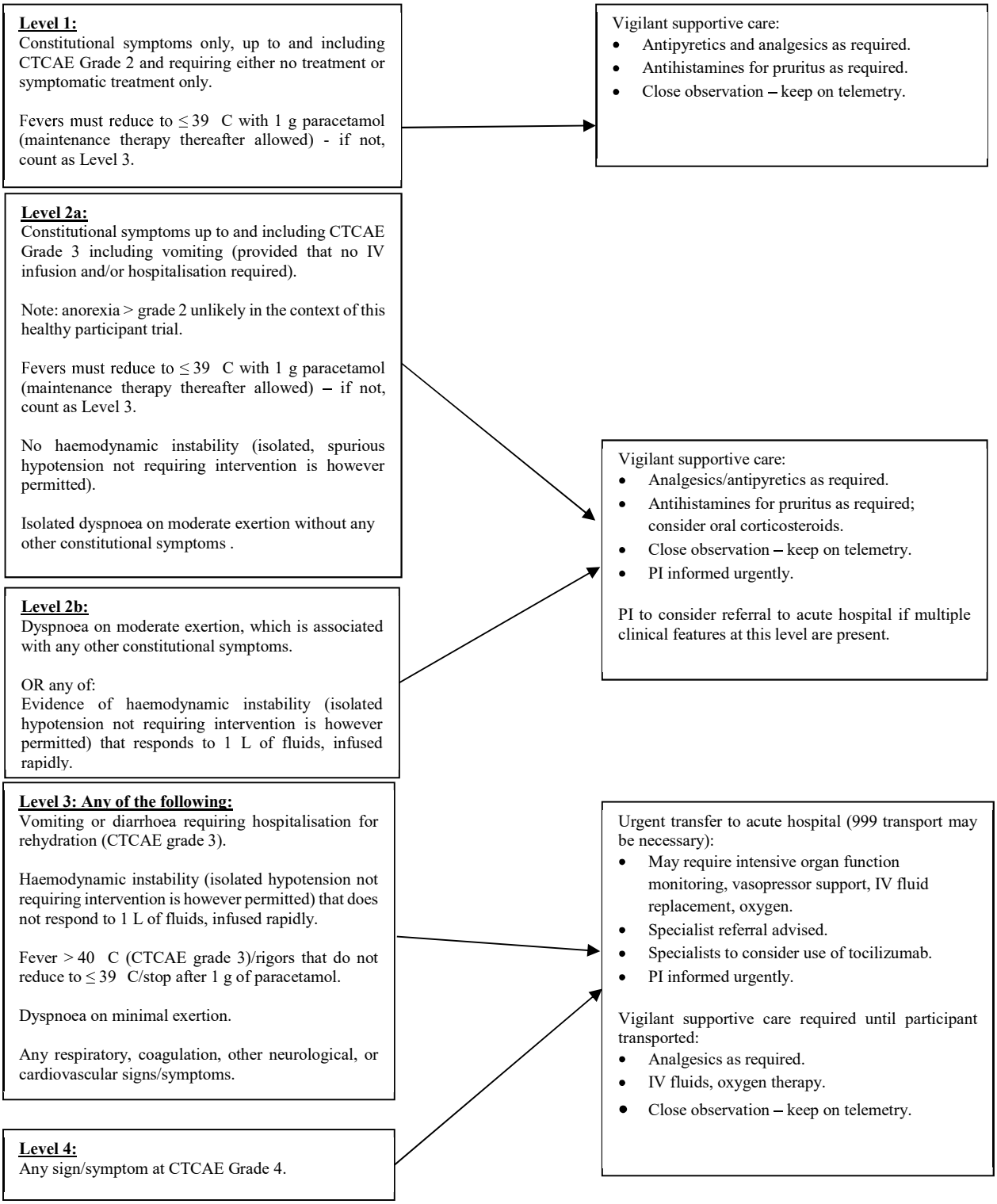
Serious Adverse Event Reporting to Alexion or Designee via Paper Case Report Form

- All AEs must be assessed by the Investigator to determine if they meet criteria for an SAE. All SAEs must be reported to Alexion or designee immediately, or within 24 hours of the Investigator and/or study site staff becoming aware of the event, regardless of the presumed relationship to the study drug.

Serious Adverse Event Reporting to Alexion or Designee via Paper Case Report Form

- 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]
  - Facsimile: [redacted]
- Additional follow-up information, if required or available, should be entered into the CRF and sent to Sponsor within 24 hours of the Investigator or study site staff becoming aware of this additional information via the reporting process outlined above. These reporting timelines need to be followed for all initial SAE cases and follow-up versions of the initial cases.
- For all SAEs, the Investigator must provide the following:
  - Appropriate and requested follow-up information in the time frame detailed above
  - Causality of the serious event(s)
  - Treatment of/intervention for the SAE(s)
  - Outcome of the serious event(s)
  - Redacted medical records and laboratory/diagnostic information
- If applicable, additional information such as relevant medical records should be submitted to Alexion via the email address or facsimile number noted above.
- All forms and follow-up information submitted to Alexion (eg, discharge summary) should be kept in the appropriate section of the study file.

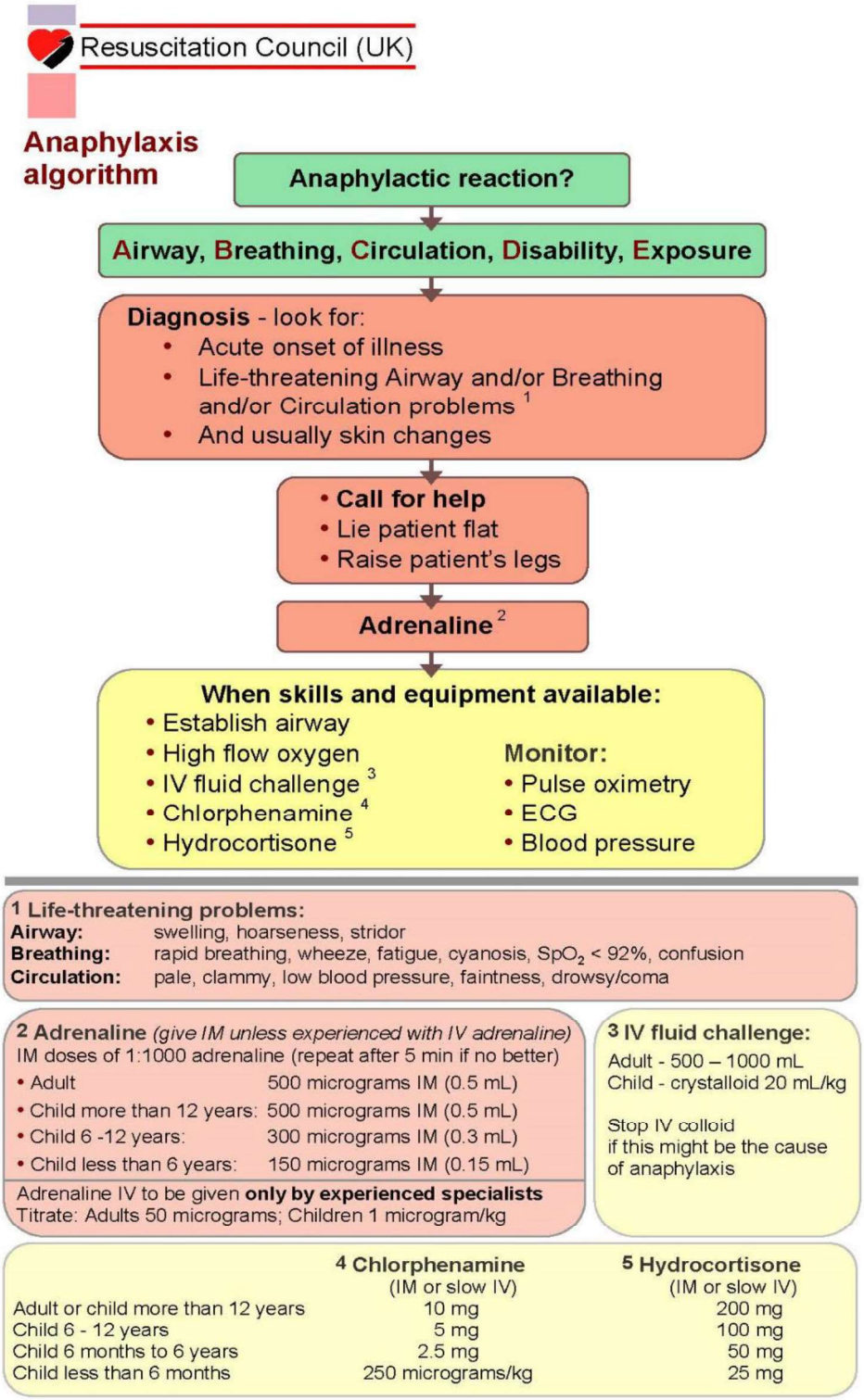
10.4. Appendix 4: Infusion Related Reactions – Definitions of Severity Levels and Management Algorithm



Level (see algorithm above for explanation on levels):	**DECISION 1 Individuals:**	**DECISION 2 Continuation within a dosing regimen:**	**DECISION 3 Study progression:**
Level 1 (Mild to moderate, not serious)	Continue as per protocol	Continue as per protocol	Continue as per protocol
Level 2a (Severe, not serious)	Study drug administration will be discontinued	1 participant: Continue as per protocol. ≥ 2 participants: Dosing of the remainder of the dosing regimen stopped. Continuation and extension requires substantial amendment.	1 participant: Continue as per protocol. ≥ 2 participants: Dose escalation and progression to study parts with an equal or higher dose stopped. Dosing regimens on lower dose levels can continue. Progression to successive cohorts or study parts is permitted only with doses below this current level (at which this toxicity was observed). Escalation or progression to study parts with an equal or higher dose requires substantial amendment.
Level 2b (Severe, not serious)	Study drug administration will be discontinued	≥ 1 participant: Dosing of the remainder of the dosing regimen stopped. Continuation and extension requires substantial amendment.	≥ 1 participant: Dose escalation and progression to study parts with an equal or higher dose stopped. Dosing regimens on lower dose levels can continue. Progression to successive cohorts or study parts is permitted only with doses below this current level (at which this toxicity was observed). Escalation or progression to study parts with an equal or higher dose requires substantial amendment.
Level 3 (Severe, serious AR)	Study drug administration will be discontinued		
Level 4 (Life-threatening. serious AR)	Study drug administration will be discontinued	≥ 1 participant: Dosing of the remainder of the dosing regimen stopped. Continuation and extension requires substantial amendment.	Study stopped (ie this dosing regimen and all ongoing dosing regimens including those at lower doses, and upcoming dosing regimens, are immediately stopped). Continuation of the study requires a substantial amendment.

Abbreviations: AR = adverse reaction

10.5. Appendix 5: United Kingdom Resuscitation Council Anaphylaxis Algorithm



Abbreviations: ECG = electrocardiogram; IM = intramuscular; IV =intravenous

10.6. Appendix 6 Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential

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

Women in the Following Categories are Not Considered Women of Childbearing Potential

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

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

2. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range, as per local laboratory reference ranges, may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    - Female participants on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Female Participants

Female participants who are documented as being of non-childbearing potential are exempt from contraception requirements.

Female participants of childbearing potential, if heterosexually active, must use highly effective contraception as defined below. Antibiotic prophylaxis may be administered during this study (see Section 6.5.3), which can compromise the efficacy of hormonal contraception. Therefore, participants using hormonal contraception must also use barrier contraception (eg, condom or diaphragm with spermicide) for the duration of antibiotic prophylaxis.

Highly effective contraceptive methods for females are as follows:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation as follows:

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

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

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

Male Participants

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

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

Contraception for all cohorts must start during Screening and continue for at least 3 months after last dose.

Male participants must not donate sperm and female participants must not donate ova until at least 3 months after last dose.

Collection of Pregnancy Information

- Pregnancy data will be collected during this study for all female participants and any female spouse/partner of a male participant, who become pregnant. Exposure during pregnancy (also referred to as exposure in utero) can be the result of either maternal exposure or transmission of drug product via semen following paternal exposure.
- If a female participant or a male participant's female sexual partner of childbearing potential becomes or is found to be pregnant while being treated or exposed to study drug, the Investigator must submit the "Pregnancy Reporting and Outcome/Breastfeeding" form to Alexion or designee via the same method as SAE reporting (Section 10.3). When the outcome of the pregnancy becomes known, the form should be updated and submitted to Alexion or designee. If additional follow-up is required, the Investigator will be requested to provide the information.
- Exposure of an infant to a Sponsor product during breastfeeding must also be reported (via the "Pregnancy Reporting and Outcome Form/Breastfeeding" form) and any AEs experienced by the infant must be reported to Alexion or designee via facsimile or email.
- A pregnancy in and of itself is not regarded as an AE unless there is a suspicion that the study 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). Elective abortions without complications should not be reported as AEs (Section 8.3.5).
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

10.7. Appendix 7: Justification for Protective Measures

This study has adopted a comprehensive approach to minimize the potential risk of infection in healthy participants, which emerges from theoretical concerns associated with reduced total IgG.

Protective measures have been implemented including vaccination/confirmation of vaccination, continuous IgG monitoring, stopping rules based on the reduction of IgG level to ≤ 300 mg/dL (the lower bound of the mild-moderate range), and prophylactic antibiotic or IVIG treatment when warranted further mitigate the risk of infection.

To mitigate AEs, which are associated with anti-FcRn agents and other Igs (eg, headache), this study proposes to implement premedication and hydration measures.

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 et al, 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 et al, 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 et al, 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 et al, 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 et al, 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 et al, 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 et al, 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 five 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 - 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, 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-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 criteria 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.

In addition, if there is any reason to believe the participant is at risk of infection or exhibits evidence/signs of infection, we offer an antibiotic prophylaxis as an additional layer of risk mitigation against potential infections. 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, evidenced by documents showing that vaccinations occurred in the relevant time window advised in the "Green Book" (Public Health England, 2016). Further details are provided in Section 6.5.3. These vaccinations are based on the recommended from Chapter 7 of the Public Health England Green Book for "Immunisation of Individuals with Underlying Medical Conditions."

10.7.2. Hydration

Adverse events of anti-FcRn agents and other Ig are commonly reported to be associated with headaches (Robak et al, 2010; Ling et al, 2019; Kiessling et al, 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 et al, 2006). Hydration was considered to be an important factor for improvement of infusion-induced headaches (Feldmeyer et al, 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 8: 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
NAb	neutralizing antibody
NOAEL	no observed adverse effect level

Abbreviation	Explanation
OP	outpatient
PBO	placebo
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
SOC	System Organ Class
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

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