Protocol Title:

A Partially Randomized, Sequential Cohort, Single Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Subcutaneous Ravulizumab Coadministered With rHuPH20 in Healthy Adult Volunteers

Protocol Number: ALXN1210-HV-105

Amendment Number: 1

Compound Number: ALXN1210

USAN/INN: Ravulizumab

Short Title: Pharmacokinetic Study of Ravulizumab Administered Subcutaneously With rHuPH20 in Healthy Adult Volunteers

Sponsor Name: Alexion Pharmaceuticals, Inc.

Sponsor Address:

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Regulatory Agency Identifying Number(s):

Date of Amendment:	Not applicable
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Sponsor Signatory:

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INVESTIGATOR'S AGREEMENT

I have read the ALXN1210-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.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	20 Jul 2018
Original Protocol	17 May 2018

Amendment 1 (20 Jul 2018)

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

Overall Rationale for the Amendment

To align contraception language with national guidelines and address minor inconsistencies as described below.

Section # and Name	Description of Change	Brief Rationale
Section 5.2 Exclusion Criteria	Changed exclusion criterion no. 16 for use of nonprescription medications from 7 days to 14 days prior to dosing on Day 1.	Alignment of exclusion criterion with requirements stated in Section 6.5, Concomitant Therapy.
Table 2: Schedule of Activities – Visit 2 Through Visit 14	Added pregnancy testing on Day 57 and Day 120.	Additional pregnancy testing is appropriate for a trial in healthy subjects with requirements for highly effective contraception for an extended period.
Section 6.6 Contraception Guidance	• Removed definition of non-childbearing potential, replaced with cross reference to Appendix where required information is presented. • Replaced definition of highly effective contraception. • Added restriction on ova donation for female subjects.	Alignment with guidelines from Clinical Trial Facilitation Group (CFTG).
Section 10.4 Appendix 4: Pregnancy Information	Added specific FSH level requirement for establishing postmenopausal state.	Clarification.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Partially Randomized, Sequential Cohort, Single Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Subcutaneous Ravulizumab Coadministered With rHuPH20 in Healthy Adult Volunteers

Short Title: Pharmacokinetic Study of Ravulizumab Administered Subcutaneously With rHuPH20 in Healthy Adult Volunteers

Rationale: Ravulizumab subcutaneous (SC) is being developed to provide patients with a self-administered dosing option that will eliminate the patient burden associated with intravenous (IV) infusions (eg, loss of work time, disruption of routine associated with prolonged infusion times). Recombinant human hyaluronidase PH20 (rHuPH20), the active ingredient in the commercial product Hylenex® recombinant (hyaluronidase human injection), was approved by the US Food and Drug Administration in 2005 as an adjuvant to increase the dispersion and absorption of other injected drugs. Recombinant human hyaluronidase PH20 is a dispersion agent that modifies the permeability of connective tissue through the hydrolysis of hyaluronic acid (HA), a polysaccharide found in the intercellular ground substance of connective tissue. Recombinant human hyaluronidase PH20 hydrolyzes HA by splitting the glucosaminidic bond between C1 of an N-acetylglucosamine moiety and C4 of a glucuronic acid moiety. This depolymerization of HA results in a transient reduction in the viscosity of the gel-like phase of the extracellular matrix and increased hydraulic conductance that facilitates the dispersion and absorption of injected drugs, and may also increase their bioavailability. Coadministration of ravulizumab SC with rHuPH20 is expected to facilitate a larger amount of ravulizumab to be administered at a single time, thereby potentially allowing less frequent dosing.

Study ALXN1210-HV-105 Objectives and Endpoints

Objectives	Endpoints
Primary	
– To estimate the absolute bioavailability of ravulizumab SC/rHuPH20 – To assess the safety and tolerability of ravulizumab SC/rHuPH20	– Serum concentration of ravulizumab will be used to determine the GMR of the AUC values – Safety assessed by incidence of TEAEs and SAEs, physical examination, vital sign measurements, clinical laboratory and electrocardiogram results, and measurement of ADA
Secondary	
To estimate the relative bioavailability of ravulizumab SC/rHuPH20 compared with ravulizumab SC	Serum concentration of ravulizumab will be used to determine the GMR of the AUC values
To explore the PD effects of ravulizumab SC coadministered with rHuPH20	– Change in serum levels of total and free C5 concentrations over time – Change in ex vivo cRBC hemolysis activity over time

Abbreviations: ADA = antidrug antibodies; AUC = area under the concentration time curve; C5 = complement component 5; cRBC = chicken red blood cell; GMR = geometric mean ratio; PD = pharmacodynamic(s); rHuPH20 = recombinant human hyaluronidase PH20; SAE = serious adverse events; SC = subcutaneous; TEAE = treatment-emergent adverse events.

Overall Design:

This is a Phase 1 study designed to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity, and absolute and relative bioavailability of single ascending doses of ravulizumab SC coadministered with recombinant human hyaluronidase PH20 (rHuPH20) compared to a single dose of ravulizumab IV 400 mg or a single dose of ravulizumab SC 400 mg in 48 healthy adult subjects. Five treatment cohorts are planned. A Safety Review Committee (SRC) will evaluate the study data for subject safety and make recommendations on dose escalation, dose modification, or termination of the study. When cohorts are being enrolled in parallel, subject assignment to a cohort will be done through randomization. Subjects may be randomly assigned up to 7 days prior to dosing on Day 1. The study will be conducted at a single site in the United Kingdom.

- Eighteen subjects will be randomly assigned in a 1:2 ratio between the first 2 cohorts to receive either a single dose of ravulizumab SC 400 mg (Cohort 1, n = 6) or a single dose of ravulizumab SC 500 mg/rHuPH20 10,000 units (Cohort 2, n = 12).
- The SRC will review Cohort 2 ravulizumab SC/rHuPH20 safety data and make their recommendation for escalating the dose of the ravulizumab SC/rHuPH20 combination cohort.
- If the SRC recommendation following the review of data from Cohort 2 is to initiate the next cohort and proceed with the planned dose escalation, 18 subjects will be randomly assigned in a 2:1 ratio between Cohort 3 (n = 12) and Cohort 5 (n = 6) to receive either a single dose of ravulizumab SC 1000 mg/rHuPH20 20,000 units or a single dose of ravulizumab IV 400 mg, respectively.
  - The SRC will subsequently review Cohort 3 ravulizumab SC/rHuPH20 safety data and make their recommendation to proceed with planned dose escalation in Cohort 4 or a reduced dose in Cohort 4.
  - Whether the recommendation is to initiate Cohort 4 with the planned dose escalation or at a reduced dose, 12 subjects will be enrolled in Cohort 4 to receive a single dose of ravulizumab SC/rHuPH20 (dose to be determined based on SRC recommendation).
- If the SRC recommendation following the review of ravulizumab SC/rHuPH20 safety data from Cohort 2 is to proceed with Cohort 3 at a reduced dose, 18 subjects will be randomly assigned in a 2:1 ratio between Cohort 3 (n = 12) and Cohort 5 (n = 6) to receive either a single dose of ravulizumab SC/rHuPH20 (dose to be determined based on SRC recommendation) or a single dose of ravulizumab IV 400 mg, respectively.
  - In this scenario, Cohort 4, if conducted, will be enrolled at a reduced dose, following completion of Cohort 3 based on SRC review of ravulizumab SC/rHuPH20 safety data from Cohort 3 and a favorable recommendation to enroll subjects in Cohort 4.
  - This protocol allows for reduced doses to be administered to subjects in Cohorts 3 and 4, based on SRC recommendation, without a protocol amendment. If a

reduced dose is administered, the SRC reduced dose recommendation will be documented on the escalation/progression approval form.

- If the SRC determines that no further ravulizumab SC/ rHuPH20 combination dosing cohorts should be enrolled following Cohort 2, then Cohort 5 may still be enrolled as a stand-alone cohort at the discretion of the Sponsor.
- Sentinel dosing will be employed in Cohorts 1 through 4 (ie, 2 subjects in a cohort with 12 subjects and 1 subject in a cohort with 6 subjects will be dosed prior to dosing the remaining subjects within the cohort). The remaining subjects in a cohort will be dosed at least 24 hours following dosing of the sentinel subjects.
- The SRC will review all available safety data through 168 hour (Day 8) assessments to determine initiation of the next dose cohort.
- At the Sponsor's discretion, and after consultation with the SRC, up to 16 additional subjects may be enrolled as replacement subjects if a subject discontinues prior to Day 50 for reasons other than drug-related adverse events.

ALXN1210-HV-105 Study Design

Cohort	N	Study Drug	Route (SC/IV)	Planned Dose
1	6	ravulizumab	SC	400 mg
2	12	ravulizumab/rHuPH20	SC	500 mg/10,000 units
3	12	ravulizumab/rHuPH20	SC	1000 mg/20,000 units
4	12	ravulizumab/rHuPH20	SC	2000 mg/40,000 units
5	6	ravulizumab	IV	400 mg

Abbreviations: IV = intravenous; N = number [of subjects]; rHuPH20 = recombinant human hyaluronidase PH20; SC = subcutaneous.

Number of Subjects:

An appropriate number of subjects will be screened and assigned to each cohort, as described in the table above, to allow for approximately 48 subjects to complete the study.

Intervention Groups and Duration:

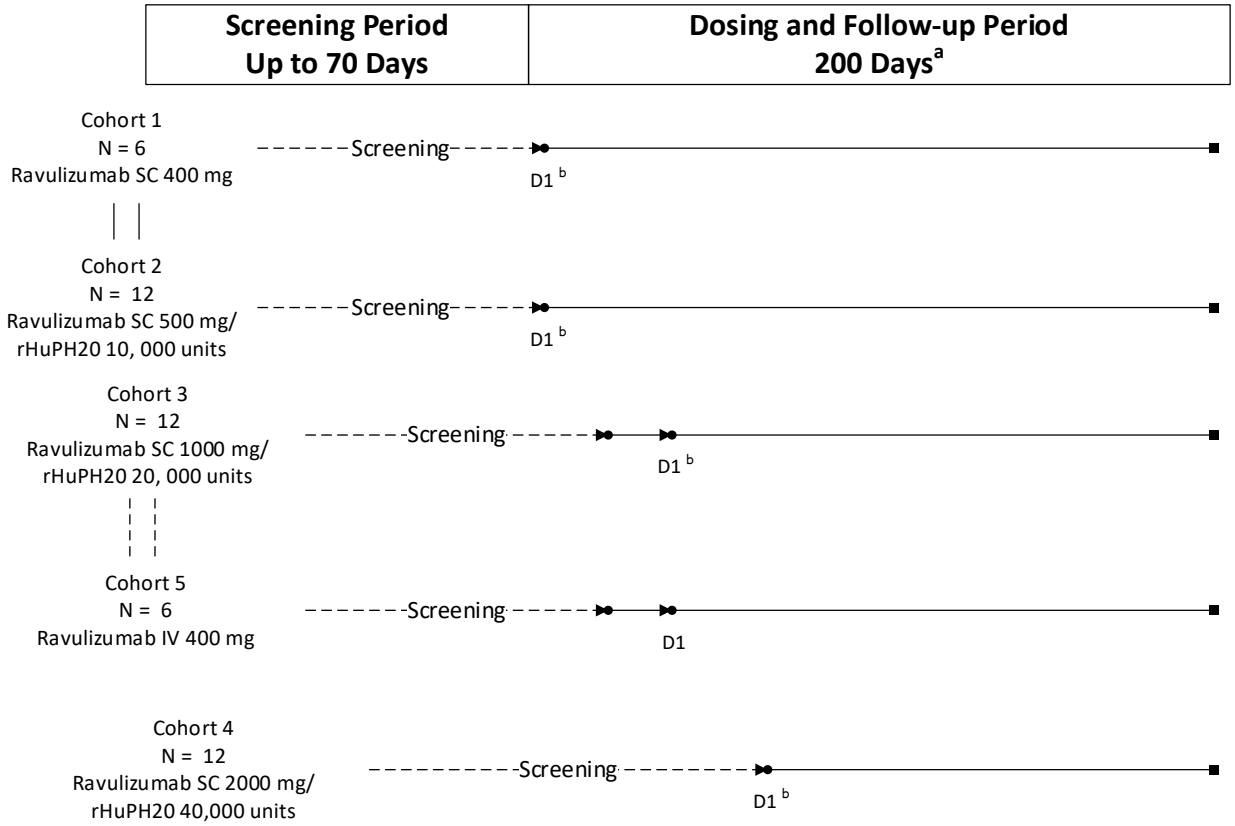
The planned study duration is approximately 39 weeks: up to 70 days for screening and approximately 200 days for dosing and follow-up. For the first 5 days during the Dosing and Follow-up Period, subjects will be admitted to an inpatient facility. Dosing will be staggered within and between cohorts, but the end of study for each individual subject is anticipated to be Day 200 or the time point at which complement activity has normalized, if later than Day 200.

Safety Review Committee:

The SRC will review all available safety data for at least the first 168 hours after dose administration from a given cohort in order to determine whether to initiate the next cohort and escalate the dose of ravulizumab SC/rHuPH20. Data through 168 hours must be available for at least 11 of the 12 subjects. Dose escalation will occur based on the recommendation of the SRC and only applies to Cohorts 3 and 4. SRC decisions will be documented in study minutes and archived in the trial master file.

1.2. Schema

Study ALXN1210-HV-105 Schematic



Note: Subjects will be randomly assigned to Cohort 1 or Cohort 2, randomly assigned to Cohort 3 or Cohort 5, and sequentially assigned to Cohort 4.
[a] Dosing will be staggered, but the end of study for each subject is Day 200 or the time point at which complement activity has normalized, if later than Day 200.
[b] For Cohorts 1 through 4, a sentinel dosing approach will be used (ie, 2 subjects in a cohort with 12 subjects and 1 subject in a cohort with 6 subjects will be dosed prior to dosing the remaining subjects within the cohort).
Abbreviations: D = day; IV = intravenous; N = number [of subjects]; SC = subcutaneous.

1.3. Schedule of Activities

Table 1: Schedule of Activities – Screening Through Visit 1

				Visit 1								
Study Day	**Screening**	**Day –1**		**Day 1**						**Day 2**	**Day 3**	**Day 5**
Assessments[a]	**Day –70 to Day –2**	**Admit Day –1**	**Predose**	**0 h (SOI)**	**EOI (SC)[b]**	**30 min post SOI**	**2 h post SOI**	**4 h post SOI**	**8 h post SOI**	**24 h**	**48 h**	**96 h**
Status (OP or CRU)	OP	Admit	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU	CRU[c]
Informed consent[d]	X											
MCV4 immunization[e]	X											
Meningococcal serogroup B immunization[e]	X											
Vaccine titer (meningococcal serogroups A, C, W135, and Y)[f]	X											
Medical history and demographics	X											
Physical examination	X	X										X
Height, weight, and BMI	X											
QuantiFERON®-TB test	X											
Biochemistry	X	X								X		
Hematology	X	X								X		
Coagulation	X	X								X		
Hepatitis B and C screen	X											
HIV(types 1 and 2) screen	X											
Complement activity[g]	X											
CH50			X									
Serum pregnancy test[h]	X	X										
Alcohol breath test	X	X										
Urinalysis (via dipstick)	X	X								X		X
Urine drug screen	X	X										
Vital sign measurements	X	X	X		X	X	X	X	X	X	X	X
ECG	X		X[i]							X		
Cardiac telemetry[j]			X	X	X	X	X					
Randomization[k]			X									

				Visit 1								
Study Day	**Screening**	**Day –1**		**Day 1**						**Day 2**	**Day 3**	**Day 5**
Assessments[a]	**Day –70 to Day –2**	**Admit Day –1**	**Predose**	**0 h (SOI)**	**EOI (SC)[b]**	**30 min post SOI**	**2 h post SOI**	**4 h post SOI**	**8 h post SOI**	**24 h**	**48 h**	**96 h**
Study drug administration				X								
PK samples			X		X	X	X	X	X	X	X	X
PD panel (serum C5, cRBC hemolysis)			X		X	X	X	X	X	X	X	X
Infusion/injection site evaluation[l]			X			X	X	X	X	X	X	
Immunogenicity (ravulizumab ADA)			X									
Review potential safety risks of ravulizumab[m]	X	X	X									X
Concomitant medications		←Monitor continuously (after ICF is signed at screening)→										
Adverse events[n]		←Monitor continuously (after ICF is signed at screening)→										
Prophylactic antibiotic tx[o]		←Antibiotic prophylaxis→										

[a] Permissible windows for study assessments are described in the study operations manual.

[b] The EOI sample applies to the SC cohorts only and should be obtained within 10 min after the completion of SC infusion.

[c] Subject will be discharged from the CRU after completing all Day 5 assessments. Subjects will be provided a “Study Participant ID card” with information for healthcare provider and subject on symptoms of meningitis infection.

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

[e] For subjects who do not have adequate documentation of prior MCV4 immunization or serogroup B vaccination, MCV4 immunization will be performed at least 56 days prior to dosing on Day 1, and vaccination for serogroup B meningococcal infections will be administered at least 56 days prior to Day 1 dosing with a booster administered at least 28 days prior to dosing on Day 1.

[f] For subjects with a documented vaccine titer within 6 months prior to screening, the titer does not need to be repeated.

[g] Complement activity, confirmed by a suitable assay such as CAP ELISA/C5 (hemolysis) inhibition, will be performed at screening to confirm subjects do not have a complement deficiency.

[h] Serum pregnancy test for all female subjects of childbearing potential to confirm that a female subject is not pregnant prior to dosing.

[i] On Day 1, triplicate 12-lead ECGs will be performed predose and approximately 15 minutes after the EOI (Cohorts 1 through 4 only).

[j] Continuous cardiac registration predose and until 3 hours after the SC injection (Cohorts 2, 3, and 4).

[k] Planned randomization for Cohorts 1, 2, 3, and 5 may be up to 7 days prior to dosing on Day 1.

[l] Injection site evaluations will be performed within 15 minutes after EOI and ± 15 minutes of the other scheduled times on Day 1.

[m] The Investigator or qualified designee will meet with the subject at each visit to discuss the potential safety risks of ravulizumab, and to address any safety concerns of the subject.

[n] Collection of adverse events and serious adverse events will begin after ICF signing.

[o] Subjects will be administered prophylactic antibiotic treatment, oral penicillin V 500 mg twice daily (equivalent to 1 × 106 units), beginning on the evening of Day -1 through Day 200, or until complement activity has normalized (as determined by CH50 assay).

Abbreviations: ADA = antidrug antibody; AE = adverse event; BMI = body mass index; CAP = complement alternative pathway; cRBC = chicken red blood cell; CRU = clinical research unit; ECG = electrocardiogram; EOI = end-of-infusion/injection; h = hour; HIV = human immunodeficiency virus; ICF = informed consent form; IV = intravenous; MCV4 = tetravalent meningococcal conjugate vaccine; min = minute; OP = outpatient; PD = pharmacodynamic(s); PK = pharmacokinetic (s) SC = subcutaneous; SOI = start-of-infusion/injection; TB = tuberculosis; tx = treatment.

Table 2: Schedule of Activities – Visit 2 Through Visit 14

	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14
Procedures[a]	**Day 8 (168h ± 2)**	**Day 15**	**Day 22**	**Day 29**	**Day 36**	**Day 43**	**Day 50**	**Day 57**	**Day 71**	**Day 92**	**Day 120**	**Day 150**	**Day 200 / ET**
Status (OP or CRU)	OP	OP	OP	OP	OP	OP	OP	OP	OP	OP	OP	OP	OP
Physical examination	X			X									X
Vital sign	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG												X	X
Biochemistry	X			X				X					X
Hematology	X			X				X					X
Coagulation	X			X				X					X
Urinalysis (via dipstick)	X			X				X					X
Serum pregnancy test								X			X		X
CH50 testing						X		X[b]					
Pharmacokinetic	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacodynamics panel (serum C5, cRBC hemolysis)	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity (ravulizumab ADA)		X		X				X		X	X	X	X
Review potential safety risks of ravulizumab[c]	←Discuss potential safety risks of ravulizumab→												
Concomitant	←Monitor continuously (after ICF is signed at screening)→												
Adverse events[d]	←Monitor continuously (after ICF is signed at screening)→												
Prophylactic antibiotic tx[e]	←Antibiotic prophylaxis→												

[a] Permissible windows for study assessments are described in the study operations manual.

[b] Additional samples may be taken after Day 57 if complement has not normalized.

[c] The Investigator or qualified designee will meet with the subject at each visit to discuss the potential safety risks of ravulizumab, and to address any safety concerns on the part of the subject.

[d] Collection of adverse events and serious adverse events will begin after ICF signing.

[e] Subjects will be administered prophylactic antibiotic treatment, oral penicillin V 500 mg twice daily (equivalent to 1 × 106 units) through Day 200 or until complement activity has normalized (as determined by CH50 assay).

Abbreviations: ADA = antidrug antibody; cRBC = chicken red blood cell; CRU = clinical research unit; ECG = electrocardiogram; ET = early termination; h = hour; ICF = informed consent form; OP = outpatient; tx = treatment.

2. INTRODUCTION

2.1. Study Rationale

The subcutaneous (SC) formulation of ravulizumab is being developed to provide patients with a self-administered dosing option that will eliminate the patient burden associated with IV infusions (eg, loss of work time, disruption of routine associated with dosing frequency, and prolonged infusion times). The purpose of this study is to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity, absolute and relative bioavailability of single ascending doses of ravulizumab SC coadministered with recombinant human hyaluronidase PH20 (rHuPH20).

Recombinant human hyaluronidase PH20, the active ingredient in the commercial product Hylenex® recombinant (hyaluronidase human injection), was approved by the US Food and Drug Administration in 2005 as an adjuvant to increase the dispersion and absorption of other injected drugs. Recombinant human hyaluronidase PH20 is a transiently and locally-acting permeation enhancer that increases the dispersion and absorption of other injected agents. Recombinant human hyaluronidase PH20 depolymerizes hyaluronic acid (HA) at the injection site causing rapid decrease in the viscosity of the extracellular matrix, allowing bulk fluid flow and facilitating dispersion and absorption of coadministered agents (rHuPH20 Investigator's Brochure, 2018).

Recombinant human hyaluronidase PH20 has been injected SC immediately prior to another therapeutic agent or coadministered SC to healthy subjects and patients in 28 clinical studies conducted under the rHuPH20 US IND, including studies with single doses up to 96,000 units. No safety concerns were identified in these studies (rHuPH20 Investigator's Brochure, 2018). In addition, rHuPH20 is an excipient in 3 marketed products (Herceptin® SC, HyQvia®, and MabThera SC®) available collectively in at least 50 countries, including countries in the European Union (approvals on file at Alexion).

Data from Study ALXN1210-SC-101 suggest that bioavailability of ravulizumab SC alone is < 100%. While coadministration of ravulizumab SC with rHuPH20 may improve bioavailability, it is expected to facilitate a larger amount of ravulizumab to be administered as a single dose, thereby potentially allowing less frequent dosing.

Ravulizumab IV has been administered safely to healthy subjects in single doses (ravulizumab IV 200 mg and 400 mg) and multiple doses on a 4-week regimen (ravulizumab 400 mg and 800 mg). Ravulizumab SC has been administered safely to healthy subjects in single doses (ravulizumab SC 400 mg). In patients with paroxysmal nocturnal hemoglobinuria (PNH), IV doses much greater than those evaluated in Study ALXN1210-HV-102 (ie, up to 5400 mg every 12 weeks) are being evaluated for an extended period (up to 3 years). Data obtained from patients administered 5400 mg IV every 12 weeks provide a significant systemic PK margin for the proposed SC doses. Data have shown both multiple doses ravulizumab IV and a single dose of ravulizumab SC to be safe and well-tolerated.

2.2. Background

Ravulizumab was engineered from eculizumab to preserve immediate and complete C5 inhibition while providing sustained complement inhibition throughout a prolonged dosing interval (1 month or longer). Ravulizumab and eculizumab share > 99% amino-acid sequence

homology. Ravulizumab is a recombinant, humanized protein produced in Chinese hamster ovary (CHO) cells and was designed through minimal targeted engineering to substitute 4 amino acids in the eculizumab heavy chain. Two of these substitutions are in the complementarity determining regions, enhancing the pH-dependence of ravulizumab binding to C5; the other 2 are in the Fc binding region which improves recycling of ravulizumab into the vascular space instead of degrading. These changes were specifically designed (and have subsequently been proven) to increase the half-life of ravulizumab relative to eculizumab, increasing the duration of terminal complement inhibition, while preserving both the high degree of specificity for binding to C5 and the effectorless nature of the antibody.

Recombinant human hyaluronidase PH20 is a glycosylated single chain protein with up to 447 amino acids, synthesized in CHO cells. Recombinant human hyaluronidase PH20 degrades HA under physiologic conditions and acts as a spreading factor in vivo. Therefore, when combined (co-mixed) or coformulated with certain injectable drugs, rHUPH20 facilitates the absorption and dispersion of these drugs by temporarily reducing resistance to bulk fluid flow in the SC space. The permeability barrier in these tissues is restored to preinjection levels within 24 to 48 hours after injection of rHuPH20.

Detailed descriptions of the chemistry, pharmacology, efficacy, and safety of ravulizumab and rHuPH20 are provided in their respective Investigator's Brochures (IB).

2.3. Benefit/Risk Assessment

This is a healthy volunteer study and there is no direct benefit to study subjects. Identified and potential risks are described below.

More detailed information about the known and expected benefits/risks and expected adverse events of ravulizumab and rHuPH20 is provided in their respective IBs.

2.3.1. Infections With *Neisseria meningitidis*

A risk associated with complete terminal complement inhibition, such as that anticipated with ravulizumab, is infection with *N meningitidis*. Clinically, this risk is mitigated in patients receiving complement inhibitors such as eculizumab by vaccinating all patients against *N meningitidis* with a tetravalent meningococcal conjugate vaccine (MCV4) before dosing.

In this clinical study, normal healthy subjects will experience an induced transient state of complement deficiency, therefore subjects will receive the MCV4 vaccination at least 56 days prior to dosing with ravulizumab (if not vaccinated with MCV4 within the last 2 years and 4 months, or if adequate documentation to verify previous vaccination is unavailable). A titer to the tetravalent vaccine will be established prior to enrollment to confirm immunization status. Subjects who are not already vaccinated for serotype B meningococcal infections will also receive that vaccination at least 56 days prior to Day 1 dosing with a booster administered at least 28 days prior to dosing on Day 1.

In addition to vaccination against *N meningitidis* with MCV4 and the serogroup B vaccine, all subjects will be treated with prophylactic antibiotics (oral penicillin V 500 mg twice daily) for the duration of reduced complement activity. Unless the Investigator and Sponsor agree to an alternative regimen, all subjects will take prophylactic antibiotics (oral penicillin V 500 mg twice daily) until complement activity has normalized. If penicillin is not tolerated, second-line antibiotics (eg, ciprofloxacin) will be initiated.

Analysis of serum samples to establish actual complement activity will be performed using a CH50 in vitro liposome immunoassay (LIA). The analysis will take place approximately when complement activity is expected to normalize. Results will be used to confirm that complement activity has returned to normal and once confirmed, prophylactic antibiotic treatment can be stopped. All subjects will be closely monitored for signs of infection throughout the study.

2.3.2. Injection Site Reactions

Injection site reactions are a potential risk with any agent administered subcutaneously. Sporadic localized transient erythema has been observed at the site of injection in a nonclinical study with large volume SC administration of rHuPH20 formulated in the same buffer intended for ravulizumab SC (50 mM sodium phosphate, 25 mM arginine, 5% sucrose, and 0.05% polysorbate 80, pH 7.4). Monitoring for injection site reactions will be conducted as part of routine safety assessments for this study.

2.3.3. Immunogenicity and Hypersensitivity

As with any humanized mAb, ravulizumab has the potential to be immunogenic and may be associated with hypersensitivity reactions. During the ravulizumab development program, a small proportion of patients were positive for ravulizumab ADAs; these were laboratory findings with no clinical manifestations. No hypersensitivity reactions have been observed in clinical studies with ravulizumab.

Antibodies to rHuPH20 have been observed and evaluated in several nonclinical and clinical studies. No clinical signs or symptoms have been associated with positive anti-rHuPH20 antibody titers in clinical studies with rHuPH20, and no rHuPH20-neutralizing antibody activity has been detected (rHuPH20 Investigator's Brochure, 2018).

Monitoring of immunogenicity for ravulizumab is in place for this study as specified in the Schedule of Activities (Table 1 and Table 2) and Section 10.7 (Appendix 6).

2.3.4. Conclusion

This is the first time that the SC formulation of ravulizumab will be combined with rHuPH20 to facilitate a larger amount of ravulizumab SC delivered as a single infusion. Healthy volunteers are the appropriate population for this single-dose study, as they will enable PK and PD assessments without the potential of confounding effects due to other disease activity, comorbidities, or medications. This healthy subject study has been designed to minimize risk to the subjects participating: it is a single dose study with strict inclusion/exclusion criteria (Section 5.1 and Section 5.2) and there is a robust safety monitoring and risk mitigation plan in place. The single SC doses to be studied in healthy volunteers in this study are predicted to be within the safety exposure margins from healthy subjects or patients with PNH following IV dosing. In addition, available healthy subject data, as well as extensive patient data from the ongoing PNH and aHUS clinical programs support the initiation of Study ALXN1210-HV-105 in healthy subjects.

As this is a healthy volunteer study, there is no direct benefit to study subjects. The data obtained from this healthy volunteer study may inform future clinical studies in patients with PNH or other indications under study.

3. OBJECTIVES AND ENDPOINTS

The study objectives and corresponding endpoints are presented in Table 3.

Table 3: Study ALXN1210-HV-105 Objectives and Endpoints

Objectives	Endpoints
Primary	
– To estimate the absolute bioavailability of ravulizumab SC/rHuPH20 – To assess the safety and tolerability of ravulizumab SC/rHuPH20	– Serum concentration of ravulizumab will be used to determine the GMR of the AUC values – Safety assessed by incidence of TEAEs and SAEs, physical examination, vital sign measurements, clinical laboratory and electrocardiogram results, and measurement of ADA
Secondary	
To estimate the relative bioavailability of ravulizumab SC/rHuPH20 compared with ravulizumab SC	Serum concentration of ravulizumab will be used to determine the GMR of the AUC values
To explore the PD effects of ravulizumab SC coadministered with rHuPH20	– Change in serum levels of total and free C5 concentrations over time – Change in ex vivo cRBC hemolysis activity over time

Abbreviations: ADA = antidrug antibody; AUC = area under the concentration time curve; C5 = complement component 5; cRBC = chicken red blood cell; GMR = geometric mean ratio; PD = pharmacodynamic(s); rHuPH20 = recombinant human hyaluronidase PH20; SAE = serious adverse event; SC = subcutaneous; TEAE = treatment-emergent adverse events.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1 study designed to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity, and absolute and relative bioavailability of single ascending doses of ravulizumab SC coadministered with rHuPH20 compared to a single dose of ravulizumab IV 400 mg or a single dose of ravulizumab SC 400 mg in 48 healthy adult subjects across treatment cohorts (Table 4). A Safety Review Committee (SRC) will evaluate the study data for subject safety and make recommendations on dose escalation, dose modification, or termination of the study. When cohorts are being enrolled in parallel, subject assignment to a cohort will be done through randomization. Subjects may be randomized up to 7 days prior to dosing on Day 1. The study will be conducted at a single site in the United Kingdom (UK).

- Eighteen subjects will be randomly assigned in a 1:2 ratio between the first 2 cohorts to receive either a single dose of ravulizumab SC 400 mg (Cohort 1, n = 6) or a single dose of ravulizumab SC 500 mg/rHuPH20 10,000 units (Cohort 2, n = 12).
- The SRC will review Cohort 2 ravulizumab SC/rHuPH20 safety data and make their recommendation for escalating the dose of the ravulizumab SC/rHuPH20 cohort.
- If the SRC recommendation following the review of data from Cohort 2 is to initiate the next cohort and proceed with the planned dose escalation, 18 subjects will be randomly assigned in a 2:1 ratio between Cohort 3 (n = 12) and Cohort 5 (n = 6) to receive either a single dose of ravulizumab SC 1000 mg/rHuPH20 20,000 units or a single dose of ravulizumab IV 400 mg, respectively.
  - The SRC will subsequently review Cohort 3 ravulizumab SC/rHuPH20 safety data and make their recommendation to proceed with planned dose escalation in Cohort 4 or a reduced dose in Cohort 4.
  - Whether the SRC recommendation is to initiate Cohort 4 with the planned dose escalation or at a reduced dose, 12 subjects will be enrolled in Cohort 4 to receive a single dose of ravulizumab SC/rHuPH20 (dose to be determined based on SRC recommendation).
- If the recommendation following the review of ravulizumab SC/rHuPH20 safety data from Cohort 2 is to proceed with Cohort 3 at a reduced dose, 18 subjects will be randomly assigned in a 2:1 ratio between Cohort 3 (n = 12) and Cohort 5 (n = 6) to receive either a single dose of ravulizumab SC/rHuPH20 (dose to be determined based on SRC recommendation) or a single dose of ravulizumab IV 400 mg, respectively.
  - In this scenario, Cohort 4, if conducted, will be enrolled at a reduced dose, following completion of Cohort 3 based on SRC review of ravulizumab SC/rHuPH20 safety data from Cohort 3 and a favorable recommendation to enroll subjects in Cohort 4.
  - This protocol allows for reduced doses to be administered to subjects in Cohorts 3 and 4, based on SRC recommendation, without a protocol amendment. If a

reduced dose is administered, the SRC reduced dose recommendation will be documented on the escalation/progression approval form.

- If the SRC determines that no further ravulizumab SC/ rHuPH20 combination dosing cohorts should be enrolled following Cohort 2, then Cohort 5 may still be enrolled as a stand-alone cohort at the discretion of the Sponsor.
- Sentinel dosing will be employed in Cohorts 1 through 4 (ie, 2 subjects in a cohort with 12 subjects and 1 subject in a cohort with 6 subjects will be dosed prior to dosing the remaining subjects within the cohort). Remaining subjects in a cohort will be dosed at least 24 hours following dosing of the sentinel subjects.
- The SRC will review all available safety data through 168 hour (Day 8) assessments to determine initiation of the next dose cohort.
- At the Sponsor's discretion, and after consultation with the SRC, up to 16 additional subjects may be enrolled as replacement subjects if any subject discontinues prior to Day 50 for reasons other than drug-related adverse events (AE).

An appropriate number of subjects will be screened and randomly or sequentially assigned to each cohort to allow for approximately 48 subjects to complete the study. In order to minimize selection bias in treatment assignment, subjects who are randomized or assigned subject numbers will have them assigned consecutively at the point of study drug dosing, in the same order as they have become eligible.

The planned study duration is approximately 39 weeks; up to 70 days for screening and approximately 200 days for dosing and follow-up.

For the first 5 days during the Dosing and Follow-up Period, subjects will be admitted to an inpatient facility. Dosing will be staggered within and between cohorts, but the end of study for each individual subject is anticipated to be Day 200 or the time point at which complement activity has normalized, if later than Day 200.

Table 4: ALXN1210-HV-105 Study Design

Cohort	N	Study Drug	Route (SC/IV)	Planned Dose
1	6	ravulizumab	SC	400 mg
2	12	ravulizumab/rHuPH20	SC	500 mg/10,000 units
3	12	ravulizumab/rHuPH20	SC	1000 mg/20,000 units
4	12	ravulizumab/rHuPH20	SC	2000 mg/40,000 units
5	6	ravulizumab	IV	400 mg

Abbreviations: IV = intravenous; N = number [of subjects]; rHuPH20 = recombinant human hyaluronidase PH20; SC = subcutaneous.

4.2. Scientific Rationale for Study Design

- As this is the first study of ravulizumab SC/rHuPH20, a single ascending dose design was chosen for initial assessment of the safety and tolerability, PK, and PD of the combination cohorts.
- This study is being conducted in healthy subjects and not patients so that the assessments are not confounded by disease activity, comorbidities, or concomitant medications.
- A sentinel dosing paradigm is being used since this is the first administration of ravulizumab SC/rHuPH20, and it is also the first administration of ravulizumab SC 400 mg administered as a single infusion. Previous studies of ravulizumab SC utilized 4 separate injections of 100 mg each.
- The ravulizumab IV cohort will provide the reference arm for assessing absolute bioavailability. Data from earlier ravulizumab IV studies in healthy subjects cannot be used for this purpose, as these data were generated using a different bioanalytical assay for quantitation of ravulizumab.
- The ravulizumab SC cohort will provide a reference arm for relative bioavailability and to understand the impact of the addition of rHuPH20 to ravulizumab SC.
- The 200-day washout period corresponds to nearly 5 half-lives where ravulizumab is expected to be completely eliminated from the systemic circulation and complement activity restored to normal with near-baseline levels in the study subjects. The expected terminal elimination half-life for the highest SC dose being evaluated in this study is approximately 42 days.

4.3. Justification for Dose

This is the first time ravulizumab SC will be combined with rHuPH20 for coadministration in humans. The starting dose of ravulizumab 500 mg was determined via PK modelling and simulation studies using data from the Phase 1 Study ALXN1210-SC-101 and the ravulizumab IV clinical development program. The escalating ravulizumab doses proposed in this protocol allow for two-fold dose escalations at each dose level and are justified based upon the safety, tolerability, and PK margins generated from previous clinical studies. Table 5 summarizes the PK exposure margins estimated for the planned dose levels for the combined SC Cohorts 2, 3 and 4 in this study using the PK exposures from the highest IV dose cohort in healthy volunteers in Study ALXN1210-HV-102 (800 mg every 4 weeks) as the reference. The

estimated margins illustrate that PK exposures to ravulizumab expected following the planned single doses in the SC Cohorts 2, 3 and 4 in this study are well within those previously evaluated clinically and determined to be well-tolerated. The estimated exposure at the planned doses in this study is expected to be less than that of the healthy subjects who received multiple doses of ravulizumab IV 800 mg every 4 weeks in Study ALXN1210-HV-102 (ie, an approximately 9-month duration of effect). It is noteworthy that in patients with PNH, IV doses much greater than those evaluated in Study ALXN1210-HV-102 (ie, up to 5400 mg every 12 weeks) are being studied for an extended period (up to 3 years) and those doses have been well-tolerated.

Recombinant human hyaluronidase PH20 has been safely administered via SC injection/infusion in combination with large proteins, up to a maximum volume of 30 mL (Chari, 2017; Usmani, 2016; Wasserman, 2012). Recombinant human hyaluronidase PH20 administered SC has been generally well-tolerated; the most commonly reported adverse reactions were mild, transient, local, injection site reactions (ISRs) (rHuPH20 Investigator's Brochure, 2018). The rHuPH20 dose (2,000 U/mL) combined with the ravulizumab SC dose is based upon the previous clinical experience in 28 clinical studies with rHuPH20 conducted under the rHuPH20 US IND and data from 3 marketed products Herceptin® SC, HYQVIA®, and MabThera® SC.

Table 5: Pharmacokinetic Exposure Margins Estimated for the Proposed Ravulizumab/rHuPH20 Subcutaneous Dose Cohorts Using the Highest Intravenous Dose Cohort From Study ALXN1210-HV-102 as the Reference

Pharmacokinetic Exposure Margins for Ravulizumab/rHuPH20 Subcutaneous Cohorts[a]					
Cohort 2		Cohort 3		Cohort 4	
C_{max}	AUC_{∞}	C_{max}	AUC_{∞}	C_{max}	AUC_{∞}
8.2	13.4	4.1	6.7	2.1	3.4

[a] A potential improvement in ravulizumab SC bioavailability due to rHuPH20 was accounted for in the margin estimation.
Abbreviations: AUC_{∞} = area under the concentration versus time curve from zero to infinity; C_{max} = maximum observed serum concentration; SC = subcutaneous.

4.4. End of Study Definition

A subject is considered to have completed the study if he/she has completed all visits of the study including the last scheduled visit specified in the Schedule of Activities (Table 1 and Table 2).

The end of the study is defined as the last scheduled visit for the last subject, specified in the Schedule of Activities (Table 1 and Table 2). No further study assessments beyond CH50 evaluation, as needed based on individual subject results, will be performed after Day 200.

5. STUDY POPULATION

5.1. Inclusion Criteria

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

Age/Sex

1. Male or female subject must be at least 18 and 65 years of age, inclusive, at the time of signing the informed consent.

Weight

2. Body weight within 60 – 90 kg, inclusive, and body mass index within the range 18 – 29.9 kg/m^2, inclusive.

Pregnancy

3. Negative serum pregnancy test at screening and Day -1

Contraception

4. Female subjects of childbearing potential and male subjects with female partners of childbearing potential must be willing to follow protocol-specified contraception guidance while on treatment and for up to 8 months after last dose of study drug (described in Section 6.6).

Other Inclusion Criteria

5. QT interval corrected using the Fridericia's formula (QTcF) ≤ 450 msec for male subjects and ≤ 470 msec for female subjects at screening and prior to dosing on Day 1.
6. Documented vaccination with MCV4 at least 56 days and not more than 2 years, 4 months prior to dosing. Documentation must include a positive titer to confirm an immune response before study drug administration.
7. Vaccination with serogroup B meningococcal vaccine at least 56 days prior to dosing on Day 1, with a booster administered at least 28 days prior to dosing on Day 1, with at least 28 days between the first and second injections.
8. Satisfactory medical assessment with no clinically significant or relevant abnormalities as determined by medical history, physical examination, vital signs, 12-lead ECG, and clinical laboratory evaluation (hematology, biochemistry, coagulation, and urinalysis) that is reasonably likely to interfere with the subject's participation in or ability to complete the study, or to potentially confound interpretation of study results, as assessed by the Investigator.

Informed Consent

9. Willing and able to give written informed consent as described in Section 10.1 (Appendix 1) which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

1. Current or recurrent disease (eg, cardiovascular, hematological, neurological, endocrine, immunological, rheumatological, renal, hepatic or gastrointestinal or other conditions) that or could affect clinical assessments or clinical laboratory evaluations.
2. Current or relevant history of physical or psychiatric illness that are not stable or may require a change in treatment, use of prohibited therapies during the study or make the subject unlikely to fully comply with the requirements of the study or complete the study, or any condition that presents undue risk from the investigational product or study procedures.
3. Any other significant disease or disorder which, in the opinion of the Investigator, may put the subject at risk.
4. History of any *Neisseria* infection.
5. History of unexplained, recurrent infection, or infection requiring treatment with systemic antibiotics within 90 days prior to dosing on Day 1.
6. History of complement deficiency or complement activity below the reference range as evaluated at screening.
7. History of malignancy with the exception of a nonmelanoma skin cancer or carcinoma *in-situ* of the cervix that has been treated with no evidence of recurrence within 5 years.
8. Human immunodeficiency virus (HIV) infection (evidenced by HIV-1 or HIV-2 antibody titer).
9. Acute or chronic hepatitis B virus infection. Hepatitis B surface antigen (HBsAg) testing is required for all subjects prior to enrollment. Subjects with positive HBsAg will not be enrolled.

   For subjects with negative HBsAg, the following testing algorithm will be required:
   a. If hepatitis B core antibody (HBcAb) is negative, the subject is eligible to enroll.
   b. If HBcAb is positive, the hepatitis B surface antibody (HBsAb) will be tested.
      - If both HBcAb and HBsAb are positive, the subject is eligible to enroll
      - If HBcAb is positive and HBsAb is negative, the subject will not be enrolled
10. Acute or chronic hepatitis C virus infection (evidenced by antibody titer).
11. Active systemic viral or fungal infection within 14 days prior to dosing.
12. History of latent or active tuberculosis (TB) or exposure to endemic areas within 8 weeks prior to the screening visit.
13. Documented history of allergy to penicillin or cephalosporin.
14. History of significant allergic reaction (eg, anaphylaxis or angioedema) to any product (eg, food, pharmaceutical).

Prior/Concomitant Therapy

15. Use of prescription medications (excluding oral contraceptives) within 14 days prior to dosing on Day 1, except with prior approval of the Sponsor.

16. Regular use of nonprescription, over-the-counter medications, including herbal remedies and supplements, within 14 days prior to dosing on Day 1. Multivitamins, paracetamol (acetaminophen) ≤ 2 g per day, and topical skin products without significant systemic absorption are allowed.

Prior/Concurrent Clinical Study Experience

17. Participation (ie, last protocol-required study visit) in a clinical study within 90 days before initiation of dosing on Day 1.
18. Participation in more than 1 clinical study of a mAb, or participation (ie, last protocol-required study visit) in a clinical study of a mAb within the 12 months prior to screening, during which the subject was exposed to the active study drug.

Diagnostic Assessments

19. Positive or indeterminate QuantiFERON®-TB test indicating possible tuberculosis (TB) infection.
20. Presence of fever (confirmed body temperature > 37.6°C) (eg, a fever associated with a symptomatic viral or bacterial infection) within 14 days prior to dosing on Day 1.
21. Serum creatinine greater than the upper limit of normal (ULN) of the reference range of the testing laboratory at screening or on Day -1.
22. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > ULN of the reference range of the testing laboratory at screening or > 1.5 × ULN of the reference range of the testing laboratory on Day -1.
23. Any clinically significant abnormal hematological parameters (per the Investigator's discretion).
24. Positive urine drug toxicology screen at screening or on Day -1.
25. Alcohol consumption within 48 hours prior to study drug administration or positive alcohol breath test on Day -1.
26. Donation of plasma within 7 days prior to dosing on Day 1. Donation or loss (excluding volume drawn at screening) of more than 50 mL of blood within 30 days prior to dosing or more than 499 mL of blood within 56 days prior to dosing on Day 1.

Other Exclusion Criteria

27. Female subjects who are breastfeeding.
28. Subjects who are in intimate and prolonged contact with (defined as living under the same roof or providing personal care to) people younger than 2 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); congenital complement, properdin, factor D, or primary antibody deficiencies; acquired complement deficiencies (eg, those receiving eculizumab); or HIV.
29. Subjects who are one of the following:
    a. Professionals who are exposed to environments of greater risk for meningococcal disease

b. Research, industrial, and clinical laboratory personnel who are routinely exposed to *N meningitidis*
c. Military personnel during recruit training (military personnel may be at increased risk of meningococcal infection when accommodated in close quarters)
d. Daycare center workers
e. Those living on a college or university campus
f. Those who plan to travel during the course of the study to or have travelled to endemic areas for meningococcal meningitis (eg, India, Sub-Saharan Africa, pilgrimage to Saudi Arabia for Hajj) within 6 months prior to dosing

30. Immunization with a live-attenuated vaccine 28 days prior to dosing on Day 1 or planned vaccination during the course of the study (except for the vaccination planned by the study protocol). Immunization with inactivated or recombinant influenza vaccine is permitted.
31. Prior exposure to ravulizumab or eculizumab.
32. Major surgery or hospitalization within 90 days prior to dosing on Day 1.
33. History of allergy or hypersensitivity to excipients of ravulizumab (eg, polysorbate 80), rHuPH20, or other hyaluronidases.
34. Currently smokes > 10 cigarettes daily (former smokers may be permitted to enroll at the Investigator's discretion) and is unwilling to refrain from smoking while a resident in the clinical research unit or comply with the smoking restrictions detailed in Section 5.3.2.
35. 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 abuse within the 2 years before screening. Alcohol abuse is defined as regular weekly intake of more than 14 units (for both males and females), using the following NHS alcohol tracker http://www.nhs.uk/Tools/Pages/drinks-tracker.aspx.

5.3. Study Restrictions

5.3.1. Meals and Dietary Restrictions

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

5.3.2. Caffeine, Alcohol, and Tobacco

Subjects will be required to abstain from:

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

- Smoking tobacco products from 2 hours before admission through discharge from the inpatient facility.

5.3.3. Activity

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

5.4. Screen Failures and Replacements

Screen failures are defined as subjects who consent to participate in the clinical study and are not subsequently assigned to study drug due to failure to meet eligibility criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and occurrence of any serious adverse event (SAE).

Subjects who do not meet the criteria for participation in this study (ie, screen failures) may be rescreened. Any abnormal laboratory parameter(s) resulted outside of the reference range at screening may be repeated per the Investigator's discretion for the purpose of further determining eligibility.

In order to meet minimum data requirements for SRC meetings, subjects who withdraw consent from the study within the first 7 days may be replaced. Subjects who withdraw consent between Days 7 and 50 may be replaced at the Sponsor's discretion.

5.4.1. 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 subjects enrolled in the study
- Decision on the part of the Sponsor 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 the Sponsor and/or regulatory authorities

6. STUDY DRUG

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

6.1. Study Drug Administered

The study drug composition and doses to be administered in this study are presented in Table 6.

Table 6: Dose Reference Chart for Study ALXN1210-HV-105

Study Drug Name:	Ravulizumab IV	Ravulizumab SC	rHuPH20	Ravulizumab SC/rHuPH20
Dosage Formulation:	Ravulizumab IV is formulated at pH 7.0 and each vial contains 300 mg of ravulizumab in 10 mM sodium phosphate, 150 mM sodium chloride, 0.02% polysorbate 80. Each vial contains 10 mg/mL.	Ravulizumab SC is formulated at pH 7.4 and each vial contains 1100 mg of ravulizumab in 50 mM sodium phosphate, 25 mM arginine, 5% sucrose, and 0.05% polysorbate 80. Each vial contains 100 mg/mL.	rHuPH20 is supplied as ENHANZE® drug product (EDP) is supplied in vials as a sterile, single-dose, injectable liquid at approximately 110 kU/mL. The solution has a pH of 6.5 and contains 130 mM sodium chloride, 10 mM L-Histidine/ hydrochloride as a buffer, 10 mM L-Methionine, and 0.2% w/w polysorbate 80. The solution is filled to 0.5 mL in a 2-mL glass vial.	Ravulizumab SC/rHuPH20 is formulated per the individual components of the drug product.
Unit Dose Strength(s)/ Dosage Level(s):	400 mg	400 mg	NA	ravulizumab SC 500 mg/rHuPH20 10,000 units ravulizumab SC 1000 mg/rHuPH20 20,000 units ravulizumab SC 2000 mg/rHuPH20 40,000 units
Route of Administration	IV	SC	SC	SC

Study Drug Name:	Ravulizumab IV	Ravulizumab SC	rHuPH20	Ravulizumab SC/rHuPH20
Dosing Instructions:	A single dose of ravulizumab IV will be administered via IV infusion and 80 mL of ravulizumab IV will be administered at a maximum infusion rate of 333mL/hr, for a minimum infusion duration of approximately 15 minutes. Use of an in-line filter for infusion is required.	A single dose of ravulizumab SC will be administered via SC infusion administered by a syringe pump. The total volume to be administered will be 4 mL at an infusion rate of 0.5 mL/min.	NA	Ravulizumab will be co-mixed with EDP in empty, sterile 20-mL glass vials. A single dose of ravulizumab SC/rHuPH20 will be administered via SC infusion, administered via an infusion pump. The total volume to be administered for the combination cohorts will be 5.23 mL in Cohort 2, 10.46 mL in Cohort 3, and 20.91 mL in Cohort 4 at an infusion rate of 2 mL/min..
Packaging and Labeling *Additional instructions are provided in the pharmacy manual.*	Ravulizumab IV drug product will be provided in a single-use, USP/Ph Eur Type 1 clear and colorless glass vial, stoppered with a gray butyl rubber stopper, and sealed with aluminum seal with a polypropylene flip-off cap.	Ravulizumab SC drug product will be provided in a single-use, USP/Ph Eur Type 1 clear and colorless glass vial, stoppered with a gray butyl rubber stopper, and sealed with aluminum seal with a polypropylene flip-off cap.	rHuPH20 for coadministration will be provided as single-use, USP/Ph Eur Type I clear and colorless glass vial.	Individual components of ravulizumab SC/ rHuPH20 drug product will be packaged and labeled according to their respective manufacturers.
Manufacturer	Alexion	Alexion	Halozyme	Alexion/Halozyme

Abbreviations: IV = intravenous; NA = not applicable; SC = subcutaneous.
Source: rHuPH20 Investigator's Brochure (2018), pharmacy manual

6.2. Preparation/Handling/Storage/Accountability

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received and that any discrepancies are reported and resolved before use of the study drug.
2. Only subjects enrolled in the study may receive study drug and only authorized site staff may supply or administer study drug. All study drugs must be stored in a secure, environmentally controlled, and monitored (manually or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

3. Preparation of ravulizumab IV, ravulizumab SC, and the ravulizumab SC/rHuPH20 drug products must be performed in accordance with local standards by qualified pharmacy personnel at the investigative site.
4. The handling and preparation of materials used to prepare and administer the study drug must be carried out using aseptic techniques for sterile products. For each subject, doses will be prepared as required per the dose cohort.
5. The entire dosing apparatus (ie, syringe and infusion tubing) should be weighed before and after infusion and the weights recorded for the purpose of recoding the exact dose administered.
6. Recombinant human hyaluronidase PH20 will be supplied as ENHANZE drug product (EDP; 1 mg/mL [0.5 mg of active ingredient per vial; approximately 110,000 units/mg]) in 2-mL single use glass vials.
7. The volume of drug product to be prepared will be based on the cohort to which a subject is assigned. For Cohort 1, ravulizumab will be administered undiluted via SC infusion administered by a syringe pump. For Cohorts 2 through 4, ravulizumab will be co-mixed with EDP in empty, sterile glass vials. A single dose of ravulizumab SC/rHuPH20 will be administered via SC infusion administered by a syringe pump. For Cohort 5, the IV admixture will consist of ravulizumab diluted in a 1:1 ratio with 0.9% sodium chloride, Ph Eur, or BP. Do not flush the IV infusion line. The rate at which study drug will be administered in Cohorts 1 through 4 will be provided in the pharmacy manual.
8. The Investigator or qualified designee is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

   Additional instructions are provided in the pharmacy manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study. Eligible subjects who meet all inclusion and no exclusion criteria will be assigned unique numbers for enrollment and randomization. Randomization will only be used when cohorts are being enrolled in parallel.

- In order to minimize selection bias in treatment assignment, subjects will be randomly or sequentially assigned subject numbers, depending upon cohort, up to 7 days prior to dosing on Day 1, in the same order as they have become eligible.
- Sentinel dosing will be employed in Cohorts 1 through 4 (ie, 2 subjects in a cohort with 12 subjects and 1 subject in a cohort with 6 subjects will be dosed prior to dosing the remaining subjects within the cohort). Remaining subjects within the cohort will be dosed at least 24 hours following dosing of the sentinel subjects.
- At the Sponsor's discretion, and after consultation with the SRC, up to 16 additional subjects may be enrolled as replacement subjects if any subject discontinues prior to Day 50 for reasons other than drug-related AE.
- Study numbers will not be reallocated once assigned.

6.4. Study Drug Compliance

Subjects will be administered study drug in a controlled setting under the supervision of the Investigator, thereby ensuring compliance with study drug administration. Study center personnel will ensure that all subjects are adequately informed about the specific study drug dosing regimen required for compliance with the study protocol.

6.5. Concomitant Therapy

Subjects must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 14 days before the start of study drug until completion of the follow-up visit, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.

Multivitamins, paracetamol (acetaminophen) (at doses of ≤ 2 g/day), and topical skin products without significant systemic absorption are permitted for use during the study at the Investigator's discretion. Topical skin products should not be administered at the site of study drug injection from 24 hours prior until 24 hours following study drug administration. Subjects are also permitted to receive a booster vaccine, if required.

Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the medical monitor if required. Concomitant procedures are not allowed unless medically indicated.

6.6. Contraception Guidance

Female subjects who are documented as being of non-childbearing potential as defined in Section 10.4 (Appendix 4) are exempt from contraception requirements.

Female subjects of childbearing potential, if heterosexually active, must use highly effective or acceptable contraception as defined below. Antibiotic prophylaxis is required during this study, which can compromise the efficacy of hormonal contraception. Therefore, subjects 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

Male subjects, if heterosexually 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 subjects who are of childbearing potential must use highly effective contraception as defined above, or acceptable contraception as defined below. Male subjects must not donate sperm and female subjects must not donate ova.

Acceptable contraceptive methods are as follows:

- Simultaneous use of male condom and, for the female partner, occlusive cap (diaphragm or cervical/vault caps) with intravaginally applied spermicide

Contraception must start during screening and continue after the end of the systemic exposure of the study drug as specified below:

- Cohorts 1 and 5 – contraception must continue for at least 6 months after last dose. Male subjects must not donate sperm and female subjects must not donate ova until at least 6 months after last dose.
- Cohorts 2, 3, and 4 – contraception must continue for at least 8 months after last dose. Male subjects must not donate sperm and female subjects must not donate ova until at least 8 months after last dose.

6.7. Dose Modification

Decisions to continue, modify (explore the dose cohort further), or escalate dosing will be made by the Investigator and/or SRC as described in Table 7. The SRC may also make recommendations regarding safety issues, study conduct, or study suspension. The SRC is composed of the Sponsor's medical monitor, biostatistician, pharmacovigilance representative, clinical pharmacologist, and the Investigator. The membership roster, schedule of meetings, data required for each safety review, and requirements for documenting meeting discussions and outcome will be outlined in the SRC charter.

The SRC will review all available safety and tolerability data from a given cohort for at least the first 168 hours after study drug administration in order to determine whether to escalate the ravulizumab SC/rHuPH20 dose and initiate the next cohort. Data through 168 hours must be available for at least 11 of the 12 subjects. Dose escalation or modification will occur based on the recommendation of the SRC to dose escalate and only applies to Cohort 3 and Cohort 4.

Table 7: Study ALXN1210-HV-105 Dose Continuation/Escalation Decision Pathway

Dosing Decision	Responsible Party	Data to be Reviewed	Documentation/Communication Methods
Continuation from the sentinel subject to the remaining subjects in Cohort 1	Investigator	A minimum of 24 hours post-dose safety and tolerability data from the sentinel subject.	The Investigator will document the decision in an email to the Sponsor. The email does not require the Sponsor's response, unless there is disagreement with the Investigator's decision.
Continuation from the sentinel subjects to the remaining subjects in Cohort 2	Investigator	A minimum of 24 hours post-dose safety and tolerability data from the sentinel subjects.	The Investigator will document the decision in an email to the Sponsor. The email does not require the Sponsor's response, unless there is disagreement with the Investigator's decision.
Escalation to Cohort 3	SRC	A minimum of 168 hours post-dose safety and tolerability data from at least 11 subjects (all of whom have received treatment) from the previous cohort that was on the next lowest dose level (and hence, next lowest exposure) of ravulizumab SC/rHuPH20.	The SRC will document the decision on the escalation/progression approval form.
Continuation from the sentinel subjects to the remaining subjects in Cohort 3	Investigator	A minimum of 24 hours post-dose safety and tolerability data from the sentinel subjects.	The Investigator will document the decision in an email to the Sponsor. The email does not require the Sponsor's response, unless there is disagreement with the Investigator's decision.
Escalation to Cohort 4	SRC	A minimum of 168 hours post-dose safety and tolerability data from at least 11 subjects (all of whom have received treatment) from the previous cohort that was on the next lowest dose level (and hence, next lowest exposure) of ravulizumab SC/rHuPH20.	The SRC will document the decision on the escalation/progression approval form.
Continuation from the sentinel subjects to the remaining subjects in Cohort 4	Investigator	A minimum of 24 hours post-dose safety and tolerability data from the sentinel subjects.	The Investigator will document the decision in an email to the Sponsor. The email does not require the Sponsor's response, unless there is disagreement with the Investigator's decision.

Abbreviations: SC = subcutaneous; SRC = Safety Review Committee.

6.7.1. Toxicity Rules for Adverse Events Deemed Related to Study Drug

These rules apply to AEs that are assessed as related to study drug by the Investigator. Dose continuation or escalation will proceed as scheduled (Table 7) and the study will continue as planned provided no prespecified toxicity events occur.

- The entire study will be suspended if any life-threatening (Common Terminology Criteria for Adverse Events [CTCAE] v4.03; published 14 Jun 2010, Grade 4) or fatal (CTCAE Grade 5) SAEs occur. If any of the following occur, dosing within the affected cohort will be suspended and dose escalation cannot commence. Interim lower doses may be subsequently administered at the discretion of the SRC.
  - A treatment-related SAE, irrespective of the CTCAE grade, in 1 subject. This includes any subject potentially meeting the criteria for Hy's Law (ALT $\geq 3 \times$ ULN) and bilirubin $\geq 2 \times$ ULN (ie, > 35% direct bilirubin) or ALT $\geq 3 \times$ ULN and international normalized ratio (INR) > 1.5, if INR was measured, which may indicate severe liver injury (possibly Hy's Law).
  - Severe (CTCAE Grade 3) nonserious treatment-related AEs in 2 subjects in the same cohort, independent of whether the AEs are within the same System Organ Class (SOC).

For Cohorts 2 through 4 (ravulizumab SC/rHuPH20):

- Any number of Grade 1 ISRs are permitted to allow continuation of dosing within a cohort and escalation to the next highest dose level.
- Any number of Grade 2 ISRs that have resolved or reduced to Grade 1 by the time of the minimum data review period (168 hours post-dose) are permitted to allow continuation of dosing within a cohort and escalation to the next highest dose level.
- If, at the end of the minimum data review period (168 hours post-dose) there are more than 2 subjects with ISRs that are still Grade 2, dose escalation cannot occur and the period of observation should be extended by a further 168 hours (or shorter, if all subjects recover to at least Grade 1 before that time point). If all affected subjects show sign of recovery (at least to Grade 1), dose escalation can then proceed. If all affected subjects remain at Grade 2 after the additional 168-hour observation period, the SRC will make the decision to either prolong further the observation period or progress to subsequent combination cohorts at a lower dose/smaller volume of study drug.

6.8. Intervention After the End of the Study

This is a healthy volunteer study and no follow-up intervention is planned.

7. DISCONTINUATION OF STUDY DRUG AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Drug

Subjects who experience a severe reaction during study drug administration resulting in interruption without completion of the administration should undergo all scheduled safety, immunogenicity, PK, and PD evaluations required by the protocol (refer to Schedule of Activities, Table 1 and Table 2). Subjects will be instructed to present for all scheduled visits and undergo all procedures per protocol.

7.2. Subject Discontinuation/Withdrawal From the Study

A subject 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.

- If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- Data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed are specified in the Schedule of Activities (Table 1 and Table 2).

7.3. Lost to Follow-up

A subject 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 subject fails to return to the clinic for a required study visit:

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

8. STUDY ASSESSMENTS AND PROCEDURES

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator or qualified designee will maintain a screening log to record details of all subjects 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 presented in the Schedule of Activities (Table 1 and Table 2).

8.2.1. Physical Examination

Each examination will include the following assessments: general appearance; skin; head, ears, eyes, nose, and throat; neck; lymph nodes; chest; heart; abdominal cavity; limbs; central nervous system; and musculoskeletal system. Height and weight (screening only) will also be measured and recorded. Body mass index will be calculated and recorded at screening.

8.2.2. Vital Signs

Vital sign measurements will be taken after the subject has been resting in the supine or semi-recumbent position for at least 5 minutes and will include temperature (°C; oral), respiratory rate, supine blood pressure, and pulse. The timing of vital sign measurements is described in the Schedule of Activities (Table 1 and Table 2). Out of range blood pressure or heart rate measurements will be repeated at the Investigator's discretion. Confirmed, clinically significant vital sign measurements will be recorded as AEs.

8.2.3. Electrocardiograms

A triplicate 12-lead ECG will be obtained after the subject has been resting for at least 5 minutes. The timing of ECGs is described in the Schedule of Activities (Table 1 and Table 2). At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes, 30 seconds. In addition, continuous cardiac registration will be performed in Cohorts 2, 3, and 4 as specified in Table 1.

8.2.4. Laboratory Assessments

All protocol-required laboratory assessments, as defined in Section 10.2 (Appendix 2), must be conducted in accordance with the Schedule of Activities and the laboratory manual. Clinical and laboratory assessments will be performed by a local laboratory to assess safety of ravulizumab.

- The Investigator must review the laboratory report, document this review, and record all clinically relevant changes occurring during the study in the AE section of the electronic case report form (eCRF). The laboratory reports must be filed with the source documents.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study will be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or medical monitor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
  - If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.
- The maximum amount of blood to be collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL. Repeat or unscheduled samples may be obtained for safety and/or eligibility reasons or if there are any technical issues with the samples.

8.2.4.1. Virus Serology

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

Hepatitis B surface antigen testing is required for all subjects prior to enrollment. Subjects with positive HBsAg will not be enrolled.

8.2.4.2. Vaccine Titer

A titer against meningococcal serogroups A, C, W135, and Y will be performed at screening (Schedule of Activities [Table 1 and Table 2]). Titer measurements will be used to exclude subjects without a confirmed immune response.

8.2.4.3. Immunogenicity Assessments

Antibodies to ravulizumab will be evaluated in serum samples collected from all subjects according to the Schedule of Activities (Table 1 and Table 2).

Serum samples will be screened for antibodies that bind to ravulizumab and the titer of confirmed positive samples will be reported. The detection and characterization of antibodies to ravulizumab will be performed using a validated assay method by or under the supervision of the Sponsor. Samples may be banked for a period of up to 5 years in order to perform additional safety assessments, as necessary.

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

8.2.5. Drug and Alcohol Screen

A urine sample for drug screen will be analyzed for the substances listed in Section 10.2 (Appendix 2). Timing of urine drug and alcohol breath tests is specified in the Schedule of Activities (Table 1 and Table 2).

8.2.6. Pregnancy Testing

Pregnancy testing will be performed for all female subjects at the time points specified in the Schedule of Activities (Table 1 and Table 2).

8.2.7. Tuberculosis Testing

Serum samples for a QuantiFERON-TB test will be obtained at the time points specified in the Schedule of Activities (Table 1 and Table 2).

8.2.8. Injection or Infusion-Site Evaluation

Subcutaneous injection or IV infusion-site evaluations will be performed at the time points specified in the Schedule of Activities (Table 1 and Table 2). Injection site reactions (eg, indurations ≤ 1 cm in size) will not be listed as an AE unless they persist for more than 24 hours.

8.2.9. Vaccine and Antibiotic Prophylaxis

To mitigate the risk of *N meningitidis* infection associated with terminal complement inhibition, subjects in this study will be administered the following:

1. A MCV4 vaccination at least 56 days prior to dosing of ravulizumab on Day 1 (if not vaccinated with MCV4 within the last 3 years, or if subjects have been previously vaccinated but there is not adequate documentation to verify prior vaccination).
2. Two injections of the serogroup B meningococcal vaccine. The first injection must be administered at least 56 days prior to dosing on Day 1, with a booster administered at least 28 days prior to dosing on Day 1, with at least 28 days between the first and second injections.
3. Prophylactic antibiotic treatment, oral penicillin V 500 mg twice daily (equivalent to 1×10^6 units) until complement activity has normalized (as determined by CH50 assay).

The first dose of antibiotic will be administered orally on Day -1 in the evening, prior to the Day 1 (dose administration) of study drug. For the outpatient portion of the study, subjects will be instructed to take the antibiotic approximately at the same times (twice daily) on each scheduled day. A suitable system (such as text messaging) will be used for daily monitoring of subjects' compliance with the antibiotic prophylaxis regimen.

The following observations support the administration of antibiotic prophylaxis in this single-dose study:

1. Penicillin is the drug of choice in eradication of *N meningitidis* in carriers.
2. Complement-deficient patients who received monthly injections with benzathine penicillin G as prophylaxis for recurrent meningococcal disease during a 2- to 4-year period experienced significantly fewer episodes of *Neisseria* infection than deficient individuals not receiving prophylaxis (Figueroa, 1991).

3. High levels of resistance to penicillin caused by plasmid-encoded β-lactamases are rarely encountered in meningococcal strains (Yazdankhah, 2004).
4. Antibiotic prophylaxis with orally administered penicillin V 500 mg twice daily has been provided in the treatment of PNH and aHUS patients with eculizumab by some physicians and is generally well-tolerated (Kelly, 2011; Leeds Teaching Hospitals NHS Trust, 2013).

8.2.10. Risk of Infection Reminders

Risk of infection will be explained and discussed with subjects during the informed consent process, occurring at the screening visit. In order to increase the risk awareness and promote quick disclosure of any potential signs or symptoms of infection experienced by the subjects during the course of the study, additional discussion and explanation of the potential risks, signs, and symptoms, as described in the ICF, will take place at specific time points throughout the study as noted in the Schedule of Activities (Table 1 and Table 2). Subjects will also be provided a safety card to carry with them at all times.

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 (Appendix 3). Adverse events will be reported to the Investigator or qualified designee by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study drug or study procedures, or that caused the subject to discontinue the study drug (see Section 7).

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

All AEs and SAEs will be collected from the signing of the ICF until the last follow-up visit.

Medical occurrences that begin before the start of study drug and after obtaining informed consent will be recorded on the eCRF, and will be considered as medical history.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Section 10.3 (Appendix 3). The Investigator will submit updated SAE data to the Sponsor within 24 hours of the data being available.

Investigators are not obligated to actively seek AEs or SAEs after the conclusion of study participation (ie, after Day 200).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports to Sponsor are provided in Section 10.3 (Appendix 3).

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the subject 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 subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 10.3 [Appendix 3]). Further information on follow-up procedures is provided in Section 10.3 (Appendix 3).

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study drug under clinical investigation are met.
- The Sponsor 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. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- The Council for International Organizations of Medical Sciences or MedWatch reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- Incidence of all pregnancies in female subjects and if indicated female sexual partners of male subjects will be collected after the administration of study drug and for at least 6 months (Cohorts 1 and 5) or 8 months (Cohorts 2, 3, and 4) thereafter.
- Complications of abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are AEs and may meet the criteria for SAEs (Section 10.3 [Appendix 3]).
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy. Specific pregnancy information to be collected is outlined in Section 10.4 (Appendix 4).

8.3.6. Management of Potential Adverse Events During Study Drug Administration

Infusion of other monoclonal antibodies has been associated with infusion reactions, with onset typically during or shortly after completion of the infusion. For this reason, subjects will be carefully observed during each infusion.

Subjects will be closely monitored during and after study drug administration for any symptoms of anaphylaxis and other hypersensitivity reactions, including circulatory and/or respiratory changes or arrest, or urticaria, arthralgias, myalgias, or other signs of related reactions. Adequate treatment will be immediately available. Infusion-associated AEs may occur, and depending on their type and severity, discontinuation of infusion may be required. Subjects will be informed of early symptoms and signs of hypersensitivity reactions including hives, swollen face, eyelids, lips, or tongue, or trouble with breathing. An acute infusion reaction algorithm will be used to manage infusion-related reactions (Section 10.7 [Appendix 6: Acute Infusion Reactions Algorithm]). In this study, regular assessments to monitor infusion reactions and infusion-site reactions will be done. To ensure that reactions can be dealt with promptly, there will be at least 15 minutes between the end of IV/SC infusion in 1 subject and the start of IV/SC infusion in the next subject. No more than 6 subjects assigned to receive ravulizumab IV will be dosed per day. Any reactions will be treated and taken into account in the dose continuation/escalation and toxicity rules (Table 7). If anaphylactic reactions occur, the current "UK Treatment Guideline for Anaphylactic Reactions" of the UK Resuscitation Council will be followed (Section 10.7 [Appendix 7: United Kingdom Resuscitation Council Anaphylaxis Algorithm]).

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

8.3.7. Study Drug Administration Reactions

8.3.7.1. Infusion-site Reactions

Infusion-site reactions are defined as AEs localized to the site of IV or SC route of study drug administration, occurring at any time during study participation that are assessed by the Investigator to be possibly, probably, or definitely related to study drug.

8.3.7.2. Infusion-associated Reactions

Infusion-associated reactions are defined as systemic AEs (eg, fever, chills, flushing, alterations in heart rate and blood pressure, dyspnea, nausea, vomiting, diarrhea, and generalized skin rashes) occurring during or within 24 hours of the start of IV or SC infusion that are assessed by the Investigator to be possibly, probably, or definitely related to the study drug.

8.4. Treatment of Overdose

No cases of overdose have been reported during ravulizumab IV or SC clinical studies. A single dose of study drug will be administered and monitored by site personnel.

8.5. Pharmacokinetics

Whole blood samples will be collected for measurement of serum concentrations of study drug as specified in the Schedule of Activities (Table 1 and Table 2). Additional samples may be collected during the study if warranted and agreed upon between the Investigator and the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded. Additional details, including further handling and processing instructions and sampling time windows will be provided in the study laboratory manual.

8.6. Pharmacodynamics

After study drug administration, whole blood samples will be collected for measurement of serum free C5 concentrations, chicken red blood cell (cRBC) hemolytic activity, and potentially other measures of C5 activation as specified in the Schedule of Activities (Table 1 and Table 2). Additional samples may be collected during the study if warranted and agreed upon between the Investigator and the Sponsor.

Serum samples will be collected at baseline and during follow-up for measurement of CH50 activity using an in vitro LIA to confirm normalization of complement activity. If a normal CH50 result is obtained from a subject's first CH50 sample collected during follow-up, antibiotic prophylaxis can be stopped and the second scheduled CH50 sample is not required. If the first and second CH50 samples are not normal, the baseline sample may be analyzed, and further CH50 samples will be taken until complement activity has been normalized.

8.7. Genetics

Genetics will not be evaluated in this study.

8.8. Biomarkers

Biomarkers will not be evaluated in this study.

8.9. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data will not be evaluated in this study.

9. STATISTICAL METHODS AND PLANNED ANALYSES

9.1. Statistical Hypotheses

Not applicable.

9.2. Sample Size Determination

The sample size is based on PK rather than statistical considerations. A total sample size of 48 subjects (6 subjects each in the control cohorts [Cohort 1 and 5] and 12 subjects each in the combination cohorts [Cohorts 2, 3, and 4]) will serve to estimate bioavailability.

9.3. Populations for Analyses

The analysis sets are defined in Table 8.

Table 8: Study ALXN1210-HV-105 Analysis Sets

Set	Description
Safety	All subjects who receive at least 1 dose of study drug
Pharmacokinetic	All subjects who have sufficient serum concentration data to enable the calculation of PK parameters
Pharmacodynamic	All subjects who have sufficient total and free C5 concentration data and cRBC hemolysis data which will enable the evaluation of the PD effects
Immunogenicity	All subjects who have a predose and post-dose ADA sample collected

Abbreviations: ADA = antidrug antibody; C5 = complement component 5; cRBC = chicken red blood cell; PD = pharmacodynamic(s); PK = pharmacokinetic(s).

9.4. Statistical Analyses

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

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

9.4.1. Efficacy Analyses

No efficacy analyses will be performed for this study.

9.4.2. Safety Analyses

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

Safety analyses will include an analysis of all AEs, 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 incidence of AEs and SAEs will be summarized, by 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 AEs resulting in withdrawal from the study will be listed. Subjects having multiple AEs within a category (eg, overall, SOC, Preferred Term) will be counted once in that category. For severity tables, a subject'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 CTCAE. Shift tables by cohort will be produced for these laboratory parameters. These tables will summarize the number of subjects 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 subjects 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 World Health Organization Drug Dictionary, and the frequency and percentage of concomitant medications will be summarized.

9.4.3. Other Analyses

9.4.3.1. Pharmacokinetic Analyses

The individual serum concentration data for ravulizumab IV-, ravulizumab SC/rHuPH20-, ravulizumab SC-treated subjects, with actual sampling dates and times, will be used to derive the PK parameters by noncompartmental analyses methods using Phoenix WinNonlin 6.3 or higher.

The following PK parameters will be derived: maximum observed serum concentration (C_{max}), time to maximum observed serum concentration (tmax), area under the serum concentration versus time curve from time 0 to the last quantifiable concentration (AUC_t), area under the curve from time 0 (dosing) to time infinity ($AUC_{0-\infty}$), apparent terminal-phase elimination rate constant (λ_z), terminal elimination half-life ($t_{½}$), total clearance (CL) or apparent clearance (CL/F), volume of distribution (V_d) or apparent volume of distribution (V_d/F), absolute bioavailability (F), and relative bioavailability (F_{rel}). The absolute bioavailability for the ravulizumab SC/rHuPH20 cohorts will be defined by the ratio of the geometric means for the $AUC_{0-\infty}$ parameter for the ravulizumab SC/rHuPH20 cohort over the ravulizumab IV cohort. The relative bioavailability for the ravulizumab SC/rHuPH20 cohorts will be defined by the ratio of the geometric means for the $AUC_{0-\infty}$ parameter for the ravulizumab SC/rHuPH20 cohort over the

ravulizumab SC cohort. For the absolute and relative bioavailability estimates, a 95% CI for each of the ratio of the geometric means will be provided.

Additional details will be provided in the SAP.

9.4.3.2. Pharmacodynamic Analyses

The PD effects of ravulizumab SC and IV will be evaluated by assessing changes in serum free C5 concentrations, cRBC hemolysis, and other measures of C5 activation over time as appropriate.

9.4.3.3. Immunogenicity Analysis

Immunogenicity, as measured by ADA, will be summarized for ravulizumab.

9.5. Interim Analyses

An interim assessment of PK data through Day 50 may be performed.

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 International Ethical Guidelines
  - Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Informed Consent Process

The Investigator will ensure that the subject is given full and adequate verbal and written information about the nature, purpose, possible risk, and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated ICF must be obtained before conducting any study procedures, and documented in the subject's study record.

The Investigator must maintain the original of all signed ICF versions. A copy of the signed ICF(s) must be given to the subject.

If emerging study information warrants an update to ICF content, the subject will sign an ICF addendum. The site will retain the original addendum and a copy of the signed addendum will be provided to the subject.

10.1.3. Data Protection

- Subjects will be assigned a unique identifier. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.4. Dissemination of Clinical Study Data

Study-related information and study results may be posted on the US website www.clinicaltrials.gov, and EU website www.clinicaltrialsregister.eu/, or other publically accessible websites as appropriate and in accordance with local regulations.

10.1.5. Data Quality Assurance

- All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects 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. Study monitors will communicate with investigative sites on a regular basis regarding study protocol deviations. All protocol deviations will be appropriately documented by the Investigator or designee, and study monitors.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for a minimum of 5 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 the Sponsor. No records may be transferred to another party without written notification to the Sponsor. Unless otherwise specified, procedures, data collection, and evaluation will be conducted as per the study center's standard operating procedures.

10.1.6. Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. The Investigator or designee will prepare and maintain adequate and accurate source documents (medical records, ECG readings, AE and concomitant medication reporting, raw data collection forms) designed to record all observations and other pertinent data for each subject. Source documents are filed at the Investigator's site.
- Data reported entered in the eCRF 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.

10.1.7. Study and Site Closure

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites 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 a study site by the Sponsor 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, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the Investigator
- Discontinuation of further study drug development

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 9 will be performed by the local laboratory.
- The maximum amount of blood to be collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL. Please refer to the laboratory manual for specific details regarding serum sampling volumes.
- Protocol-specific requirements for inclusion or exclusion of subjects 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. Investigators must document their review of each laboratory safety report and indicate whether out of range results are clinically significant ("CS") or not clinically significant ("NCS").

Table 9: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**		
Hematology	Platelet count Red blood cell (RBC) count Free hemoglobin Hematocrit	RBC Indices: Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) %Reticulocytes	White blood cell (WBC) count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry	Lactate dehydrogenase Blood urea nitrogen (BUN) Potassium	Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) Gamma glutamyltransferase (GGT)	Total and direct bilirubin Indirect bilirubin
	Creatinine Sodium Chloride Potassium	Alanine aminotransferase (ALT)/Serum glutamic-pyruvic transaminase (SGPT)	Total protein
	Glucose (nonfasting) Total carbon dioxide	Alkaline phosphatase	Albumin
Coagulation	Prothrombin time	Partial thromboplastin time	International normalized ratio
Routine Urinalysis (by dipstick)	- Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase - Microscopic examination (if any leucocytes, trace protein, nitrites, and blood [if not menstruating] are abnormal)		
Other Screening Tests	- Serum QuantiFERON-TB test - Urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, benzodiazepines cocaine, opiates, phencyclidine, methamphetamine, 3,4-methylenedioxy-methamphetamine, methadone, and tetrahydrocannabinol [cannabinoids]) - Serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) - Human immunodeficiency virus (HIV)-1 and HIV-2 antibodies, hepatitis B surface antigen (HBsAg), and hepatitis C virus (HCV). The results of each test must be entered into the eCRF.		
Complement Activity	Complement activation products	CH50	Total and free C5

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Adverse Event Definition
• An AE is any untoward medical occurrence in a patient or clinical study subject, 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 Adverse Event 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 of a suspected drug-drug interaction.

Events NOT Meeting the Adverse Event 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.

Serious Adverse Event Definition

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

A serious adverse event is defined as any untoward medical occurrence that, at any dose:
1. Results in death
2. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject 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 subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

A serious adverse event is defined as any untoward medical occurrence that, at any dose:

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 subject 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.

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

Adverse Event and Serious Adverse Event Recording

- When an AE or 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 eCRF.
- It is not acceptable for the Investigator to send photocopies of the subject's medical records to the Sponsor or designee in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission.
- 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 v4.03, published 14 Jun 2010:

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

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

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study drug and each occurrence of each AE/SAE. An Investigator causality assessment must be provided for all AEs (both nonserious and serious). This assessment must be recorded in the data capture system and on any additional forms, as appropriate. The definitions for the causality assessments are as follows:
  - Not related (unrelated): This relationship suggests that there is no association between the investigational product and the reported event.
  - Unlikely related: This relationship suggests that the clinical picture is highly consistent with a cause other than the investigational product, but attribution cannot be made with absolute certainty, and a relationship between the investigational product and AE cannot be excluded with complete confidence.
  - Possibly related: This relationship suggests that treatment with the investigational product may have caused or contributed to the AE; ie, the event follows a reasonable temporal sequence from the time of study drug administration, and/or follows a known response pattern to the investigational product, but could also have been produced by other factors.
  - Probably related: This relationship suggests that a reasonable temporal sequence of the event with the investigational product administration exists, as well as the likely association of the event with the investigational product. This will be based upon the known pharmacological action of the investigational product, known or previously reported adverse reactions to the investigational product or class of drugs, or judgment based on the Investigator's clinical experience.
  - Definitely related: Temporal relationship to the investigational product. 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 Investigator's Brochure as the Reference Safety Document. The expectedness and reporting criteria of an SAE will be determined by the Sponsor, based on the Reference Safety Document. The Investigator will also consult the Investigator's Brochure (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 the Sponsor or designee. 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 the Sponsor or designee.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a 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 the Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor or designee with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of receipt of the updated information.

Reporting of Serious Adverse Events

Serious Adverse Event Reporting to the Sponsor 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 the Sponsor 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.
- 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 eCRF 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)
  - Outcome of the serious event(s)
  - Medical records and laboratory/diagnostic information
- If applicable, additional information such as relevant medical records should be submitted to the Sponsor via the email address or facsimile number noted above.
- All forms and follow-up information submitted to the Sponsor (eg, discharge summary) should be kept in the appropriate section of the study file.

10.4. Appendix 4: 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 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy
   - Note: Documentation can come from the site personnel's review of the subject'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 and a documented serum follicle-stimulating hormone level ≥ 40 mIU/mL during screening. A high FSH level in the postmenopausal range must 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 subjects 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.

Pregnancy Testing

- Women of childbearing potential should only be included after a negative serum pregnancy test. Additional pregnancy testing should be performed per the time points specified in the Schedule of Activities (Table 1 and Table 2).

Collection of Pregnancy Information

- Pregnancy data will be collected during this study for all subjects and a female spouse/partner of male subjects. 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 subject participating in this study or a male subject'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/Breast Feeding Form" to the Sponsor or designee via the same method as

SAE reporting. (Section 10.3 [Appendix 3]). When the outcome of the pregnancy becomes known, the form should be updated and submitted to the Sponsor's GPV. 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 the Sponsor's GPV or designee via facsimile or email (Section 10.3 [Appendix 3]).
- A pregnancy in 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 subject who becomes pregnant while participating in the study may not be withdrawn from the study.

10.5. Appendix 5: Abbreviations

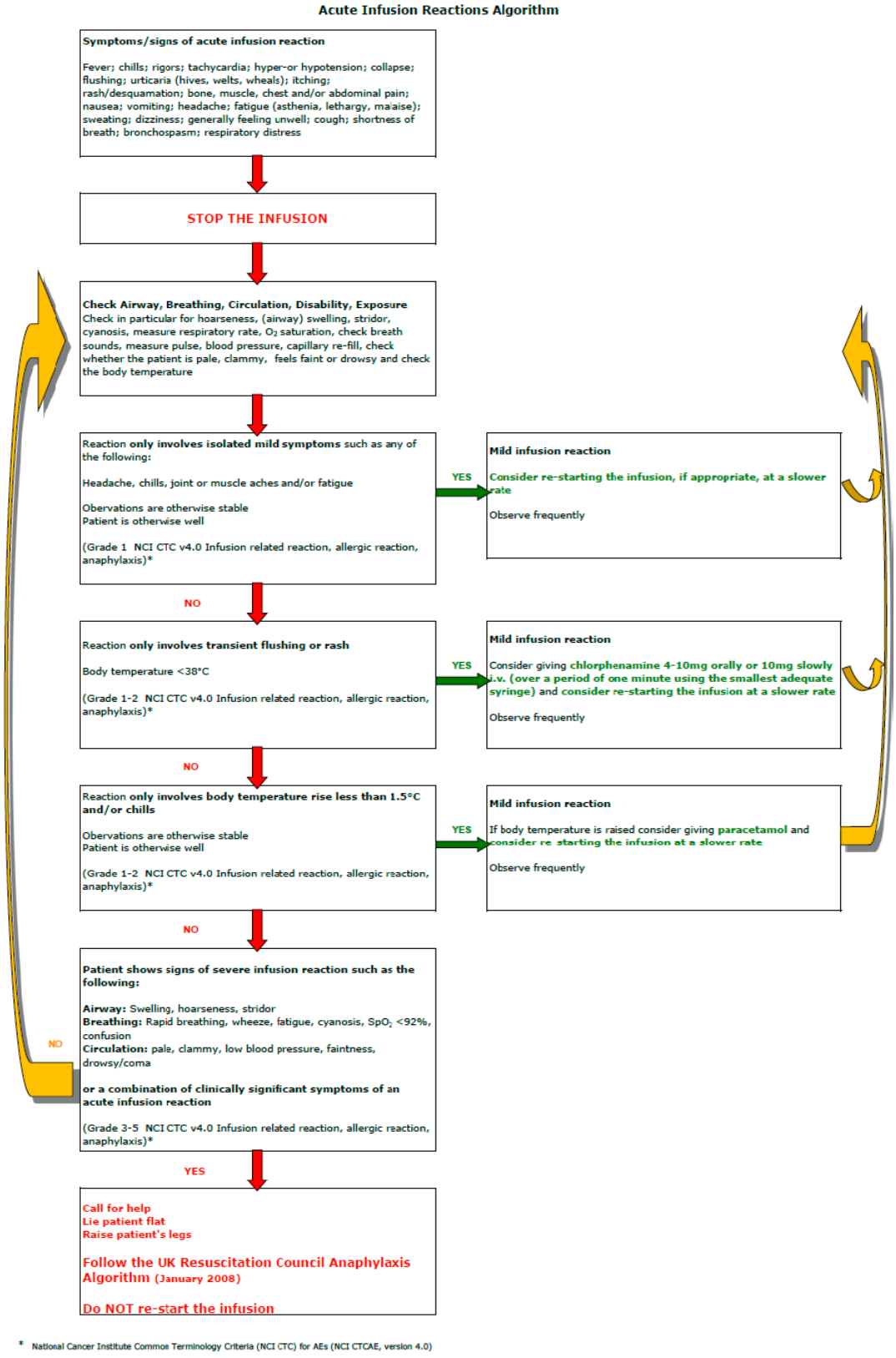
The following abbreviations and terms are used in this study protocol.

Table 10: Abbreviations and Specialist Terms

Abbreviation or Term	Explanation
ADA	antidrug antibody
AE	adverse event
aHUS	atypical hemolytic uremic syndrome
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{∞}	area under the serum concentration versus time curve from zero to infinity
BMI	body mass index
CAP	complement alternative pathway
CH50	50% hemolytic complement activity (screening test for deficiency of classical complement pathway in which hemolysis of liposomes sensitized by specific antibodies is measured; one CH50 unit is the volume or dilution of serum that lyses 50% of liposomes)
CL	total body clearance of drug from the serum
C_{max}	maximum observed serum concentration
cRBC	chicken red blood cell
CRU	clinical research unit
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
EOI	End-of-infusion
F	absolute bioavailability
F_{rel}	relative bioavailability
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GPV	Global Pharmacovigilance
HA	hyaluronic acid
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HIV	Human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IRB	institutional review board
IV	intravenous(ly)
mAb	monoclonal antibody
MCV4	tetravalent meningococcal conjugate vaccine
OP	outpatient
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PNH	paroxysmal nocturnal hemoglobinuria
QTcF	QT interval corrected using the Fridericia's formula

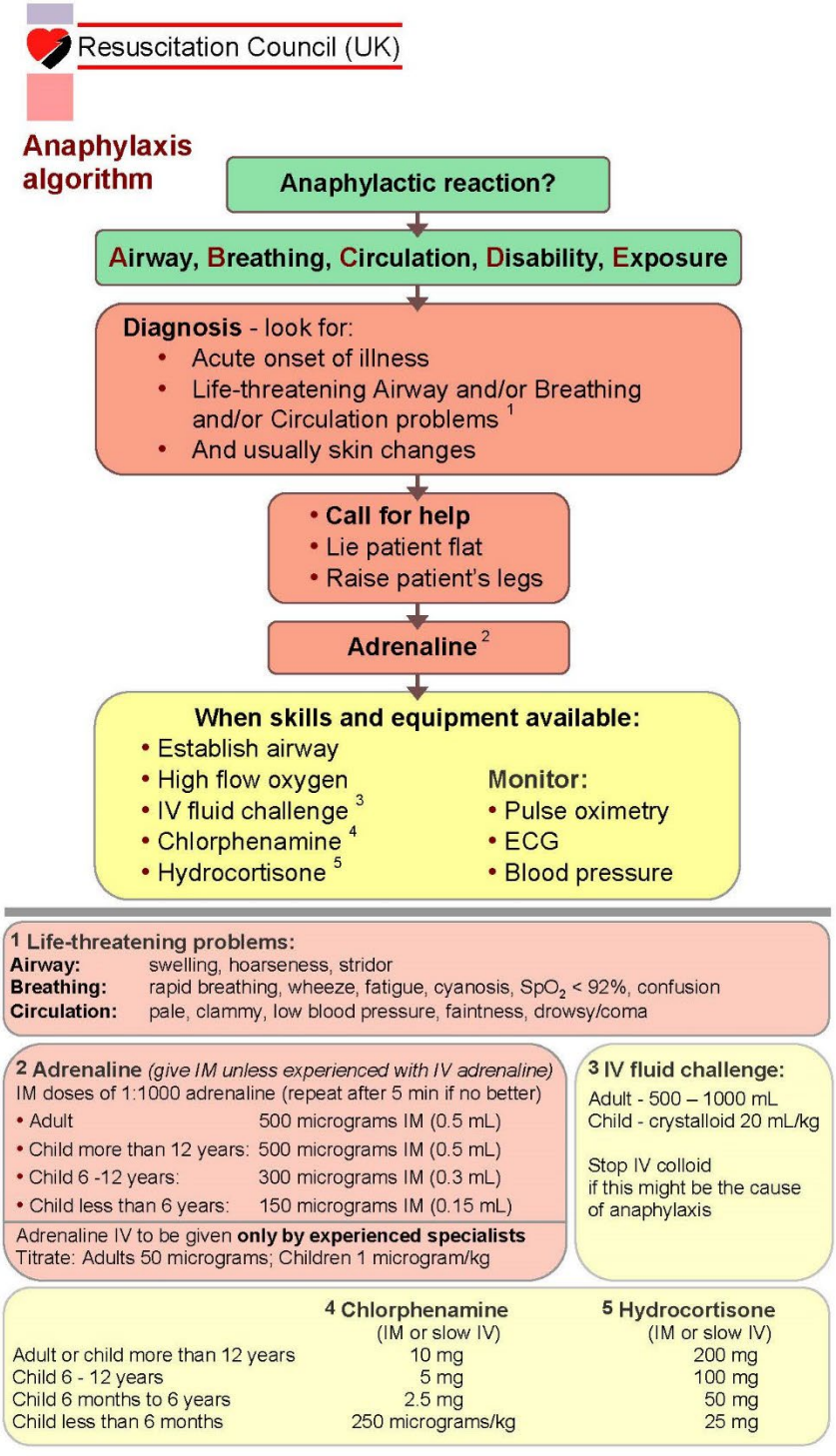
Abbreviation or Term	Explanation
rHuPH20	recombinant human hyaluronidase PH20
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SOC	System Organ Class
SOI	Start-of-infusion
SRC	Safety Review Committee
TB	tuberculosis
TEAE	treatment-emergent adverse events
ULN	upper limit of normal
V_d	volume of distribution

10.6. Appendix 6: Acute Infusion Reaction Algorithm



* National Cancer Institute Common Terminology Criteria (NCI CTC) for AEs (NCI CTCAE, version 4.0)

10.7. Appendix 8: United Kingdom Resuscitation Council Anaphylaxis Algorithm



10.8. Appendix 10: Protocol Amendment History

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

Amendment 1 (20 Jul 2018)

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

Overall Rationale for the Amendment

To align contraception language with national guidelines and address minor inconsistencies as described below.

Section # and Name	Description of Change	Brief Rationale
Section 5.2 Exclusion Criteria	Changed exclusion criterion no. 16 for use of nonprescription medications from 7 days to 14 days prior to dosing on Day 1.	Alignment of exclusion criterion with requirements stated in Section 6.5, Concomitant Therapy.
Table 2: Schedule of Activities – Visit 2 Through Visit 14	Added pregnancy testing on Day 57 and Day 120.	Additional pregnancy testing is appropriate for a trial in healthy subjects with requirements for highly effective contraception for an extended period.
Section 6.6 Contraception Guidance	• Removed definition of non-childbearing potential, replaced with cross reference to Appendix where required information is presented. • Replaced definition of highly effective contraception. • Added restriction on ova donation for female subjects.	Alignment with guidelines from Clinical Trial Facilitation Group (CFTG).
Section 10.4 Appendix 4: Pregnancy Information	Added specific FSH level requirement for establishing postmenopausal state.	Clarification.

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