Official Title:	**A Phase 1/2 Single-ascending and Multiple-ascending Dose, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics Study of Subcutaneously Administered ALN-CC5 in Healthy Adult Volunteers and Patients with Paroxysmal Nocturnal Hemoglobinuria**
NCT Number:	**NCT02352493**
Document Date:	**Amendment 5, 12 June 2017**

CLINICAL STUDY PROTOCOL

ALN-CC5-001

A Phase 1/2 Single-ascending and Multiple-ascending Dose, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics Study of Subcutaneously Administered ALN-CC5 in Healthy Adult Volunteers and Patients with Paroxysmal Nocturnal Hemoglobinuria

Final Protocol:	21 November 2014
Amendment 1:	08 December 2014
Amendment 2:	16 June 2015
Amendment 3:	13 November 2015
Amendment 4:	16 August 2016
Amendment 5	12 June 2017
EUDRACT Number:	2014-002462-69
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: 617-551-8200 Fax: 617-551-8101
Sponsor Contact:	[redacted]

Signature

12 JUNE 2017

Date

The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without expressed written authorization of Alnylam Pharmaceuticals, Inc.

The study will be completed according to guidelines of Good Clinical Practice. Compliance with this practice provides public assurance that the rights, safety, and well-being of study subjects are protected consistent with the principles that have their origin in the Declaration of Helsinki.

INVESTIGATOR'S AGREEMENT

I have read the protocol for study ALN-CC5-001 and agree to conduct the study as outlined. I 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 SYNOPSIS

Name of Sponsor/Company: Alnylam Pharmaceuticals, Inc.

Name of Investigational Product: ALN-CC5

Name of Active Ingredient: [redacted]

Title of Study: A Phase 1/2 Single-ascending and Multiple-ascending Dose, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics Study of Subcutaneously Administered ALN-CC5 in Healthy Adult Volunteers and Patients with Paroxysmal Nocturnal Hemoglobinuria

Study center(s): This multinational study will be conducted at up to 6 clinical study centers.

Studied period: It is anticipated that this study will last for a maximum of 3 years from screening through the last subject/patient, last visit. End of study is defined as last subject/patient, last visit. It is anticipated that the duration of study participation for a subject/patient will be 665 days (1 year and 10 months).	**Phase of development:** 1/2

Objectives:

Primary:

- To evaluate the safety and tolerability of single-ascending doses (SAD) or multiple-ascending doses (MAD) of ALN-CC5 when administered to healthy adult subjects and of multiple doses (MD) in patients with paroxysmal nocturnal hemoglobinuria (PNH)

Secondary:

- To characterize the pharmacokinetics (PK) of ALN-CC5
- To assess the pharmacodynamic (PD) effect of ALN-CC5 on levels of complement component 5 (C5) protein and complement activity

Exploratory:

- To assess the PD effect of ALN-CC5 on inhibition of hemolysis in healthy adult subjects and in patients with PNH
- [redacted]
- To explore the PD effect of ALN-CC5 on lactate dehydrogenase (LDH) levels in patients with PNH
- [redacted]
  - Eculizumab levels
  - [redacted]

Methodology: This study is designed to evaluate the safety, tolerability, PK, and PD of ALN-CC5 in a randomized, double-blind, placebo-controlled manner in healthy adult subjects and in an open-label manner in patients with PNH. A Safety Review Committee (SRC) will perform regular reviews (at predefined decision-making time points) of safety, tolerability, and available PD data collected during the study with the primary purpose of protecting the safety of subjects and patients participating in the study. The study will be conducted in the following parts:

- **Part A:** SAD phase in healthy adult subjects
- **Part B:** MAD phase in healthy adult subjects
- **Part C:** multiple dose phase in patients with confirmed PNH who are either naïve to, or on a stable dose of, eculizumab (as assessed by the Investigator)

Part A: Subjects will be screened from -90 to -2 days before study drug administration. Eligible subjects will be admitted to the clinical study site on Day -1 to determine continued eligibility and for pretreatment assessments. Subjects will be randomized on Day 0 and will receive a single dose of study drug. Subjects will be discharged from the clinical study site after completing the 24 hour postdose follow-up assessments.

Subjects will return to the clinical study site on an outpatient basis for safety, tolerability, PK, and PD monitoring at specified time points through the last postdose follow-up visit (Day 70). For subjects with serum complement activity below normal range at Day 70, monitoring visits will occur every 28±7 days until serum complement activity is within the normal reference range as assessed by complement alternative pathway (CAP) enzyme-linked immunosorbent assay (ELISA) or until the SRC makes a decision on a case-by-case basis to discontinue follow-up, whichever is sooner. The decision cannot be made until after completion of the last postdose follow-up visit.

Subjects in each cohort will be randomized in a 3:1 ratio (ALN-CC5:placebo) in a double-blind, placebo-controlled manner. Study drug will be administered according to a sentinel dosing strategy. The first sentinel subject in each cohort will receive study drug (ALN-CC5 or placebo) followed by an approximately 24 hour safety follow-up. The second sentinel subject in each cohort will then receive study drug (ALN-CC5 or placebo) followed by an approximately 24 hour safety follow-up, after which remaining subjects in the cohort will be dosed.

The starting dose for subjects in Cohort 1 will be 50 mg of study drug (ALN-CC5 or placebo). The following are planned dose levels for subsequent cohorts in Part A; however, the actual dose administered will be determined by the SRC:

- Cohort 2: 200 mg
- Cohort 3: 400 mg
- Cohort 4: 600 mg
- Cohort 5: 900 mg

The highest dose of study drug proposed for Part A will not exceed 900 mg.

Part B: Subjects will be screened from -90 to -2 days before dose administration. Eligible subjects will be admitted to the clinical study site on Day -1 to determine continued eligibility and for pretreatment assessments. Subjects will be randomized on Day 0 and will receive an initial dose of study drug. Subjects will be discharged from the clinical study site following the completion of the 24 hour postdose follow-up assessments. Subjects will return to the clinical study site for study drug administration and safety, tolerability, PK, and PD monitoring over the treatment period and for postdose follow-up. For subjects with serum complement activity below normal range at the last postdose follow-up visit, monitoring visits will occur every 28±7 days until serum complement activity

is within the normal reference range as assessed by CAP ELISA or until the SRC makes a decision on a case-by-case basis to discontinue follow-up, whichever is sooner. The decision cannot be made until after completion of the last postdose follow-up visit.

Dose levels for Part B will be selected after SRC review of safety, tolerability, and available PD data from Part A. Dosing in each Part B cohort will begin at a dose that is no greater than the highest safe and tolerated dose explored in Part A. If recommended by the SRC, weekly, once every 2 weeks, or monthly dosing regimens to assess safety and PD parameters, and corresponding PK sampling schedules may be investigated. Subjects in each cohort will be randomized in a 3:1 ratio (ALN-CC5:placebo) in a double-blind, placebo-controlled manner. The following are planned dose levels for subsequent Part B cohorts; however, the actual dose administered will be determined by the SRC:

- Cohort 1: 50 mg
- Cohort 2: 200 mg
- Cohort 3: 400 mg
- Cohort 4: 600 mg

The highest dose of study drug proposed for Part B will not exceed 600 mg.

Part C: The start of Part C and the study drug dose will depend on SRC review of safety, tolerability, and available PD data from Part A and Part B. A maximum of 3 cohorts comprised of at least 4 patients each will be enrolled in Part C.

Patients will be screened from -90 to -2 days before dose administration. Patients will have a consultation at the clinical study site on Day -1 to determine continued eligibility and for pretreatment assessments. Patients will be admitted and dosed on Day 0. Patients will be discharged from the clinical study site following the completion of the 24 hour postdose follow up assessments. Patients will return to the clinical study site for study drug administration and for safety, tolerability, PK, and PD monitoring over the treatment period and for postdose follow-up. For patients with serum complement activity below normal range at the last postdose follow-up visit, monitoring visits will occur every 28±7 days until serum complement activity is within the normal reference range as assessed by CAP ELISA or until the SRC makes a decision on a case-by-case basis to discontinue follow-up, whichever is sooner. The decision cannot be made until after completion of the last postdose follow-up visit.

During the dosing period, the SRC will meet at regular intervals to recommend cohort initiation and the dose and regimen to be administered to all patients in a cohort or all patients in Part C. Dosing will begin at a dose no greater than the highest safe and tolerated dose explored in Part B. During the dosing period, the SRC may recommend the ALN-CC5 dose and regimen be modified for all patients, based on safety, tolerability, and available PD, including the degree of complement inhibition and clinically meaningful suppression of intravascular hemolysis as evaluated by LDH. Weekly, once every 2 weeks, or monthly dosing regimens may be investigated. The SRC may recommend de-escalation to a lower dose and regimen or re-escalation to a higher dose and regimen.

Optional Cohorts: Based on the evaluation of safety, tolerability, and available PD data, it may be decided by the SRC that optional cohorts may be enrolled and dosed according to the same eligibility criteria, corresponding randomization scheme, and sentinel dosing strategy detailed in Part A and Part B. In both Part A and Part B, up to 3 exploratory cohorts (exploring additional dosing and/or dose regimen) may be added. The dose levels for optional cohorts may be at intermediate dose levels compared to those administered in Part A and Part B, but will not exceed 900 mg and 600 mg, respectively, provided the dose is considered safe and tolerable.

Number of subjects (planned): Up to 76 subjects will be enrolled in the study.

- Part A: Up to 32 healthy adult subjects (including optional cohorts)
- Part B: Up to 28 healthy adult subjects (including optional cohorts)
- Part C: Up to 16 patients with confirmed PNH (approximately 8 patients on a stable dose of eculizumab as assessed by the Investigator)

Diagnosis and eligibility criteria for Part A and Part B: Adult healthy subjects meeting the following eligibility criteria will be enrolled in Part A or Part B.

Inclusion Criteria:

1. Male and female subjects aged 18 to 45 years, inclusive.
2. 12-lead electrocardiogram (ECG) within normal limits or with no clinically significant abnormalities in the opinion of the Investigator.
3. Body mass index $\geq$18.0 kg/m^2 and $\leq$30 kg/m^2.
4. Systolic blood pressure $\leq$140 mmHg and a diastolic blood pressure of $\leq$90 mmHg after 10 minutes supine rest.
5. Female subjects of childbearing potential agreeing to use one of the acceptable methods of contraception listed below from the time of signing the informed consent until 5 months following administration of the last dose of study medication:
   - The subject's male partner has undergone documented vasectomy with documentation of azoospermia (male sterilization) and the use of a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
   - A documented placement of an intrauterine device (IUD) or intrauterine system (IUS) and the use of a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
   - Oral contraceptives (combination estrogen/progesterone pills), injectable progesterone, or subdermal implants and the use of a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository]).
   - Documented tubal ligation (female sterilization). In addition, a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
   - True abstinence: when this is in line with the preferred and usual lifestyle of the subject, including female subjects with same sex partners. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent subjects have to agree to use one of the above-mentioned contraceptive methods, if they start sexual relationships during the study and for up to 5 months after the last dose of study drug.
6. Male subjects agreeing to use acceptable methods of contraception if the male subject's partner could become pregnant from the time of the first administration of study medication until 5 months following administration of the last dose of study medication. One of the following acceptable methods of contraception must be utilized:
   - Surgical sterilization (vasectomy with documentation of azoospermia) and a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).

- The subject's female partner uses oral contraceptives (combination estrogen/progesterone pills), injectable progesterone, or subdermal implants and a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
- The subject's female partner uses medically prescribed topically-applied transdermal contraceptive patch and a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
- The subject's female partner has undergone documented tubal ligation (female sterilization). In addition, a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository) must be used.
- The subject's female partner has undergone documented placement of an IUD or IUS and the use of a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
- True abstinence: when this is in line with the preferred and usual lifestyle of the subject, including male subjects with same sex partners. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent subjects have to agree to use one of the above-mentioned contraceptive methods, if they start sexual relationships during the study and for up to 5 months after the last dose of study drug.

7. Vaccinated against *Neisseria meningitides* with meningococcal group A, C, W-135, and Y (ACWY) conjugate vaccine and meningococcal group B vaccine and confirmed seroconversion to ACWY on Day -1.
8. Willing to comply with protocol-required visit schedule and visit requirements and provide written informed consent.
9. Light smokers and users of nicotine (defined as the equivalent of 10 cigarettes per day) or nonsmokers and non-users of nicotine.

Exclusion Criteria for all Subjects in Part A and Part B:

1. Any uncontrolled or serious disease, or any medical or surgical condition, that may either interfere with participation in the clinical study and/or put the subject at significant risk (according to Investigator's judgment) if he/she participates in the clinical study.
2. A known underlying disease, or surgical or medical condition that, in the opinion of the Investigator, may interfere with interpretation of the clinical study results.
3. Active serious mental illness or psychiatric disorder, including, but not limited to, schizophrenia, bipolar disorder, or severe depression requiring current pharmacological intervention.
4. Clinically significant illness within the 7 days before administration of the first dose of study drug.
5. Alanine aminotransferase (ALT) or aspartate aminotransferase above the normal range; total bilirubin, alkaline phosphatase, or albumin outside the reference range and considered clinically relevant in the opinion of the Investigator at screening and Day -1.
6. Complete blood count (CBC) laboratory results that are considered clinically relevant and unacceptable by the Investigator at screening and Day -1.
7. International normalized ratio above the reference range at the Screening visit.

8. Complement activity below normal reference range as evaluated by CAP ELISA.
9. Known or suspected hereditary asymptomatic complement deficiency.
10. Any other clinical safety laboratory test result considered clinically significant and unacceptable by the Investigator.
11. Clinical laboratory evidence or clinical diagnosis of human immunodeficiency virus (HIV) infection, hepatitis C virus (HCV) infection, or chronic hepatitis B virus (HBV) infection (as shown by hepatitis B surface antigen [HBsAg] positivity).
12. Positive screen for alcohol or drugs of abuse at screening and Day -1 and consume more than 14 (female) or 21 (male) units of alcohol a week (unit: 1 glass of wine [125 mL] = 1 measure of spirits = ½ pint of beer).
13. History or clinical evidence of alcohol abuse, within the 12 months before screening. Alcohol abuse is defined as regular weekly intake of more than 21 units for males and 14 units for females (using alcohol tracker http://www.nhs.uk/Tools/Pages/NHSAlcoholtracker.aspx).
14. History or clinical evidence of drug abuse, within the 12 months before screening. Drug abuse is defined as compulsive, repetitive, and/or chronic use of drugs or other substances with or without problems related to their use and/or where stopping or a reduction in dose will lead to withdrawal symptoms.
15. Donated more than 500 mL of blood within 90 days before the first dose of study drug.
16. Received an investigational agent (including complement C5 inhibitors) within 90 days before the first dose of study drug or are in follow-up of another clinical study.
17. Used prescription medications within 14 days or 7 half-lives (whichever is longer) of administration of the first dose of study drug.
18. Used over-the-counter medication, excluding routine vitamins, within 7 days before the first dose of study drug, unless determined by the Investigator and Sponsor to be not clinically relevant, and unlikely to impact on study outcomes.
19. History of intolerance to subcutaneous (SC) injection or relevant abdominal scarring (surgical, burns, etc.).
20. History of meningococcal infection.
21. History of vaccinations with evidence of insufficient immunizations.
22. History of significant recurrent infections in the opinion of the Investigator or delegate.
23. Presence or suspicion of active viral, bacterial, fungal, or parasitic infection including herpes, herpes zoster, or cold sores within 14 days before the first study drug administration (patients may be rescreened).
24. Subjects who have had their spleen removed for any reason.
25. History of multiple drug allergies or history of allergic reaction to an oligonucleotide or N-acetylgalactosamine (GalNAc).
26. Known hypersensitivity or contraindication to any medication, including any vaccine component, or current manifestation of any significant allergic disorder.
27. Clinically significant allergic reactions to antibiotics in the opinion of the Investigator and not willing to use antibiotic prophylaxis as specified in protocol.
28. Legal incapacity or limited legal capacity.
29. Any other conditions which, in the opinion of the Investigator, would make the subject unsuitable for enrollment or could interfere with the subject's participation in or completion of the study.
30. Travelled to Saudi Arabia or Africa within 90 days of screening, or who plan to do so during the study (patients may be rescreened).

31. Women who are pregnant or breastfeeding.

Diagnosis and Eligibility Criteria for Part C: Adult patients with PNH meeting the following eligibility criteria will be enrolled in Part C.

Inclusion Criteria

1. Adults aged minimum 18 years at screening.
2. Granulocyte and monocyte PNH clone >1% as documented by medical records.
3. LDH ≥1.5 upper limit of normal (ULN) in the absence of eculizumab. If on stable eculizumab therapy, as assessed by the Investigator, patients must have historical laboratory values documenting elevated LDH levels before administration of the first dose of eculizumab.
4. Female patients of childbearing potential agreeing to use one of the acceptable methods of contraception listed below from the time of signing the informed consent until 5 months following administration of the last dose of study medication:
   - The subject's male partner has undergone documented vasectomy with documentation of azoospermia (male sterilization) and the use of a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
   - A documented placement of an IUD or IUS and the use of a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
   - Oral contraceptives (combination estrogen/progesterone pills), injectable progesterone, or subdermal implants and the use of a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
   - Documented tubal ligation (female sterilization). In addition, a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
   - True abstinence: when this is in line with the preferred and usual lifestyle of the patient, including female subjects with same sex partners. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent patients have to agree to use one of the above-mentioned contraceptive methods, if they start sexual relationships during the study and for up to 5 months after the last dose of study drug.
5. Male patients agreeing to use acceptable methods of contraception if the male patient's partner could become pregnant from the time of the first administration of study medication until 5 months following administration of the last dose of study medication. One of the following acceptable methods of contraception must be utilized:
   - Surgical sterilization (vasectomy with documentation of azoospermia) and a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
   - The patient's female partner uses oral contraceptives (combination estrogen/progesterone pills), injectable progesterone, or subdermal implants and a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).

- The patient's female partner uses medically prescribed topically-applied transdermal contraceptive patch and a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
- The patient's female partner has undergone documented tubal ligation (female sterilization). In addition, a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository) must be used.
- The patient's female partner has undergone documented placement of an IUD or IUS and the use of a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
- True abstinence: when this is in line with the preferred and usual lifestyle of the patient, including male subjects with same sex partners. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent patients have to agree to use one of the above-mentioned contraceptive methods, if they start sexual relationships during the study and for up to 5 months after the last dose of study drug.

6. Willing to comply with protocol-required visit schedule and visit requirements and provide written informed consent.
7. Vaccinated against *Neisseria meningitides* according to standard practice at the clinical study site.

Exclusion Criteria:

1. History of venous or arterial thromboembolic events within the past 12 months.
2. Active serious mental illness or psychiatric disorder, including, but not limited to, schizophrenia, bipolar disorder, or severe depression requiring current pharmacological intervention.
3. ALT > 2 × ULN and considered clinically relevant in the opinion of the Investigator.
4. CBC laboratory results that are considered clinically relevant and unacceptable by the Investigator.
5. Any other clinical safety laboratory test result considered clinically significant and unacceptable by the Investigator.
6. Known or suspected hereditary asymptomatic complement deficiency.
7. Known clinical laboratory evidence or clinical diagnosis of HIV infection, HCV infection, or chronic HBV infection (as shown by HBsAg positivity).
8. History or clinical evidence of alcohol abuse, within the 12 months before screening. Alcohol abuse is defined as regular weekly intake of more than 21 units for males and 14 units for females (using alcohol tracker http://www.nhs.uk/Tools/Pages/NHSAlcoholtracker.aspx).
9. History of multiple drug allergies or history of allergic reaction to an oligonucleotide or GalNAc.
10. History of intolerance to SC injection or relevant abdominal scarring (surgical, burns, etc.).
11. History of meningococcal infection.
12. Presence or suspicion of active viral, bacterial, fungal, or parasitic infection including herpes, herpes zoster, or cold sores within 14 days before the first study drug administration (patients may be rescreened).
13. Legal incapacity or limited legal capacity at screening.
14. Any other conditions which, in the opinion of the Investigator, would make the patient

unsuitable for enrollment or could interfere with the subject's participation in or completion of the study.

15. Travelled to Saudi Arabia or Africa within 90 days of screening, or who plan to do so during the study (patients may be rescreened).
16. Women who are pregnant or breastfeeding.

Investigational product, dosage, and mode of administration:

ALN-CC5 is a synthetic, chemically modified small interfering RNA targeting CC5 messenger RNA with a covalently attached triantennary GalNAc ligand. ALN-CC5 will be supplied as a sterile 200-mg/mL solution for SC injection.

Duration of treatment:

A single SC dose of study drug will be administered in Part A. In Part B and Part C, respectively, study drug will be administered over a maximum of a 13 or a 39 week period.

Reference therapy, dosage and mode of administration:

Subjects randomized to placebo treatment in Part A or Part B will be administered placebo, which will be supplied by the clinical study site as sterile normal saline 0.9% solution for SC injection.

Criteria for evaluation:

Safety: Safety evaluation will include clinical laboratory safety tests (hematology, biochemistry, coagulation, and urinalysis), vital signs (oral body temperature, blood pressure, heart rate, and respiration rate), physical examinations, 12-lead ECGs, concomitant medications, and adverse event monitoring. [redacted] will be measured in subjects and patients

Pharmacodynamics: PD analysis will include assessment of the impact of ALN-CC5 administration on plasma levels of C5 protein (assessed by ELISA and/or mass spectrometry-based methods) and serum complement activity (assessed by CAP ELISA and complement classical pathway ELISA assays).

Pharmacokinetics: Blood and urine samples will be collected for assessment of ALN-CC5 PK parameters and possible metabolite analysis. PK parameters include, but are not limited to, maximum plasma concentration, time to reach maximum plasma concentration, area under the plasma concentration versus time curve, and apparent terminal elimination half-life.

Exploratory: Exploratory assessments include inhibition of hemolytic activity (assessed by sensitized sheep red blood cell [RBC] and[redacted]) [redacted] will be assessed only in subjects consenting to the procedure. Exploratory assessments in patients with PNH include, but are not limited to, LDH levels,[redacted] eculizumab levels (patients on stable doses of eculizumab only),[redacted]

Statistical Methods: Statistical analyses will be primarily descriptive; no formal hypotheses will be tested. Data will be analyzed separately for Part A and Part B by ALN-CC5 dosing cohorts versus placebo. Descriptive statistics will be presented for continuous variables, and frequencies and percentages will be presented for categorical and ordinal variables. Percentages will be based on the number of non-missing values in a dose group. All study data will be also presented in a listing for each subject/patient.

In Part C, data will be analyzed by cohort for patients on the same dose and dose regimen. Additionally, analysis may be based on patients who are either naïve to eculizumab treatment or on stable doses of eculizumab (as assessed by the Investigator).

Table 1: Schedule of Assessments for Single-ascending Dose Cohorts (Part A)

Study Stage		Treatment			Postdose Follow-up								
Study Day (D)	Screening	D-1[a]	D0	D1[b]	D2	D7	D14	D21	D28	D42	D56	D70/ET	PD Follow-up[c]
Visit Window (± Days)	D-90 to D-2	–	–	–	–	±1	±2	±3	±3	±4	±4	±7	every 28±7days
Informed Consent	X												
Vaccination against *Neisseria meningitides*[d]	X												
Vaccination titer[d]	X	X											
Antibiotic compliance check[e]			X	X	X	X	X	X	X	X	X	X	X
Demography	X												
Medical history	X												
Inclusion/exclusion criteria	X	X											
Full physical examination[f]	X											X	
Directed physical examination[f]		X	X	X	X	X	X	X	X	X	X		
Body weight and BMI calculation	X	X											
Height	X												
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG[h]	X	X	X	X								X	
β-HCG pregnancy test	X	X							X		X		
FSH screening	X												
Viral serology[i]	X												
Biochemistry, hematology, and coagulation[j]	X	X		X	X[k]	X[k]	X	X[k]	X	X	X	X	
Urinalysis[j]	X	X			X	X	X	X	X	X	X	X	
Urine DOA/alcohol screen	X	X											
Randomization			X										
Study drug administration[l]			X										
Blood and urine samples for PK analysis			X[m]	X[m]	X	X	X	X	X	X	X		

Table 1: Schedule of Assessments for Single-ascending Dose Cohorts (Part A)

Study Stage		Treatment			Postdose Follow-up								
Study Day (D)	**Screening**	**D-1[a]**	**D0**	**D1[b]**	**D2**	**D7**	**D14**	**D21**	**D28**	**D42**	**D56**	**D70/ET**	**PD Follow-up[c]**
Visit Window (± Days)	**D-90 to D-2**	–	–	–	–	**±1**	**±2**	**±3**	**±3**	**±4**	**±4**	**±7**	**every 28±7days**
Plasma C5 sampling[n]	X	X	X		X	X	X	X	X	X	X	X	X
Serum complement activity[o]	X	X	X		X	X	X	X	X	X	X	X	X
[redacted]			X				X					X	
[redacted]			X	X		X							
[redacted]		X											
Concomitant medications	X												
Review/record AEs			X[r]										

Abbreviations: ACWY = *Neisseria meningitides* serogroups A, C, W-135, and Y; AE = adverse event; β-HCG = beta-human chorionic gonadotropin; BMI = body mass index; C5 = component 5; CAP ELISA = complement alternative pathway enzyme-linked immunosorbent assay; CCP = complement classic pathway; D = day; DOA = drugs of abuse; ECG = electrocardiogram; ET = early termination; FSH = follicle-stimulating hormone; ISR = injection site reaction; PK = pharmacokinetic; SC = subcutaneous.

NOTE: On days when study drug is administered, assessments are performed predose only, unless otherwise noted; during postdose follow-up, assessments will be performed at any time during the visit, unless otherwise noted.

a. Subjects will be admitted to the clinical study site for predose assessments.
b. Subjects will be discharged from the clinical study unit following the completion of 24 hour postdose assessments. Remaining study visits will be completed on an outpatient basis.
c. For subjects with serum complement activity below normal range at the last postdose follow-up study visit, monitoring visits will occur until serum complement activity is within the normal reference range as assessed by CAP ELISA or until the SRC makes a decision on a case-by-case basis to discontinue follow-up, whichever is sooner (see Section 3.5.3).
d. Subjects will be vaccinated against *Neisseria meningitides* with meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine, and have a positive titer for ACWY before receiving the first dose of study drug. The vaccination program can take place at any time within the screening window. See Section 10.1.8 for vaccination program requirements.
e. Subjects will be treated with prophylactic ciprofloxacin (according to standard practice at the clinical study sites) from start of dosing with study drug through at least the Day 70 study visit and until serum complement activity, as assessed by CAP ELISA returns to within the normal reference range or until the SRC makes a decision on a case-by-case basis to discontinue follow-up and antibiotic prophylaxis, whichever is sooner (see Section 10.1.9 and Section 3.5.3).
f. See Section 10.1.4 for assessments to be performed during full and directed physical examination.
g. Vital signs include blood pressure, heart rate, oral body temperature, and respiratory rate. Vital signs will be measured in the supine position after the subject has rested comfortably for 10 minutes. On Day 0, vital signs assessments should be collected predose (-60 minutes); and 30±5 minutes and 4 hours (±15 minutes) postdose.
h. 12-lead ECGs will be measured in the supine position after the subject has rested comfortably for 10 minutes. On Day 0, the ECG should be performed postdose (±4 hours). After Day 0, the ECG should be performed up to 12 hours after administration of subsequent doses of study drug.
i. See Section 10.1.7.4 for viral serology parameters.
j. Biochemistry, hematology, coagulation, and urinalysis parameters are described in Section 10.1.7.
k. Collect blood samples for biochemistry and hematology only.
l. SC injection of study drug (ALN-CC5 or placebo) per the Study Drug Administration Manual.
m. Details regarding time points for collection of blood and urine samples for full PK analysis are outlined in Table 10 in the appendix (Section 18).

n. C5 levels will be measured by ELISA and/or mass spectrophotometry in a central laboratory.
o. Serum complement activity includes: CAP ELISA and CCP ELISA.
p. [redacted]
q. For patients in the optional cohorts, consenting to the procedure, a blood sample for [redacted] will be collected anytime during the study. Samples will be analyzed at a central laboratory.
r. See Section 10.4.2.1 for handling of ISRs.

Table 2: Schedule of Assessments for Multiple-ascending Dose Cohorts (Part B) – 5 Weekly Doses

Study Stage	Screening	Weekly Dosing (5 Weeks only)												Postdose Follow-up								PD Follow-up[c]
Study Day (D)		D-1[a]	D0	D1[b]	D2	D7[a]	D8[b]	D14[a]	D15[b]	D21[a]	D22[b]	D28[a]	D29[b]	D30	D35	D42	D56	D70	D84	D112	D140/ET	
Visit Window (± Days)	D-90 to D-2														±3	±4	±4	±4	±4	±4	±4	every 28±7 days
Informed Consent	X																					
Vaccination against *Neisseria meningitides*[d]	X																					
Vaccination titer[d]	X	X																				
Antibiotic compliance check[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Demography	X																					
Medical history	X																					
Inclusion/exclusion criteria	X	X																				
Full physical examination[f]	X																				X	
Directed physical examination[f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Body weight and BMI calculation	X	X				X		X		X		X										
Height	X																					
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG[h]	X	X	X	X		X		X		X		X									X	
β-HCG pregnancy test	X	X										X					X		X	X	X	
FSH screening	X																					
Viral serology	X																					
Biochemistry, hematology, and coagulation[j]	X	X	X[k]	X		X[k]	X	X[k]	X	X[k]	X	X[k]	X		X	X[k]	X[k]	X[k]	X[k]	X[k]	X	
Urinalysis[j]	X	X	X	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	
Urine DOA/alcohol screen	X	X																				
Randomization			X																			
Study drug administration[l]			X			X		X		X		X										
Blood and urine samples for PK			X[m]	X[m]	X[m]	X[n]		X[n]		X[n]		X[m]	X[m]	X[m]	X	X	X					

Table 2: Schedule of Assessments for Multiple-ascending Dose Cohorts (Part B) – 5 Weekly Doses

Study Stage	Screening	Weekly Dosing (5 Weeks only)												Postdose Follow-up								PD Follow-up[c]
Study Day (D)		D-1[a]	D0	D1[b]	D2	D7[a]	D8[b]	D14[a]	D15[b]	D21[a]	D22[b]	D28[a]	D29[b]	D30	D35	D42	D56	D70	D84	D112	D140/ET	
Visit Window (± Days)	D-90 to D-2														±3	±4	±4	±4	±4	±4	±4	every 28±7 days
analysis																						
Plasma C5 sampling[o]	X	X	X		X	X		X		X		X		X	X	X	X	X	X	X	X	X
Serum complement activity[p]	X	X	X		X	X		X		X		X		X	X	X	X	X	X	X	X	X
[redacted]			X																		X	
[redacted]			X	X		X	X	X	X	X	X	X	X									
Concomitant medications	X	X	X																			
Review/record AEs			X[r]																			

Abbreviations: ACWY = *Neisseria meningitides* serogroups A, C, W-135, and Y; AE adverse event; β-HCG = beta-human chorionic gonadotropin; BMI = body mass index; C5 = complement 5; CAP ELISA = complement alternative pathway enzyme-linked immunosorbent assay; CCP = complement classic pathway; D = Day; DOA = drugs of abuse; ECG = electrocardiogram; ET = early termination; FSH = follicle-stimulating hormone; ISR = injection site reaction; PK = pharmacokinetic; SC = subcutaneous.

NOTE: On days when study drug is administered, assessments are performed predose only, unless otherwise noted; during postdose follow-up, assessments will be performed at any time during the visit, unless otherwise noted.

a. Subjects will be admitted to the clinical study site for assessments and study drug administration.
b. Subjects will be discharged from the clinical study unit following the completion of 24 hour postdose assessments.
c. For subjects with serum complement activity below normal range at the last postdose follow-up study visit, monitoring visits will occur until serum complement activity is within the normal reference range as assessed by CAP ELISA or until the SRC makes a decision on a case-by-case basis to discontinue follow-up, whichever is sooner (see Section 3.5.3).
d. Subjects will be vaccinated against *Neisseria meningitides* with meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine, and have a positive titer for ACWY before receiving the first dose of study drug. The vaccination program can take place at any time within the screening window. See Section 7.1.2 for vaccination program requirements.
e. Subjects will be treated with prophylactic ciprofloxacin from the first dose of study drug until serum complement activity returns to within the normal reference range as assessed by CAP ELISA or until the SRC makes a decision on a case-by-case basis to discontinue follow-up and antibiotic prophylaxis, whichever is sooner (see Section 7.1.1 and Section 3.5.3).
f. See Section 10.1.4 for assessments to be performed during a full and directed medical examination.
g. Vital signs include blood pressure, heart rate, oral body temperature, and respiratory rate. Vital signs will be measured in the supine position after the subject has rested comfortably for 10 minutes. On Day 0, vital signs should be collected predose (-60 minutes); and 30±5 minutes and 4 hours (±15 minutes) postdose. After Day 0, vital signs should be collected predose (-60 minutes); and up to 12 hours postdose on days when study drug is administered.
h. 12-lead ECGs will be measured in the supine position after the subject has rested comfortably for 10 minutes. On Day 0, the ECG should be performed predose (-60 minutes); and ±4 hours postdose. After Day 0, the ECG should be performed predose (-60 minutes); and up to 12 hours postdose on days when study drug is administered.
i. See Section 10.1.7.4 for viral serology parameters.
j. Biochemistry, hematology, coagulation, and urinalysis parameters to be measured are described in Section 10.1.7.

k. Collect blood samples for biochemistry and hematology only.
l. SC injection of study drug per the Study Drug Administration Manual.
m. Details regarding time points for collection of blood and urine samples for full PK analysis are outlined in Table 11 in the appendix (Section 18).
n. Collect blood samples for PK analysis predose (-60 minutes) and 60±30 minutes postdose only. Collect urine samples PK analysis predose (-60 minutes) only.
o. C5 levels will be measured by ELISA and/or mass spectrophotometry in a central laboratory.
p. Serum complement activity includes: CAP ELISA and CCP ELISA.
q. [redacted]
r. See Section 10.4.2.1 for handling of ISRs.

Table 3: Schedule of Assessments for Multiple-dose Cohorts (Part C) – 13 Weekly Doses (Cohort 1)

Study Stage	Screening	Consultation	Weekly Dosing (13 Weeks only)															Postdose Follow-up or Transition to Modified Dosing Regimen[a]				PD Follow-up[d]
Study Day (D)		D-1[b]	D0	D1[c]	D7	D14	D21	D28	D35	D42	D49	D56	D63	D70	D77	D84	D85	D98	D112	D126	D140/ET	
Visit Window (± Days)	D-90 to D-2																	±3	±7	±7	±7	every 28±7days
Informed Consent	X																					
Vaccination against *Neisseria meningitides*[e]	X					X																
Demography	X																					
Medical history	X																					
Inclusion/exclusion criteria	X	X																				
Full physical examination[f]	X	X																			X	
Directed physical examination[f]			X	X	X			X				X				X	X	X	X	X		
Body weight and BMI calculation	X	X																				
Height	X																					
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECGs[h]	X	X	X	X																	X	
β-HCG pregnancy test	X	X						X				X				X			X		X	
FSH screening	X																					
Viral serology[i]	X																					
Biochemistry, hematology, and coagulation[j]	X	X	X	X	X[k]	X	X[k]	X	X[k]	X	X[k]	X	X[k]	X	X[k]	X	X[k]	X[k]	X	X[k]	X	
Urinalysis[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood sample for eculizumab level[l]	X		X																			
Study drug administration[m]			X		X	X	X	X	X	X	X	X	X	X	X	X						

Table 3: Schedule of Assessments for Multiple-dose Cohorts (Part C) – 13 Weekly Doses (Cohort 1)

Study Stage		Consul-tation	Weekly Dosing (13 Weeks only)															Postdose Follow-up or Transition to Modified Dosing Regimen[a]				PD Follow-up[d]
Study Day (D)	Screening	D-1[b]	D0	D1[c]	D7	D14	D21	D28	D35	D42	D49	D56	D63	D70	D77	D84	D85	D98	D112	D126	D140/ET	
Visit Window (± Days)	D-90 to D-2																	±3	±7	±7	±7	every 28±7days
Blood and urine samples for PK analysis			X[n]	X[n]												X	X				X	
Plasma C5 sampling[o]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X
Serum complement activity[p]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X
LDH	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X
[redacted]		X		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	
[redacted]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	
[redacted]		X					X				X							X			X	
[redacted]			X					X										X				
[redacted]		X									X							X				
[redacted]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X																					
Review/record AEs			X[r]																			

Abbreviations: ACWY = *Neisseria meningitides* serogroups A, C, W-135, and Y; AE adverse event; β-HCG = beta-human chorionic gonadotropin; BMI = body mass index; C5 = complement 5; CAP ELISA = complement alternative pathway enzyme-linked immunosorbent assay; CCP = complement classic pathway DOA = drugs of abuse; ET = early termination; ECG = electrocardiogram; FSH = follicle-stimulating hormone; LDH = lactate dehydrogenase; PK = pharmacokinetic; [redacted]; SC = subcutaneous.

NOTE: On days when study drug is administered, assessments are performed predose only, unless otherwise noted; during postdose follow-up, assessments will be performed at any time during the visit, unless otherwise noted.

a. After completing the 13 week dosing period, patients may transition to extended dosing on a modified regimen provided the Day 140/ET study visit has not been completed; these patients will resume ALN-CC5 administration at a dose and regimen recommended by the SRC.
b. Patients will be admitted to the clinical study site on Day -1 for assessments and study drug administration.
c. Patients will be discharged from the clinical study site on Day 1 following completion of 24 hour postdose assessments.

d. For patients with serum complement activity below normal range at the last postdose follow-up visit, monitoring visits will occur until serum complement activity is within the normal reference range as assessed by CAP ELISA or until the SRC makes a decision on a case-by-case basis to discontinue follow-up, whichever is sooner (see Section 3.5.3).
e. Patients will have been or will be vaccinated against *Neisseria meningitides* (see Section 10.1.8.2 for vaccination specifications).
f. See Section 10.1.4 for assessments to be performed during a full and directed medical examination.
g. Vital signs include blood pressure, heart rate, oral body temperature, and respiratory rate. Vital signs will be measured in the supine position after the subject has rested comfortably for 10 minutes. On Day 0, vital signs should be collected predose (-60 minutes); and 30±5 minutes and 4 hours (±15 minutes) postdose. After Day 0, vital signs should be collected predose (-60 minutes); and up to 12±1 hours postdose on days when study drug is administered.
h. 12-lead ECGs will be measured in the supine position after the subject has rested comfortably for 10 minutes. On Day 0, the ECG should be performed predose (-60 minutes); and ±4 hours postdose. After Day 0, the ECG should be performed predose (-60 minutes); and up to 12 hours postdose on days when study drug is administered.
i. See Section 10.1.7.4 for viral serology parameters.
j. Biochemistry, hematology, coagulation, and urinalysis parameters to be measured are described in Section 10.1.7.
k. Collect blood samples for biochemistry and hematology only.
l. For patients receiving treatment with eculizumab, a blood sample for the measurement of eculizumab levels will be collected before and 60±30 minutes after each treatment with eculizumab. Single weekly samples will be taken on the weeks between eculizumab treatments on the days that ALN-CC5 is administered. If eculizumab treatment is stopped, weekly samples will be taken, thereafter.
m. SC injection of study drug per the Study Drug Administration Manual. Patients on stable doses of eculizumab will continue receiving treatment concomitantly with ALN-CC5; patients will receive their last dose of eculizumab when at least 2 consecutive measurements of C5 levels demonstrate a degree of suppression consistent with complement inhibition. Patients who are naïve to eculizumab treatment may begin ALN-CC5 administration. ALN-CC5 may be administered at home between visits to the clinical study center by a home healthcare provider trained in the administration of ALN-CC5.
n. Details regarding time points for collection of blood and urine samples for full PK analysis are outlined in Table 13 in the appendix (Section 18).
o. C5 levels will be measured by ELISA and/or mass spectrophotometry in a central laboratory.
p. Serum complement activity includes: CAP ELISA and CCP ELISA.
q. Exploratory [redacted] are described in Section 9.3.
r. See Section 10.4.2.1 for handling of ISRs.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACWY	*Neisseria meningitides* serogroups A, C, W-135, and Y
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AUC	area under the plasma concentration-time curve
BMI	body mass index
C5	complement component 5
CAP	complement alternative pathway
CBC	complete blood count
CCP	complement classical pathway
C_{max}	maximum (peak) plasma drug concentration
CRO	Contract Research Organization
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
DOA	drugs of abuse
DSS	Drug Safety Services (Covance)
ECG	Electrocardiogram
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
[redacted]	[redacted]
[redacted]	[redacted]
ET	early termination
[redacted]	[redacted]
FSH	follicle-stimulating hormone
GalNAc	N-acetylgalactosamine
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GPI	Glycosylphosphatidylinositol

Abbreviation	Definition
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HED	human equivalent dose
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ISR	injection site reaction
IUD	intrauterine device
IUS	intrauterine system
IV	Intravenous
LDH	lactate dehydrogenase
MAC	membrane attack complex
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger RNA
NHP	non-human primate
NOAEL	no observed adverse effect level
OAE	other adverse events
OTC	over-the-counter
PD	pharmacodynamics(s)
PIGA	phosphatidylinositol glycan complementation class A
PK	pharmacokinetic(s)
PNH	paroxysmal nocturnal hemoglobinuria
PT	prothrombin time
PV	Pharmacovigilance (Covance)
[redacted]	[redacted]
QTcB	Bazett-corrected QT interval
RBC	red blood cell
REC	Research Ethics Committee
RNA	ribonucleic acid

Abbreviation	Definition
RNAi	ribonucleic acid interference
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
siRNA	small interfering ribonucleic acid
SRC	Safety Review Committee
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	apparent terminal elimination half-life
TEAE	treatment-emergent adverse events
t_{max}	time to reach maximum plasma concentration
TMF	Trial Master File
[redacted]	[redacted]
TTR	Transthyretin
UK	United Kingdom
ULN	upper limit of normal

1. INTRODUCTION

1.1. Background Information on the Disease to be Treated

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, clonal hematopoietic stem cell disorder of the blood characterized by the destruction of red blood cells (RBCs) by the complement system. The incidence is approximately 1.3 per million per year and the prevalence is 13-20 cases per million [1]. The etiology is an acquired somatic mutation in the phosphatidylinositol glycan class A (PIGA) gene that results in a clone of mature RBCs lacking glycosylphosphatidylinositol (GPI) anchored membrane proteins from their surface (PNH clone). Deficiency of the GPI-anchored complement regulatory glycoproteins, CD55 and CD59, which normally protect cells from the complement system, results in unrestrained complement activation, culminating in the assembly of the membrane attack complex (MAC) and RBC lysis.

The disorder is clinically characterized by intravascular hemolysis, bone marrow failure, and thrombosis. Intravascular hemolysis causes anemia, increased levels of free hemoglobin, and chelation of nitric oxide. Uncontrolled complement activation ultimately results in a variety of symptoms and complications such as thrombosis, extreme fatigue, dysphagia, abdominal pain, pulmonary hypertension, and renal impairment. The magnitude of intravascular hemolysis is a key determinant for the frequency and severity of symptoms. Elevated lactate dehydrogenase (LDH) is reflective of hemolysis and patients with LDH levels greater than 1.5 times the upper limit of normal (ULN) have a higher risk of thrombosis and experience more frequent and more severe symptoms [2, 3]. Up to 50% of patients with PNH have clinically evident bone marrow failure syndromes such as aplastic anemia or myelodysplastic syndrome [4].

The 10-year survival rate in patients with PNH ranges from 63% for diagnoses before 1985 to 92% for diagnoses after 1996; the increased survival rate is presumably attributed to improved standard of care [5]. The most common cause of death is thrombotic events [6]. A small proportion (5 to 15%) of PNH patients may undergo spontaneous remission of their disease [5].

The current gold-standard diagnostic test for PNH is flow cytometry of granulocytes and erythrocytes to detect the presence of CD55, CD59, and other GPI-anchored proteins [7]. Clinical management of PNH is guided by the disease-specific presentations. The majority of patients are offered supportive treatment aiming to mitigate anemia, bone marrow failure, and to treat and prevent thromboembolic events. Bone marrow transplant is considered curative of classical PNH; however, it is associated with significant morbidity and mortality [8]. Approximately 20 to 25% of patients with a PNH clone receive intravenous (IV) treatment with eculizumab (Soliris®), a humanized monoclonal antibody that specifically binds the terminal complement component 5 (C5) and blocks its cleavage to C5a and C5b, and thereby, the initiation of MAC formation, which is the key precursor of hemolysis. The safety and pharmacodynamics (PD) of eculizumab were established in multiple clinical studies [6, 9, 10, 11], leading to its approval for the treatment of PNH in 2007.

Management of PNH has been improved during the past 10 years; however, significant clinical challenges remain and justify further treatment optimization. Despite treatment with eculizumab, patients still experience breakthrough hemolysis caused by inflammatory increase in C5 [12, 13, 14]. Furthermore, eculizumab is administered every 2 weeks via IV infusion affecting the overall quality of life (QOL) of patients [6].

1.2. Background Information on the Product

Alnylam Pharmaceuticals, Inc. is developing ALN-CC5, a synthetic RNA interference (RNAi) therapeutic designed to suppress liver production of C5 protein, for the treatment of PNH. ALN-CC5 comprises a small interfering RNA (siRNA) targeting C5 messenger RNA (mRNA) that is covalently linked to a triantennary N-acetylgalactosamine (GalNAc) ligand.

1.3. Mechanism of RNA Interference

RNAi is a naturally occurring cellular mechanism for regulating gene expression that is mediated by siRNAs. Synthetic siRNAs are short (19-25 base pairs), double-stranded oligonucleotides in a staggered duplex with an overhang at one or both of the 3-prime ends. Such siRNAs can be designed to target the mRNA transcript of a given gene. When formulated for tissue delivery and introduced into cells, the guide (or antisense) strand of the siRNA loads into an enzyme complex called the RNA-induced silencing complex. This enzyme complex subsequently binds to its complementary mRNA sequence, mediating cleavage of the mRNA and the suppression of the target protein encoded by the mRNA [15]. Since unmodified siRNAs are rapidly eliminated and do not achieve significant tissue distribution upon systemic administration [16], various formulations are currently used to target their distribution to tissues, and to facilitate uptake of siRNAs into the relevant cell type. One approach that has been used successfully in vivo, in animal models (including in rodents and nonhuman primates [NHP]) and humans employs IV delivery of siRNA in lipid nanoparticle formulations [16, 17]. Another approach for liver-specific gene silencing is subcutaneously administered siRNA conjugated to a GalNAc carbohydrate ligand [18]. Conjugation of a triantennary GalNAc ligand to an siRNA enables hepatocyte binding and subsequent cellular uptake via the asialoglycoprotein receptor, resulting in engagement of the RNAi pathway and downregulation of hepatic proteins.

1.4. Rationale for ALN-CC5 for the Treatment of Complement-Mediated Disease

ALN-CC5 (containing siRNA drug substance, [redacted] targeting C5 mRNA) is a synthetic investigational RNAi therapeutic designed to suppress liver production of C5 protein, when administered via subcutaneous (SC) injection. C5 is encoded by a single gene and is expressed and secreted predominantly by hepatocytes. Through the mechanism of RNAi, the ALN-CC5 siRNA enables the downregulation of C5 mRNA in the liver, thereby reducing levels of circulating C5 protein and resulting in inhibition of terminal complement pathway activity that prevents the formation of MAC, and in PNH, reduces intravascular hemolysis of RBCs. The safety of reducing C5 is supported by clinical precedence of C5 inhibition with eculizumab treatment and the absence of any phenotypic consequences in subjects with known genetic C5 deficiencies [20].

ALN-CC5 is intended for SC injection. Subcutaneous dosing will reduce the risk of infusion-related complications such as infections and thrombophlebitis. In particular, this consequent reduced risk of pathogen penetration is crucial in PNH patients due to a predisposition for infections. Nonclinical data have shown that reducing C5 with ALN-CC5 has the potential to nullify natural and inflammatory triggered fluctuations in C5. The duration of effect anticipated with ALN-CC5 based on nonclinical data may further reduce the risk of breakthrough hemolytic events. Finally, given the mechanism for regulation of complement

activity, ALN-CC5 may be used as an alternative treatment or in combination with C5 neutralizing agents.

1.5. Nonclinical Development

[redacted]

1.5.1. Nonclinical Pharmacology

[redacted]

1.5.2. Single-dose Pharmacology in Nonhuman Primates

[redacted]

[redacted]

1.5.3. Repeat-dose Pharmacology in Nonhuman Primates

[redacted]

1.6. Clinical Development

No clinical study has been conducted with ALN-CC5 to date; however, Alnylam has substantial clinical experience with systemic siRNA investigational therapeutics delivered to the liver utilizing the triantennary GalNAc ligand approach for SC administration of ALN-CC5.

Studies are ongoing with a GalNAc-conjugated siRNA, ALN-TTRSC, employing the identical GalNAc ligand as ALN-CC5, but conjugated to an siRNA targeting the transthyretin (TTR)

mRNA for the treatment of TTR-mediated amyloidosis. ALN-TTRSC has been found to be generally safe and well tolerated in Phase 1 and Phase 2 clinical trials in >40 healthy subjects and 18 patients with familial amyloidotic cardiomyopathy and senile systemic amyloidosis (ALN-TTRSC-001; EudraCT 2012-004203-12; and ALN-TTRSC-002; EudraCT 2013-002856-33). Consistent and durable reduction in serum TTR levels of greater than 85% have been observed in healthy subjects and patients with TTR cardiomyopathy following SC administration with ALN-TTRSC. An additional GalNAc siRNA conjugate-based study drug, ALN-AT3SC, is under investigation for the treatment of hemophilia A and B in an ongoing Phase 1 study (ALN-AT3SC-001, EudraCT 2013-003135-29). Part A in healthy subjects has been completed. ALN-AT3SC was considered safe and well tolerated and a dose of 0.03 mg/kg showed an approximately 25% reduction of antithrombin. Part B of this study is ongoing.

1.7. Study Rationale

The objective of this study is to evaluate the safety, tolerability, pharmacokinetics (PK), and PD of subcutaneously administered ALN-CC5 as a single-ascending dose (SAD) and multiple-ascending dose (MAD) to healthy adult subjects, and multiple doses (MD) to patients with PNH. ALN-CC5 is comprised of an siRNA formulated in water for injection. The siRNA is a chemically synthesized double-stranded oligonucleotide covalently linked to a ligand containing GalNAc residues. This synthetic investigational RNAi therapeutic has been designed to downregulate the C5 mRNA in the liver, thereby reducing levels of circulating C5 protein and resulting in inhibition of terminal complement pathway activity and prevention of the formation of the MAC. As a result, complement-mediated intravascular hemolysis of RBCs in PNH may be reduced. Cumulatively, literature data regarding treatment of PNH with eculizumab, robust nonclinical data with ALN-CC5, and prior and ongoing clinical experience with other RNAi therapeutics in humans, suggests ALN-CC5 will have a favorable risk profile in the intended populations and supports the initial clinical development of ALN-CC5.

1.8. Rationale for Dose Selection

Table 4: Estimated NOAEL and Starting Dose Safety Margins

Species	Estimated NOAEL	Safety margin for planned starting [redacted]	
		Based on Body Weight	Based on Body Surface Area[a]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: NOAEL = no observed adverse effect level.

[a] Body surface area margin calculated using species scaled conversion assumptions outlined in Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers [http://www fda.gov/downloads/Drugs/Guidances/UCM078932.pdf]. [redacted]

[redacted]

1.9. Potential Risks and Benefits

1.9.1. Potential Benefits

In the blinded part of the study, study drug will be administered to healthy subjects for research and development purposes. Subjects receiving study drug will experience no medical benefit except for a health examination and a vaccination program against meningococcal infection. The open-label multiple-dose part of the study will include PNH patients, either naïve to complement-directed treatment or currently on stable eculizumab treatment who may benefit from ALN-CC5 treatment.

1.9.2. Potential Risks

1.9.2.1. Serious Meningococcal Infections

The potential clinical risks associated with administration of ALN-CC5 related to reduction of C5 activity can be extrapolated from the known safety profile of eculizumab [20]. ALN-CC5 is considered to have a similar clinical impact as that observed with eculizumab in that a reduction in C5 activity in plasma is anticipated. Clinical study evidence with eculizumab has shown that meningococcal infections are the most common adverse reactions experienced by patients receiving treatment for complement-mediated diseases.

Administration of a C5 inhibitor increases susceptibility to meningococcal infections (septicemia and/or meningitis). Life-threatening and fatal meningococcal infections have occurred in patients treated with eculizumab. As of November 2011, there have been 18 reported cases of *Neisseria meningitides* among patients treated with eculizumab, 3 from clinical studies and 15 during post-marketing experience [22]; however, the rate of meningococcal infections has not changed from clinical study experience and throughout post-marketing experience (less than 0.5 cases per 100 patients) [22].

The first case in a clinical study occurred in an unvaccinated, non-PNH patient before the initiation of the current risk management plan. All other 17 patients who developed a meningococcal infection were vaccinated with a meningococcal vaccine according to local availability. Eight of these patients received a tetravalent vaccine (Menactra®, Menomune®, or Meningovax®), 6 received a vaccine covering either *Neisseria* subtype C or A/C, and 3 patients received an unknown vaccine type. Thirteen of the 18 patients who developed infections underwent subtyping of *Neisseria meningitides*. The predominant subtype was B (7 patients), a serotype not covered by the vaccines available at that time. One patient had an infection caused by subtype C. Another patient had an infection caused by subtype Y. These 2 infections occurred in patients who were vaccinated with Menactra®, which includes both serotypes in the target coverage [22].

Fourteen of these 18 patients with meningococcal infection fully recovered. One patient who was not vaccinated recovered with neurological sequelae and there were 3 meningococcal infection-related fatalities in patients with PNH. Two of these patients had received a bivalent meningococcal vaccine and 1 patient had received a tetravalent vaccine. Fatal infections were due to *Neisseria meningitides* type B in 2 patients and type X in 1 patient. (In this study, the risk of infection by serotype X is minimized by excluding patients who travelled to Saudi Arabia or Africa within 90 days of screening, or who plan to do so during the study.) The time from the beginning of eculizumab treatment to the start of infection was 5 months in 2 patients and 10.5 months in 1 patient. Of the 18 patients who developed meningococcal infection, 6 remained on eculizumab without further adverse reactions, 9 discontinued eculizumab, and information is unavailable for the remaining 3 patients [22].

Vaccination against *Streptococcus pneumonia* (ie, pneumococcal polysaccharide vaccine [pnuemovax II®]) is not required for patients in this study. Terminal complement deficiency (eg, C5 deficiency) is associated with susceptibility to *Neisseria meningitides* infections; whereas, risk of infections with encapsulated bacteria is not increased. In contrast, deficiency of complement proteins more proximal in the complement cascade (eg, complement C3) are known to be associated with increased frequency of infections with encapsulated bacteria.

1.9.2.2. Allergic Reactions and Injection Reactions

Administration of ALN-CC5 may result in hypersensitivity reactions and/or injection site associated reactions. Subjects will be closely monitored during and after study drug administration for symptoms of anaphylaxis and other hypersensitivity reactions, including circulatory arrest and/or respiratory changes, urticaria, arthralgias, myalgias, and other signs of related reactions. Adequate treatment will be immediately available. Injection-associated adverse events (AEs) may occur; depending on type and severity, discontinuation of further injection(s) 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, and instructed to contact the study physician immediately if they develop any of these symptoms.

1.9.2.3. Vaccinations

As with any vaccine, an anaphylactic event following administration of the vaccine may rarely occur. Subjects will be closely monitored for allergic or any other reactions following vaccination. Any signs of injection reactions and other hypersensitivity reactions will be treated according to the anaphylaxis algorithm [23]. For the full list of all side effects reported with the following products, refer to the individual summary of product characteristics.

1.9.2.3.1. Meningococcal Group A, C, W-135, and Y Conjugate Vaccine

The most common adverse reactions (≥10%) among adults who received Menveo® were headache, nausea, myalgia, injection site reactions (ISRs; including injection site pain, injection site erythema, injection site induration), and malaise (refer to the product SmPC).

1.9.2.3.2. Meningococcal Group B Vaccine

The most common adverse reactions (≥10%) among adults who received Bexsero® were headache, nausea, ISRs (including injection site pain, injection site swelling, injection site induration, and injection site erythema), malaise, myalgia, and arthralgia (refer to the product SmPC).

1.9.2.4. Prophylactic Antibiotics

Meningitis can be caused by 13 *Neisseria meningitides* serotypes. The most common serotypes associated with this disease are: A, C, W-135, Y, (ACWY) and B [20]. To mitigate the risk of infection beyond the 5 most common serotypes, healthy subjects will be treated with ciprofloxacin prophylaxis as in previously completed Phase 1 studies (ClinicalTrials.gov Identifier: NCT02083666).

Ciprofloxacin is a broad-spectrum antibiotic active against both gram-positive and gram-negative bacteria. The safety of fluoroquinolones, including ciprofloxacin, is similar to that of other antibiotics. Most adverse reactions are mild to moderate, but serious adverse events (SAEs) have occurred. Fluoroquinolones became the most commonly prescribed class of antibiotics to adults in 2002 [21].

The most frequently reported drug-related events were nausea (2.5%), diarrhea (1.6%), abnormal liver function tests (1.3%), vomiting (1%), and rash (1%). Other AEs occurred at rates of <1%. A United Kingdom (UK) medical care database reported that fluoroquinolone use was associated with a 1.9-fold increase in tendonopathy. Resistance to ciprofloxacin and other fluoroquinolones may evolve rapidly, even during a course of treatment, although resistance to this antimicrobial drug in *Neisseria meningitides* is still rare. In the United States, *Neisseria meningitides* seldom shows resistance to commonly used antibiotics [24]. Two cases of meningococcal disease caused by ciprofloxacin-resistant *Neisseria meningitides* have been reported in North America [25]. In addition, 3 *Neisseria meningitides* clinical isolates showing resistance to ciprofloxacin have been reported in France (1999), Australia (2000), and Spain (2003), and sporadic cases of resistance to ciprofloxacin have also been reported [26].

Subjects who do not tolerate ciprofloxacin or develop persistent AEs considered related to the use of ciprofloxacin can be switched to another type of antibiotic at the discretion of the Investigator.

1.9.3. Risk Mitigation Strategy

Potential risks will be closely monitored as part of safety evaluations performed during the study. Risks to subjects will also be minimized by a maximum 4-fold increase in dose levels and the use of a sentinel dosing strategy at each dose level. Additionally, a Safety Review Committee (SRC) will perform regular reviews (at predefined decision-making time points) of safety, tolerability, and available PD data collected during the study with the primary purpose of protecting the safety of subjects and patients participating in the study.

The following additional risk mitigation strategies will be used in this study:

- Subjects and patients will be informed in detail of the early signs of infections, both orally and in writing.
- Healthy subjects will be closely monitored for early signs and symptoms of infections and will be evaluated immediately if an infection is suspected. Treatment with the study drug will be discontinued if a serious infection is suspected.
- Subjects and patients will be monitored every 28±7 days until serum complement activity is within the normal reference range as assessed by CAP ELISA if serum complement activity is below normal range at the last postdose follow-up visit or until the SRC makes a decision on a case-by-case basis to discontinue follow-up, whichever is sooner (see Section 3.5.3). The decision cannot be made until after completion of the last postdose follow-up visit.
- Subjects and patients will be issued a safety information card stating that they are enrolled in a clinical trial involving ALN-CC5, which can lower the ability of the immune system to fight infections, especially meningococcal infection, which requires immediate medical attention.
- Subjects and patients will be immunized against *Neisseria meningitides* (see Section 10.1.8).
- Subjects and patients (as specified in the protocol) will be treated with prophylactic ciprofloxacin (according to standard practice at the clinical study sites; see Section 10.1.9).

The following instructions for early recognition and management of meningitis will be included in the Informed Consent Form (ICF) and in the Study Manual/Procedures:

- Meningitis, and associated septicemia, is usually associated with fever, vomiting, severe headache, non-blanching rash, dislike of bright light, confusion, and somnolence. Not all of these signs and symptoms will show at once and the illness may progress over 1 or 2 days; however, they can develop rapidly, sometimes in a matter of hours. Subjects will be informed in detail about these signs and symptoms in the ICF.

- Rapid admission to hospital is the highest priority when meningococcal disease is suspected. Chemoprophylaxis of IV/intramuscular broad spectrum antibiotic that crosses the blood-brain barrier for suspected meningococcal infections should be started immediately. Detailed early recognition and management algorithms (such as those published by the British Infection Society and the Meningitis Research Foundation (http://www.meningitis.org/news-media/download-resources) will be included in the Study Manual/Procedures.

2. STUDY OBJECTIVES

2.1. Primary Objective

- To evaluate the safety and tolerability of SAD or MAD of ALN-CC5 when administered to healthy adult subjects and of MD in patients with PNH

2.2. Secondary Objectives

- To characterize the PK of ALN-CC5
- To assess the PD effect of ALN-CC5 on levels of C5 protein and complement activity

2.3. Exploratory Objectives

- To assess the PD effect of ALN-CC5 on inhibition of hemolysis in subjects and in patients with PNH
- [redacted]
- [redacted]
- To explore the PD effect of ALN-CC5 on lactate dehydrogenase (LDH) levels in patients with PNH
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

    Eculizumab levels
  - [redacted]
  - [redacted]

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This study is designed to evaluate the safety, tolerability, PK, and PD of ALN-CC5 in a randomized, double-blind, placebo-controlled manner in healthy adult subjects and in an open-label manner in patients with PNH. This multinational study will be conducted at up to 6 clinical study centers in the following parts:

- **Part A:** SAD phase in healthy adult subjects
- **Part B:** MAD phase in healthy adult subjects
- **Part C:** multiple-dose phase in patients with confirmed PNH, either naïve to eculizumab treatment or on stable doses of eculizumab (as assessed by the Investigator)

An SRC will perform regular reviews (at predefined decision-making time points) of safety, tolerability, and available PD data collected during the study with the primary purpose of protecting the safety of subjects and patients participating in this clinical study (see Section 3.5). Additionally, the planned study design may be modified in accordance with the adaptive features of the clinical study protocol (see Section 3.4).

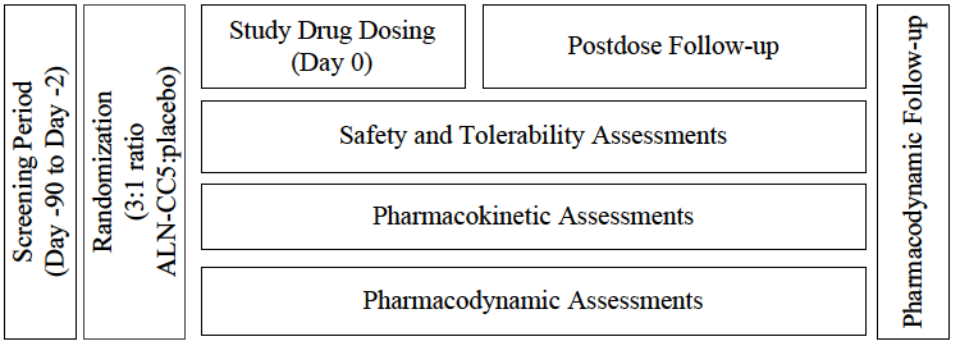
3.1.1. Single-ascending Dose Phase (Part A)

Part A of the study will be performed in a randomized (3:1), placebo-controlled, double-blind design to assess SAD of ALN-CC5 in healthy subjects (Figure 1). Study drug will be administered according to a sentinel dosing strategy (Section 4.1).

Subjects will be screened from -90 to -2 days before study drug administration. Eligible subjects will be admitted to the clinical study site on Day -1 to determine continued eligibility and for pretreatment assessments. Subjects will be randomized on Day 0 and will receive a single dose of study drug. Subjects will be discharged from the clinical study site following completion of the 24 hour postdose follow-up assessments.

Subjects will return to the clinical study site on an outpatient basis at the time points in the Schedule of Assessments (Table 1) and PK table (Table 10) for safety, tolerability, PK, and PD monitoring through Day 70. For subjects with serum complement activity below normal range at the last postdose follow up visit (Day 70), monitoring visits will occur until serum complement activity is within the normal reference range as assessed by CAP ELISA or until the SRC makes a decision on a case-by-case basis to discontinue follow-up, whichever is sooner (see Section 3.5.3). The decision cannot be made until after completion of the last postdose follow-up visit. The duration of follow up is based on PD data from nonclinical studies in NHP that demonstrated [redacted]

Figure 1: Single-ascending Dose Phase (Part A) Flow Diagram

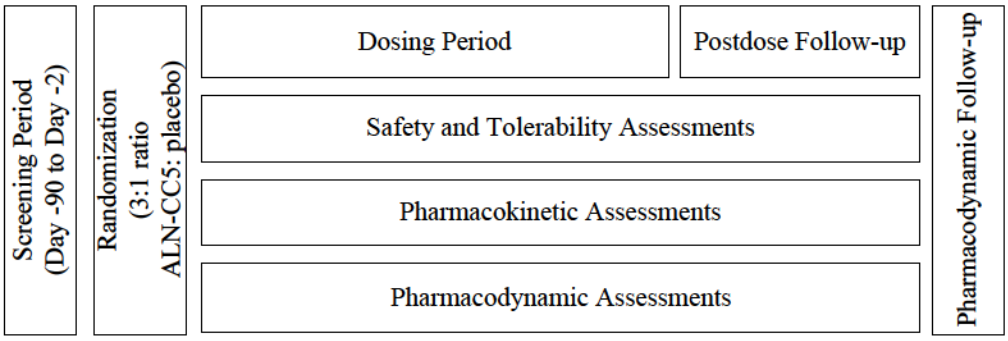


3.1.2. Multiple-ascending Dose Phase (Part B)

Part B of the study will be performed in a randomized (3:1), placebo-controlled, double-blind design to assess MAD of ALN-CC5 in healthy subjects (Figure 2).

Subjects will be screened from -90 to -2 days before dose administration. Eligible subjects will be admitted to the clinical study site on Day -1 to determine continued eligibility and for pretreatment assessments. Subjects will be randomized on Day 0 and will receive an initial dose of study drug. Subjects will be discharged from the clinical study site following the completion of the 24 hour postdose follow-up assessments. Subjects will return to the clinical study site at the time points in the Schedules of Assessments (Table 2, Table 15, Table 16, Table 17, Table 18, and Table 19) and PK tables (Table 11 and Table 12) for study drug administration and safety, tolerability, PK, and PD monitoring over the treatment period and for postdose follow-up. For subjects with serum complement activity below normal range at the last postdose follow-up visit, monitoring visits will occur until serum complement activity is within the normal reference range as assessed by CAP ELISA or until the SRC makes a decision on a case-by-case basis to discontinue follow-up, whichever is sooner (see Section 3.5.3). The decision cannot be made until after completion of the last postdose follow-up visit.

Figure 2: Multiple-ascending Dose Phase (Part B) Flow Diagram



3.1.3. Multiple Dose Phase (Part C)

Part C of the study will be conducted in patients with PNH in an open-label design to assess multiple doses of ALN-CC5. The start of Part C and the study drug dose will depend on SRC review of safety, tolerability, and available PD data from Part A and Part B (Figure 3). A

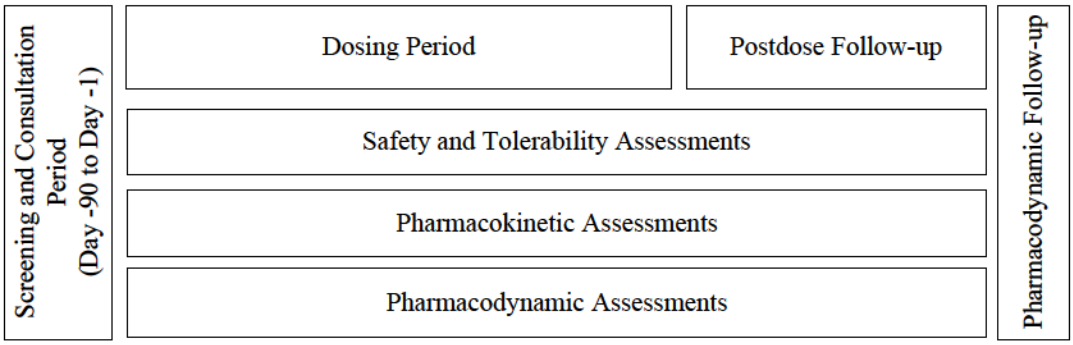
maximum of 3 cohorts, comprised of at least 4 patients each, will be enrolled in Part C. Overall, patients in Part C will undergo a maximum of 39 weeks of ALN CC5 dosing.

Patients will be screened from -90 to -2 days before dose administration. Patients will have a consultation at the clinical study site on Day -1 to determine continued eligibility and for pretreatment assessments. Patients will be admitted and dosed on Day 0. Patients will be discharged from the clinical study site following the completion of the 24 hour postdose follow-up assessments. Patients will return to the clinical study site at the time points in the Schedules of Assessments (Table 3, Table 20, Table 21, and Table 22) and PK tables (Table 13 and Table 14) for study drug administration and for safety, tolerability, PK, and PD monitoring over the treatment period and for postdose follow-up. For patients with serum complement activity below normal range at the last postdose follow-up visit, monitoring visits will occur until serum complement activity is within the normal reference range as assessed by CAP ELISA or until the SRC makes a decision on a case-by-case basis to discontinue follow-up, whichever is sooner (see Section 3.5.3). The decision cannot be made until after completion of the last postdose follow-up visit.

In Part C, ALN-CC5 may be administered at home between visits to the clinical study center by a home healthcare provider trained in the administration of ALN-CC5. Patients will return to the clinical study center every other month for assessments; however, in between, visits can be completed by a home healthcare provider.

After the last dose of study drug, eligible patients may transition to an open-label extension study immediately after administration of the last dose of study drug or obtain standard of care treatment.

Figure 3: Multiple-dose Phase (Part C) Flow Diagram



3.1.4. Optional Cohorts

Based on the evaluation of safety, tolerability, and available PD data, it may be decided by the SRC that optional cohorts may be enrolled and dosed according to the same eligibility criteria and corresponding randomization scheme and sentinel dosing strategy detailed in Part A and Part B. In both Part A and Part B, up to 3 exploratory cohorts (exploring additional dosing and dose regimens) may be added. The dose levels for optional cohorts may be at intermediate dose levels compared to those administered in Part A and Part B, but will not exceed 900 mg and 600 mg, respectively, provided the dose is considered safe and well-tolerated.

3.1.5. Treatment and Study Duration

A single SC dose of study drug will be administered in Part A. In Part B and Part C, respectively, study drug will be administered over a maximum of a 13 or a 39 week period. It is anticipated that this study will last for a maximum of 3 years from screening through the last subject/patient, last visit. End of study is defined as last subject/patient, last visit. It is anticipated that the duration of study participation for a subject/patient will be 665 days (1 year and 10 months).

3.2. Number of Subjects and Patients

Up to 76 subjects will be enrolled in the study.

- Part A: Up to 32 healthy adult subjects (including optional cohorts)
- Part B: Up to 28 healthy adult subjects (including optional cohorts)
- Part C: Up to 16 patients with PNH (approximately 8 patients on a stable dose of eculizumab as assessed by the Investigator)

3.3. Treatment Assignment

Study treatment will be assigned in a randomized, double-blind manner in a 3:1 ratio (ALN-CC5 or placebo) in Part A and in Part B. Part C is an open-label study design.

3.4. Adaptive Study Design Feature

The use of adaptive study design features will allow for the continuing development of the study as new data emerges; therefore, the study can be adjusted in accordance with the pre-specified areas, features, and limits listed in Table 5.

Table 5: Adaptive Study Design Areas, Features, and Limits

Areas	Features	Limits
A Dosing regimen	1. Dosing regimens may be determined or adapted in accordance with safety and tolerability data collected up to the decision-making time point. 2. The term dosing regimen includes: (1) the dose level administered, (2) the frequency of dosing, and (3) the duration of dosing (ie, number of doses administered). Accordingly, these can be adjusted individually or in combination.	I. The starting dose for subjects in Part A will not exceed 50 mg. II. The starting dose for subjects in Part B will not exceed doses already evaluated and considered safe and tolerable in the Part A. III. Based on data from GLP toxicology studies (see Section 1.5) and provided no safety or tolerability concerns have occurred, a maximum single dose level of 900 mg may be administered. IV. The interval between doses in Part B may be increased or decreased, but the interval between doses will not be shorter than 7 days and not longer than 30 days. V. The Part B dosing regimen may include a higher first dose, and subsequent doses administered at a lower dose level. The maximum dose level in Part B will not exceed 600 mg. VI. Different dosing regimens may be investigated, but the total number of planned study subjects/patients cannot be exceeded.
B Sentinel/ sub-groups	1. The number and size of sentinel/sub-groups within a dosing regimen may be adaptable. 2. Dose levels may be split into additional sub-groups.	I. Mandatory sentinel dosing will be performed in Part A. II. The sentinel group will consist of 2 subjects on ALN-CC5 or placebo (applicable to Feature 1). III. The remainder of the doses at a given level during Part A can be administered after a minimum of 24 hours has elapsed since dosing of the sentinel group. IV. The sentinel dosing strategy applied in Part A can be applied in Part B if deemed necessary by the SRC.
C Overlap	1. Dosing regimens may overlap.	I. Protocol-specific minimum study progression/escalation requirements must be met before dose progression/escalation (see Section 4).

Table 5: Adaptive Study Design Areas, Features, and Limits

Areas	Features	Limits
D Flexible cohort sizes	1. Withdrawn subjects can be replaced at the discretion of the Sponsor and Investigator if not withdrawn for safety reasons (see Section 5.3). 2. Replacement subjects may be enrolled in an ongoing cohort, or dosed together as a group or separately.	I. Protocol-specific minimum requirements must be met before dose escalation (see Section 4). II. No more than 10 subjects in total at the same site on the same day will be dosed at 1 time per clinical study site.
E Optional cohorts	1. Optional cohorts may be included to explore additional dosing regimens (applicable to Part A and Part B).	I. Up to 3 optional cohorts may be included in Part A. II. Up to 3 optional cohorts may be included Part B. III. Cohort sizes will not exceed 4 subjects for each optional cohort in Part A and Part B, not including replacement subjects. IV. Dosing in optional cohorts will follow the same randomization scheme as that in Part A and Part B. V. Safety, tolerability, PD, and/or PK may also be explored under the following scenarios in optional cohorts: • Escalate or de-escalate to a lower and/or to an intermediate dose level(s) for administration • Provided suspension or stopping rules have not been met, the SRC may permit a dose level to be repeated to further characterize the PD and/or PK of the study drug
F Samples and assess-ments	1. The inpatient period may be prolonged for subjects/patients in all dose levels in all cohorts if considered by the Investigator clinically necessary. Prolonged inpatient periods will be decided on a subject/patient, case-by-case basis and/or if the SRC considers it necessary for determining safety and tolerability for a future dose level cohort.	I. A maximum extended inpatient period due to clinical concerns cannot be defined as the extension will be as long as necessary to ensure the safety of the subjects/patients.
	1. Additional blood and urine samples for safety analysis may be obtained.	I. A maximum number of blood samples cannot be defined as investigations will be performed as necessary to ensure the safety of the individual subjects; however, the maximum blood volume stated in this protocol will not be exceeded (see Section 10.1.6).
	2. Timing of safety assessments (eg, vital	I. Changes to the timing of safety

Table 5: Adaptive Study Design Areas, Features, and Limits

Areas	Features	Limits
	signs, 12-lead ECGs, etc.) may be adjusted in accordance with evolving data. 3. Additional safety assessments (eg, vital signs, 12-lead ECGs, etc.) may be performed in accordance with evolving data and dosing schedule.	assessments must be a reflection of the established safety and tolerability profile up to the decision-making time point (applicable to Features 1 and 2) II. Changes to the timing of safety assessments must be made in the spirit of the current study protocol (ie, focus on the capture of essential and useful data) and not affect the risk profile of the study drug (applicable to Features 1 and 2).
	1. Specialist referrals (eg, hematologist, immunologist, etc.) may be made if considered clinically necessary by the Investigator, delegate, Sponsor, or SRC for subjects/patients on a case-by-case basis.	I. A maximum number of specialist referrals for subjects/patients will be determined on a case-by-case basis and cannot be defined as the evaluations will be performed as necessary to ensure the safety of subjects/patients.
	1. Timing of PK and/or PD samples (blood and/or urine) may be adjusted in accordance with evolving data and dosing schedule/regimen. 2. Additional or fewer PK and/or PD samples (blood and/or urine) may be obtained in accordance with evolving data and dosing schedule.	I. Maximum blood volume stated in the protocol will not be exceeded (see Section 10.1.6). II. Optional PK and/or PD analysis can be performed at any stage during or after the study to facilitate decision-making and/or to increase understanding of the compound (ie, samples will be obtained, but not necessarily analyzed) (applicable to Features 1 and 2). III. The optional analysis is limited to the protocol-specified purpose (applicable to Features 1 and 2).
	1. Except for subjects that have been randomized, screening assessments performed at the clinical study center on subjects for another study can be used for this study to avoid unnecessary tests.	I. The assessments must meet protocol criteria (eg, the method to be used). II. The assessments must be performed within the protocol screening window.

Abbreviations: ECG = electrocardiogram; GLP = Good Laboratory Practice; PD = pharmacodynamic; PK = pharmacokinetic; SRC = Safety Review Committee.

3.5. Safety Review Committee

3.5.1. Primary Responsibility

An SRC will perform regular reviews (at predefined decision-making time points) of safety, tolerability, and available PD data collected during the study with the primary purpose of protecting the safety of subjects and patients participating in the study. The planned study design may be modified in accordance with the adaptive features of the clinical study protocol (see Section 3.4).

3.5.2. Membership

To ensure timely safety, tolerability, and available PD information exchange across the participating clinical study sites, the SRC will be comprised of the following members:

- Investigator(s) or designee(s) at each clinical study site
- Alnylam Medical Monitor
- Study Medical Monitor
- Independent hematologist

Further internal or external experts may be consulted by the SRC as necessary. The membership of the SRC and reporting structure are defined in the SRC Charter.

3.5.3. Timing and Purpose of Review Meetings

The SRC will convene to review safety, tolerability, and available PD data at predefined decision-making time points (see Section 4) or when progression/escalation and dose suspension/stopping rules are met to ensure the acceptability of continued dosing, and/or dose escalation to subsequent cohorts, and/or the transition from Part A to Part B, or from Part B to Part C. In addition, there is an option for ad hoc SRC meetings to discuss safety and tolerability issues.

If any progression/escalation and dose suspension/stopping rules are met and deemed to have a reasonable possibility of causal relationship with the study drug (see Section 10.4.1), the SRC will act in accordance with the rules stipulated in Section 4.4.

The SRC will determine dose escalations, dose de-escalation, and/or cohort progressions according to the clinical study protocol, planned doses, and adaptive study features (see Section 3.4).

To balance the health risks of slightly reduced complement activity with the risks of long-term ciprofloxacin use, the SRC will also determine whether study follow-up and prophylactic ciprofloxacin treatment will be discontinued in subjects or patients with complement activity below the normal range. The decision cannot be made until after completion of the last postdose follow-up visit.

Decision of the SRC should reflect unanimity wherever possible. SRC decisions will be documented and archived in the Trial Master File (TMF). The minutes will document clearly any questions posed and decisions reached.

All data and reports provided to and reviewed by the SRC, including minutes and decisions from the meetings will be archived in the TMF.

3.5.4. Data Requirements

Before SRC review, clinical study site Investigators or designees will prepare a report presenting the following safety, tolerability, and available PD data. More detailed information on the content of such reports can be found in the SRC Charter.

3.5.4.1. Safety Data

The following data will be provided and reviewed:

- AEs (including ISRs)
- Concomitant medications
- Vital signs (oral body temperature, blood pressure, heart rate, and respiration rate)
- 12-lead ECGs
- Physical examinations (full and directed)
- Clinical laboratory parameters (hematology, biochemistry, coagulation, and urinalysis)

3.5.4.2. Pharmacodynamic Data

When available, the plasma concentration of C5 protein and serum complement activity will also be evaluated for assessment of PD effect (see Section 9.1)

3.5.4.3. Pharmacokinetic Data

Dose progression/escalation will be based on the evaluation of safety, tolerability, and available PD data, for dose levels administered in previous cohorts, rather than exposure to study drug (see Section 4.4).

4. CRITERIA FOR STUDY DRUG DOSING AND DOSE PROGRESSION/ESCALATION

4.1. Study Drug Dosing and Progression/Escalation in Part A

Subjects in each cohort will be randomized in a 3:1 ratio (ALN-CC5:placebo) in a double-blind, placebo-controlled manner. Study drug will be administered according to a sentinel dosing strategy. The first sentinel subject in each cohort will receive study drug (ALN-CC5 or placebo) followed by an approximately 24 hour safety follow-up. The second sentinel subject in each cohort will then receive study drug (ALN-CC5 or placebo) followed by an approximately 24 hour safety follow-up, after which the remaining subjects in the cohort will be dosed.

After dosing all subjects in the cohort, the SRC will review a minimum of 21 days postdose safety, tolerability, and available PD data from all subjects in that cohort before dose escalation to the following cohort. Based on nonclinical evaluation of ALN-CC5 PD, pharmacologic toxicity and on-target PD effect can be evaluated 21 days after single dose administration of ALN-CC5.

The starting dose for subjects in Cohort 1 will be 50 mg of study drug (ALN-CC5 or placebo). The following are the planned dose levels for subsequent cohorts in Part A; however, the actual dose administered will be determined by the SRC:

- Cohort 2: 200 mg
- Cohort 3: 400 mg
- Cohort 4: 600 mg
- Cohort 5: 900 mg
- Optional cohorts 6, 7, and 8: Exploring additional dose and/or dose regimens

The highest dose administered in Part A will not exceed 900 mg.

4.2. Study Drug Dosing and Progression/Escalation in Part B

Dosing in Part B, Cohort 1 may initiate 48 hours after SRC confirmation of safety, tolerability, and available PD data from the fourth subject dosed in Part A, Cohort 3. Dosing in each cohort in Part B will begin at a dose that is no greater than the highest safe and tolerated dose explored in Part A.

Subjects in each cohort will be randomized 3:1 (ALN-CC5:placebo) in a double-blind, placebo-controlled manner. All subjects in a cohort may be dosed on the same day. After dosing all subjects in the cohort, the SRC will review a minimum of 35 days postdose safety, tolerability, and available PD data from all subjects in that cohort before dose escalation to the following cohort. Based on nonclinical evaluation of ALN-CC5 PD, pharmacologic toxicity and on-target PD effect can be evaluated 35 days after multiple-dose administration of ALN-CC5.

The following are the anticipated dose levels for subsequent cohorts in Part B; however, the actual dose administered will be determined by the SRC:

- Cohort 1: 50 mg
- Cohort 2: 200 mg
- Cohort 3: 400 mg
- Cohort 4: 600 mg
- Optional cohorts 5, 6, and 7: Exploring additional dose and/or dose regimens

The highest dose administered in Part B will not exceed 600 mg. If recommended by the SRC, weekly, once every 2 weeks, or monthly dosing regimens may be investigated. Patients in Part B will receive a maximum of 13 weeks of study drug dosing.

4.3. Study Drug Dosing and Regimen Modifications in Part C

Part C will be initiated if the SRC, based on their expert clinical experience in treating PNH patients, determines that the safety, tolerability, and available PD (C5 levels and complement activity) data derived from Part A and Part B is clinically meaningful and the risk-benefit assessment is favorable.

Figure 4 illustrates the cohort enrollment and dose and dosing regimen modification plan for Part C. A maximum of 3 cohorts, comprised of at least 4 patients each, will be enrolled. The SRC will meet at regular intervals (approximately every 8 weeks) to review ongoing safety, tolerability, and available PD data from Part B and Part C to recommend cohort initiation and to determine the dose and dosing regimen to be administered to all patients in a cohort or all patients in Part C. During the dosing period, the SRC may also recommend the ALN-CC5 dose and regimen be modified for all patients, based on the degree of complement inhibition and clinically meaningful suppression of intravascular hemolysis as evaluated by LDH (Part C only). Part C does not include sentinel dosing.

Dosing in Cohort 1 may initiate after SRC review of data from Part A and Part B at a dose no greater than the highest safe and tolerated dose explored in Part B. Initially, 13 weekly doses of ALN-CC5 will be administered. After completing the 13 week dosing period, patients in Cohort 1 may transition to extended dosing on a modified regimen provided the Day 140/ET study visit has not been completed; these patients will resume ALN-CC5 administration at a dose and regimen recommended by the SRC.

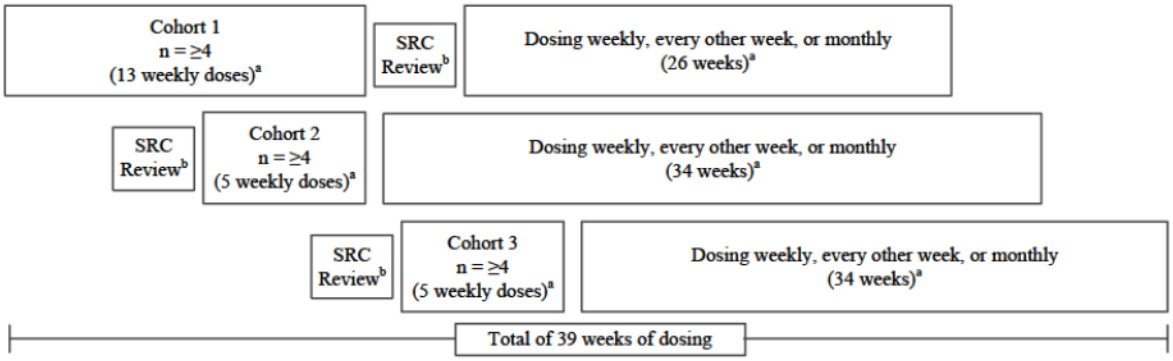
Dosing in Cohort 2 may initiate after SRC review of data from subjects in Part B, Cohorts 4, 5, and 6, who completed ≥10 weeks of dosing. Additionally, dosing in Cohort 2 may initiate after SRC confirmation that clinically meaningful suppression of intravascular hemolysis (evaluated by LDH levels) has occurred in at least 4 patients in Part C, Cohort 1, who completed ≥8 weeks of dosing. Initially, ALN-CC5 will be administered once weekly for 5 doses.

Dosing in Cohort 3 may initiate to further explore dose and dosing regimens after ≥4 patients in Part C, Cohort 2 complete ≥13 weeks of dosing data have been evaluated by the SRC. Initially, ALN-CC5 will also be administered once weekly for 5 doses.

After an initial dosing period (5 or 13 weekly doses), the SRC may recommend a dose or dosing regimen modification. The regimen can be modified in Cohorts 1, 2, and 3 to once every 2 weeks or once monthly dosing, or weekly dosing continued. The SRC may also determine that de-escalation to a lower dose and regimen or re-escalation to a higher dose and regimen is appropriate. Overall, patients in Part C will undergo a maximum of 39 weeks of ALN-CC5 dosing.

Patients with confirmed PNH and on stable doses of eculizumab (as assessed by the Investigator) will continue receiving treatment concomitantly with ALN-CC5 at a dose and regimen determined by the SRC. These patients will receive their last dose of eculizumab when at least 2 consecutive measurements of C5 levels demonstrate a degree of suppression consistent with complement inhibition (as determined by the SRC during review of data from Part A and Part B). Patients who are naïve to eculizumab treatment may begin ALN-CC5 administration at a dose and regimen determined by the SRC.

Figure 4: Study Drug Dosing in the Multiple-dose Phase (Part C)



a The SRC will meet at regular intervals to review ongoing safety, tolerability, and available PD data from Part B and Part C, and to determine clinically meaningful suppression of intravascular hemolysis as evaluated by LDH levels.

b After SRC review of data, the SRC will recommend Cohort initiation and the dose and dosing regimen to be administered.

4.3.1. Management of Breakthrough Hemolytic Events

If a patient with PNH experiences a clinically significant breakthrough hemolytic event, the Investigator can initiate treatment according to standard practice at the clinical study site, which may include treatment with eculizumab. Patients can continue treatment with ALN-CC5. If an individual patient experiences ≥2 clinically significant breakthrough hemolytic events requiring treatment with eculizumab, the SRC will evaluate whether the patient may continue ALN-CC5 administration or be withdrawn from the study.

If a patient previously treated with eculizumab has LDH levels >500 IU/L or >1.5-fold from baseline (defined as average LDH over the past 60 days before screening) for ≥2 consecutive measurements, the SRC will review if the patient should be withdrawn from the study.

4.4. Study Progression/Escalation and Dose Suspension/Stopping Rules

For the purpose of this protocol, progression rules are based on toxicity (ie, clinically significant AEs, which are at least possibly related to ALN-CC5).

For the purpose of this protocol, the term 'dose escalation' is defined as progression or escalation to the next consecutive dose in line with the dose progression/escalation rules and minimum data requirements described in Section 4.4.1.

For the purpose of this protocol, the term 'suspension' is defined as no further study drug will be administered at the dose level and that further dose escalation/progression will be suspended. If a dose level is suspended, an ad hoc SRC meeting will be held. Any resumption at the same or a higher dose level will require a substantial amendment, which will need to be approved by the Regulatory Authority and the Research Ethics Committee (REC).

For the purpose of this protocol, the term 'extension' is defined as increasing the number of subjects or patients in a cohort; however, the overall total number of planned subjects in the study will not increase.

Dose progression/escalation will be based on dose levels administered in previous cohorts with an acceptable safety and tolerability profile, rather than exposure, and no PK exposure limit has been set for this study. This is based on the following rationale:

- There is no expected on-target toxicity associated with C5 reduction. Following vaccination of study participants, use of antibiotic prophylaxis and additional safety precautions; the risk of *Neisseria* infections is considered manageable (see Section 1.9.3).
- PK data will not be used to justify dose escalation or to select dose levels for administration during the study. There have not been any PK-related toxicities observed during nonclinical studies. Additionally, nonclinical studies indicate that ALN-CC5 is rapidly eliminated from plasma (see IB).

Table 6: Study Progression/Escalation Flow Chart

Decision-making time points		
	Part A:	21 days after the last subject in a cohort is dosed with study drug
	Part B:	35 days after the last subject in the cohort received the first dose of study drug
Decision-making process		
	SRC	
	Double-blind data (blinded review)	
	Documentation of decision via meeting minutes	
Minimum data reviewed at each decision-making time point		
	4 subjects per cohort	
	Safety data	
	PD data (available)	

Dependencies following data reviewed at each decision-making time point		
	Part A to Part B:	Dosing in Part B, Cohort 1 may initiate 48 hours after confirmation of safety, tolerability, and available PD data from the fourth subject dosed in Part A, Cohort 3
	Part B to Part C:	C5 shows a degree of suppression consistent with complement inhibition (as determined by SRC in Part A and Part B)

4.4.1. Cohort Progression/Escalation and Suspension/Stopping Rules

Cohort progression/escalation and study suspension/stopping rules are described in Table 7. Dose progression/escalation will proceed according to the adaptive study design features described in Table 5 and will be limited by whether progression/escalation and dose suspension/stopping rules are met.

Standard toxicity grading according to the Common Terminology Criteria for Adverse Events (CTCAE; Version 4.0) will be used to grade AEs (see Section 10.4.2). These are the most comprehensive criteria available and have proven useful in early phase studies.

Abnormal laboratory and other tests should always be repeated before grading in order to ensure consistency and to exclude technical errors. If applicable, diurnal variations in laboratory parameters and other measurements as well as baseline status should be taken into account when assessing whether abnormal laboratory values constitute a drug-related AE and when grading AEs.

Table 7: Cohort Progression/Escalation and Suspension/Stopping Rules for Part A and Part B

AE Grade	Severity/ Seriousness	Reversibility	Number of Subjects Affected	Action	Effect on Dose Progression or Escalation
I	Mild	N/A	N/A	Next dose determined by SRC	N/A
II	Moderate	Showing signs of reversibility	≤2 subjects in different SOC	Next dose determined by SRC	N/A
			2 subjects in same SOC	Dose level may continue or be extended	Following continuation or extension, dose escalation may proceed as per clinical study protocol
			≤3 subjects in different SOC	Dose escalation on hold until results of continuation or extension are available	
			≥3 subjects in same SOC	Dose level suspended	A lower (intermediate) dose level may be administered in the next cohort
			≥4 subjects in different SOC		Dose continuation, extension, or escalation requires substantial amendment
		Showing no signs of reversibility	≥2 subjects	Dose level suspended	A lower (intermediate) dose level may be administered in the next cohort
					Dose continuation, extension or escalation requires substantial amendment
III	Severe, not serious	Showing signs of reversibility	1 subject	Dose level may continue or be extended	Following continuation or extension, dose escalation may proceed as per the clinical study protocol
				Dose escalation on hold until results of continuation or extension are available	

Table 7: Cohort Progression/Escalation and Suspension/Stopping Rules for Part A and Part B

AE Grade	Severity/ Seriousness	Reversibility	Number of Subjects Affected	Action	Effect on Dose Progression or Escalation
		Showing signs of reversibility	≥2 subjects	Dose level suspended	A lower (intermediate) dose level may be administered in the next cohort
					Dose continuation, extension or escalation requires substantial amendment
		Showing no signs of reversibility	≥1 subject	Dose level suspended	A lower (intermediate) dose level may be administered in the next cohort
					Dose continuation, extension or escalation requires substantial amendment
	Severe, serious	N/A	≥1 subject	Dose level suspended	A lower (intermediate) dose level may be administered in the next cohort
					Dose continuation, extension or escalation requires substantial amendment
IV	Life-threatening	N/A	≥1 subject	Study suspended	Study continuation requires substantial amendment
V	Fatal	N/A	≥1 subject	Study suspended	Study continuation requires substantial amendment

Abbreviations: AE = adverse event; N/A = not applicable; SOC = System, Organ, Class; SRC = Safety Review Committee.

4.4.2. Individual Patient Progression/Escalation and Suspension/Stopping Rules in Part C

Individual progression rules for Part C are presented in Table 8. These rules apply to study drug-related AEs and SAEs in individual patients enrolled in Part C only; rules do not apply to subjects in Part A and Part B of the study.

Table 8: Individual Progression Rules for Part C Only

AE Grade	Severity/Seriousness	Action
I	Mild	No action required.
II	Moderate	Study drug administration may continue at the same or a lower (intermediate) dose if the SRC considers it safe for the patient.
III	Severe, not serious	Study drug administration may continue at a lower (intermediate) dose if the SRC considers it safe for the patient.
	Severe, serious	Study drug administration will be discontinued.
IV	Life-threatening	
V	Fatal	

Abbreviations: AE = adverse event; SRC = Safety Review Committee.

5. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1. Inclusion Criteria

5.1.1. Inclusion Criteria for all Subjects in Part A and Part B

1. Male and female subjects aged 18 to 45 years, inclusive.
2. 12-lead ECG within normal limits or with no clinically significant abnormalities in the opinion of the Investigator.
3. Body mass index (BMI) $\geq$18.0 kg/m^2 and $\leq$30 kg/m^2.
4. Systolic blood pressure $\leq$140 mmHg and a diastolic blood pressure of $\leq$90 mmHg after 10 minutes supine rest.
5. Female subjects of childbearing potential agreeing to use one of the acceptable methods of contraception listed below from the time of signing the informed consent until 5 months following administration of the last dose of study medication:
   - The subject's male partner has undergone documented vasectomy with documentation of azoospermia (male sterilization) and the use of a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
   - A documented placement of an intrauterine device (IUD) or intrauterine system (IUS) and the use of a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
   - Oral contraceptives (combination estrogen/progesterone pills), injectable progesterone, or subdermal implants and the use of a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
   - Documented tubal ligation (female sterilization). In addition, a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
   - True abstinence: When this is in line with the preferred and usual lifestyle of the subject, including female subjects with same sex partners. Periodic abstinence (eg, calendar, ovulation, symptothermal, post ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent subjects have to agree to use one of the above-mentioned contraceptive methods, if they start sexual relationships during the study and for up to 5 months after the last dose of study drug.
6. Male subjects agreeing to use acceptable methods of contraception if the male subject's partner could become pregnant from the time of the first administration of study medication until 5 months following administration of the last dose of study medication. One of the following acceptable methods of contraception must be utilized:

- Surgical sterilization (vasectomy with documentation of azoospermia) and a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
- The subject's female partner uses oral contraceptives (combination estrogen/progesterone pills), injectable progesterone, or subdermal implants and a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
- The subject's female partner uses medically prescribed topically-applied transdermal contraceptive patch and a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
- The subject's female partner has undergone documented tubal ligation (female sterilization). In addition, a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository) must be used.
- The subject's female partner has undergone documented placement of an IUD or IUS and the use of a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
- True abstinence: When this is in line with the preferred and usual lifestyle of the subject, including male subjects with same sex partners. Periodic abstinence (eg, calendar, ovulation, symptothermal, post ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent subjects have to agree to use one of the above-mentioned contraceptive methods, if they start sexual relationships during the study and for up to 5 months after the last dose of study drug.

7. Vaccinated against *Neisseria meningitides* with meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine and confirmed seroconversion to ACWY on Day -1.
8. Willing to comply with protocol-required visit schedule and visit requirements and provide written informed consent.
9. Light smokers and users of nicotine (defined as the equivalent of 10 cigarettes per day) or nonsmokers and non-users of nicotine for at least 90 days before screening.

5.1.2. Inclusion Criteria for all Patients in Part C

1. Adults aged minimum 18 years at screening.
2. Granulocyte and monocyte PNH clone >1% as documented by medical records.
3. LDH ≥1.5 ULN in the absence of eculizumab. If on stable eculizumab therapy, as assessed by the Investigator, patients must have historical laboratory values documenting elevated LDH levels before administration of the first dose of eculizumab.
4. Female patients of childbearing potential agreeing to use one of the acceptable methods of contraception listed below from the time of signing the informed consent until 5 months following administration of the last dose of study medication:

- The subject's male partner has undergone documented vasectomy with documentation of azoospermia (male sterilization) and the use of a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
- A documented placement of an IUD or IUS and the use of a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
- Oral contraceptives (combination estrogen/progesterone pills), injectable progesterone, or subdermal implants and the use of a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
- Documented tubal ligation (female sterilization). In addition, a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
- True abstinence: When this is in line with the preferred and usual lifestyle of the patient, including female subjects with same sex partners. Periodic abstinence (eg, calendar, ovulation, symptothermal, post ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent patients have to agree to use one of the above-mentioned contraceptive methods, if they start sexual relationships during the study and for up to 5 months after the last dose of study drug.

5. Male patients agreeing to use acceptable methods of contraception if the male patient's partner could become pregnant from the time of the first administration of study medication until 5 months following administration of the last dose of study medication. One of the following acceptable methods of contraception must be utilized:
   - Surgical sterilization (vasectomy with documentation of azoospermia) and a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
   - The patient's female partner uses oral contraceptives (combination estrogen/progesterone pills), injectable progesterone, or subdermal implants and a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
   - The patient's female partner uses medically prescribed topically-applied transdermal contraceptive patch and a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).
   - The patient's female partner has undergone documented tubal ligation (female sterilization). In addition, a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository) must be used.
   - The patient's female partner has undergone documented placement of an IUD or IUS and the use of a barrier method (condom or occlusive cap [diaphragm or cervical/vault caps] used with spermicidal foam/gel/film/cream/suppository).

- True abstinence: When this is in line with the preferred and usual lifestyle of the patient, including male subjects with same sex partners. Periodic abstinence (eg, calendar, ovulation, symptothermal, post ovulation methods) and withdrawal are not acceptable methods of contraception. Abstinent patients have to agree to use one of the above-mentioned contraceptive methods, if they start sexual relationships during the study and for up to 5 months after the last dose of study drug.

6. Willing to comply with protocol-required visit schedule and visit requirements and provide written informed consent.
7. Vaccinated against *Neisseria meningitides* according to standard practice at the clinical study site.

5.2. Exclusion Criteria

5.2.1. Exclusion Criteria for all Subjects in Part A and Part B

1. Any uncontrolled or serious disease, or any medical or surgical condition, that may either interfere with participation in the clinical study and/or put the subject at significant risk (according to Investigator's judgment) if he/she participates in the clinical study.
2. A known underlying disease, or surgical or medical condition that, in the opinion of the Investigator, may interfere with interpretation of the clinical study results.
3. Active serious mental illness or psychiatric disorder, including, but not limited to, schizophrenia, bipolar disorder, or severe depression requiring current pharmacological intervention.
4. Clinically significant illness within the 7 days before administration of the first dose of study drug.
5. Alanine aminotransferase (ALT) or aspartate aminotransferase above normal range; total bilirubin, alkaline phosphatase, or albumin outside the reference range and considered clinically relevant in the opinion of the Investigator at screening and Day -1.
6. Complete blood count (CBC) clinical laboratory results that are considered clinically relevant and unacceptable by the Investigator at screening and Day -1.
7. International normalized ratio above the reference range at the Screening visit.
8. Complement activity below normal reference range as evaluated by CAP ELISA.
9. Known or suspected hereditary asymptomatic complement deficiency.
10. Any other clinical safety laboratory result considered clinically significant and unacceptable by the Investigator.
11. Clinical laboratory evidence or clinical diagnosis of human immunodeficiency virus (HIV) infection, hepatitis C virus (HCV) infection, or chronic hepatitis B virus (HBV) infection (as shown by hepatitis B surface antigen [HBsAg] positivity).
12. Positive screen for alcohol or drugs of abuse at screening and Day -1 and consume more than 14 (female) or 21 (male) units of alcohol a week (unit: 1 glass of wine [125 mL] = 1 measure of spirits = ½ pint of beer).

13. History or clinical evidence of alcohol abuse, within the 12 months before screening. Alcohol abuse is defined as regular weekly intake of more than 21 units for males and 14 units for females (using alcohol tracker http://www.nhs.uk/Tools/Pages/NHSAlcoholtracker.aspx).
14. History or clinical evidence of drug abuse, within the 12 months before screening. Drug abuse is defined as compulsive, repetitive, and/or chronic use of drugs or other substances with or without problems related to their use and/or where stopping or a reduction in dose will lead to withdrawal symptoms.
15. Donated more than 500 mL of blood within 90 days before the first dose of study drug.
16. Received an investigational agent (including complement C5 inhibitors) within 90 days before the first dose of study drug or are in follow-up of another clinical study.
17. Used prescription medications within 14 days or 7 half-lives (whichever is longer) of administration of the first dose of study drug.
18. Used over-the-counter (OTC) medication, excluding routine vitamins, within 7 days before the first dose of study drug, unless determined by the Investigator and Sponsor to be not clinically relevant, and unlikely to impact on study outcomes.
19. History of intolerance to SC injection or relevant abdominal scarring (surgical, burns, etc.).
20. History of meningococcal infection.
21. History of vaccinations with evidence of insufficient immunizations.
22. History of significant recurrent infections in the opinion of the Investigator or delegate.
23. Presence or suspicion of active viral, bacterial, fungal, or parasitic infection including herpes, herpes zoster, or cold sores within 14 days before the first study drug administration (patients may be rescreened).
24. Subjects who have had their spleen removed for any reason.
25. History of multiple drug allergies or history of allergic reaction to an oligonucleotide or GalNAc.
26. Known hypersensitivity or contraindication to any medication, including any vaccine component, or current manifestation of any significant allergic disorder.
27. Clinically significant allergic reactions to antibiotics in the opinion of the Investigator and not willing to use antibiotic prophylaxis as specified in protocol.
28. Legal incapacity or limited legal capacity at screening.
29. Any other conditions which, in the opinion of the Investigator, would make the subject unsuitable for enrollment or could interfere with the subject's participation in or completion of the study.
30. Travelled to Saudi Arabia or Africa within 90 days of screening, or who plan to do so during the study (patients may be rescreened).
31. Women who are pregnant or breastfeeding.

5.2.2. Exclusion Criteria for All Patients in Part C

1. History of venous or arterial thromboembolic events within the past 12 months.
2. Active serious mental illness or psychiatric disorder, including, but not limited to, schizophrenia, bipolar disorder, or severe depression requiring current pharmacological intervention.
3. ALT >2 × ULN and considered clinically relevant in the opinion of the Investigator.
4. CBC laboratory results that are considered clinically relevant and unacceptable by the Investigator.
5. Any other clinical safety laboratory result considered clinically significant and unacceptable by the Investigator.
6. Known or suspected hereditary asymptomatic complement deficiency.
7. Known clinical laboratory evidence or clinical diagnosis of HIV infection, HCV infection, or chronic HBV infection (as shown by HBsAg positivity).
8. History or clinical evidence of alcohol abuse, within the 12 months before screening. Alcohol abuse is defined as regular weekly intake of more than 21 units for males and 14 units for females (using alcohol tracker http://www.nhs.uk/Tools/Pages/NHSAlcoholtracker.aspx).
9. History of multiple drug allergies or history of allergic reaction to an oligonucleotide or GalNAc.
10. History of intolerance to SC injection or relevant abdominal scarring (surgical, burns, etc.).
11. History of meningococcal infection.
12. Presence or suspicion of active viral, bacterial, fungal, or parasitic infection including herpes, herpes zoster; or, for cold sores within 14 days before the first study drug administration (patients may be rescreened).
13. Legal incapacity or limited legal capacity at screening.
14. Any other conditions which, in the opinion of the Investigator, would make the patient unsuitable for enrollment or could interfere with the patient's participation in or completion of the study.
15. Travelled to Saudi Arabia or Africa within 90 days of screening, or who plan to do so during the study (patients may be rescreened).
16. Women who are pregnant or breastfeeding.

5.3. Withdrawal Criteria

In accordance with the Declaration of Helsinki, subjects/patients will be free to withdraw from the study at any time if they wish so, for any reason specified or unspecified, without penalty to their continuing medical care.

5.3.1. Reason for Withdrawal

The Investigator, or designee, may withdraw a subject/patient from the study if the subject/patient:

- Is in violation of the protocol
- Has an AE
- Meets individual stopping criteria
- Requires the use of/need for a prohibited medication, which in the opinion of the Sponsor or Investigator, may jeopardize the study results or represent a risk to the participant
- Requests to be withdrawn from the study (subject/patient withdrawal of consent)
- Is found to be considerably non-compliant with the protocol-required study drug dosing visits
- In the Investigator's opinion, is unable to continue study participation
- Is withdrawn from the study upon the request of Sponsor or the SRC, including Sponsor termination of the study

Where a subject/patient meets withdrawal criteria for the study, no further study drug will be administered and, wherever possible, such study participants will continue to be followed for safety (see Section 5.3.2).

5.3.2. Handling of Withdrawals

In the event that a subject/patient withdraws or is withdrawn from the study, the Investigator will inform the Medical Monitor and Sponsor immediately. If a subject/patient is withdrawn because individual stopping criteria have been met, the subject/patient requires the use of a prohibited medication, which in the opinion of the Sponsor or Investigator, may jeopardize the study results or represent a risk to the participant, or there is another medical reason for withdrawal, no further study drug will be administered and the subject/patient will remain under the supervision of the Investigator for protocol specified safety follow-up procedures. The SRC will be notified.

When a subject/patient withdraws or is withdrawn from the study, every effort should be made to conduct the Early Termination (ET) visit as soon as possible following withdrawal.

A subject/patient who fails to return for ET evaluations will be contacted by the site in an attempt to have the subject/patient comply with the protocol. The site will follow-up by telephone at least twice and send a letter to the subject/patient who fails to return for the ET visit.

If a subject/patient is withdrawn for an AE, appropriate medical care should be provided and, if possible, the AE should be followed until resolution.

When a subject/patient withdraws from the study, the primary reason for discontinuation must be recorded in the appropriate section of the electronic case report form (eCRF) and all efforts will be made to complete and report the observations as thoroughly as possible.

5.3.3. Replacements

Subjects/patients who voluntarily withdraw or are withdrawn are termed dropouts.
Subjects/patients who withdraw or are withdrawn from the study due to an AE that does not meet progression/escalation and dose suspension/stopping rules may be replaced with confirmation by the SRC. Subjects/patients who withdraw from the study for reasons other than experiencing an AE may be replaced following discussion between the Sponsor and the Investigator.

6. TREATMENT OF SUBJECTS

6.1. Description of Study Drug

Table 9: Investigational Product

	Investigational Product
Product Name:	ALN-CC5
Dosage Form:	Solution for injection
Route of Administration	SC injection
Physical Description	Clear, colorless to pale yellow solution

6.2. Concomitant Medications

6.2.1. Permitted Concomitant Medications

The following medications/treatments are permitted for all subjects/patients during the study:

- Oral contraceptives (combination estrogen/progesterone pills), injectable, progesterone, or subdermal implants
- Study applicable vaccinations
- Hormone replacement therapy
- Acetaminophen (maximum 2 g daily) for treatment of AEs
- Ciprofloxacin or other penicillin antibiotics
- At the discretion of the Investigator, prescription or nonprescription medications may be permitted when necessary to treat an AE. Before the subject/patient uses any prescription or nonprescription medications, the Investigator or delegate must be consulted.

6.2.2. Prohibited Concomitant Medications

The following medications/treatments are not permitted for subjects in Part A and Part B of the study:

- Any OTC medications, except routine vitamins from 7 days before the first dose of study drug, unless considered not clinically relevant by the Investigator and the Sponsor
- Prescription medications not specified in Section 6.2.1 from 14 days or 7 half-lives (whichever is longer) before the first dose of study drug

There are no prohibited concomitant medications for patients in Part C.

6.3. Subject Restrictions

Subjects in Part A and Part B will be required to comply with the following restrictions during the study:

- When subjects are confined to the clinical study site, only the drinks and meals provided by the study site personnel will be allowed.
- Intake of alcohol will not be allowed for 24 hours before all study visits.
- Subjects can be light smokers/users of nicotine products (including snuff and chewing tobacco, and other nicotine-containing products).
- Intake of caffeine will not be allowed 24 hours before screening and all study visits.
- Blood donation will not be allowed at any time during the study and for up to 90 days after postdose follow-up is completed.
- Subjects must refrain from unaccustomed strenuous physical exercise for 48 hours before screening, study visits, and until postdose follow-up is completed.
- Subjects must not consume poppy seeds 48 hours before screening, before study drug administration, and until postdose follow-up is completed.
- Subjects must abstain from the consumption of energy drinks containing taurine or glucuronolactone 24 hours before screening, before study drug administration, until discharge, and before study visits and postdose follow-up.

There are no restrictions for patients in Part C.

6.4. Treatment Compliance

Subject/patient compliance with study drug use is not relevant because all doses will be administered by qualified clinical study site personnel; any missed doses will be reported.

6.5. Assignment to Dose Cohort and Subject Number

The assignment of number and code for subject/patient identification is based on the requirement for anonymity. Subjects/patients will be assigned a study identification number at screening. In Part A and Part B, after confirmation of eligibility, during screening, and upon admission to the clinical study site, subjects will be assigned to a dose level cohort. No subject will be a member of more than one cohort. A unique subject identification number, incorporating the site number, will be assigned sequentially after the subject/patient has completed all of the screening procedures and is determined to be eligible and dosed for the study.

6.6. Randomization and Blinding

Part A and Part B will be conducted in a randomized 3:1 (ALN CC5:placebo), double-blinded, placebo-controlled manner.

The study subjects, Investigators, Medical Monitors, and members of the study team at the Sponsor and at the Contract Research Organization(s) (CROs), clinical study site personnel, and members of the SRC will remain blinded to the treatment assignment for a minimum of 9 months

after a subject receives his or her last dose of study drug. If an individual subject's complement functional activity as measured by CAP ELISA is within the reference range, prophylactic antibiotics will be stopped after unblinding and that subject will have completed the study. If an individual subject who received ALN-CC5 has a CAP ELISA result that has not returned to within the reference range after unblinding, then prophylactic antibiotics will continue and the subject will be required to attend follow-up visits until the CAP ELISA result returns to within the reference range or until the SRC makes a decision on a case-by-case basis to discontinue follow-up and prophylactic antibiotics, whichever is sooner (see Section 3.5.3).

A biostatistician at the CRO, who is not related to the conduct of the study, and the pharmacokineticist at the Sponsor will be unblinded. The biostatistician at the Sponsor, who is related to the conduct of the study, will not be unblinded. Dummy identifiers will be assigned to PK, PD, and safety data by the unblinded statistician at the CRO to maintain double-blind status of the study.

The clinical study site pharmacist will receive a cohort-specific randomization list and will prepare and dispense the study drug according to that list. The clinical study site pharmacist will be unblinded, but will maintain the blind according to site-specific procedures and the Pharmacy Manual. ALN-CC5 may be visually distinguishable from placebo; therefore, syringes will be masked in the pharmacy before transfer to the clinic for dose administration.

For optional cohorts (Part A and Part B) the same randomization procedures will be applied.

Part C of the study will be conducted as an open-label portion of the study. No blinding procedures will be needed.

The information provided to the Sponsor for subject identification will be the assigned subject identification number, the randomization number (for subjects admitted to the study), age and gender. The subject identification number will appear on all documents relating to that subject and will be cross-referenced by the randomization number for the enrolled subjects.

Further details will be included in the Study Manual/Procedures and in the Statistical Analysis Plan (SAP).

6.6.1. Breaking the Blind

In case of emergency, the clinical study site pharmacist will have access to the randomization list, which contains the study drug assignment for subjects.

The coding system in the blinded part of the study includes a mechanism permitting rapid unblinding. If the blind is prematurely broken, the investigator will promptly document and explain any unblinding to the sponsor. In emergency situations, the investigator may need to break the treatment code immediately, or as quickly as possible, if it is in the best interest of the subject; thus, the investigator will have unrestricted and immediate access to break the treatment code via the randomization list held by the site pharmacist.

If a subject becomes pregnant or seriously ill during the study or follow-up period, the blind should be broken only if knowledge of the treatment administered will affect treatment options available for the subject. If possible, before breaking the blind, the Investigator, or designee, should attempt to contact the Medical Monitor and the Sponsor. If there is a requirement to unblind subjects at the cohort level, only the subjects in that cohort will be unblinded.

A record of when the blind was broken, who broke the blind, and why it was broken, will also be maintained in the TMF. Should unblinding occur, it will not have an impact on the planned study analyses.

7. STUDY DRUG MATERIALS AND MANAGEMENT

7.1. Study Drug

ALN-CC5 is a synthetic, chemically modified siRNA targeting CC5 mRNA ([redacted]) with a covalently attached triantennary GalNAc ligand. ALN-CC5 will be supplied as a sterile 200-mg/mL solution for SC injection. In Part A and Part B, study drug is defined as ALN-CC5 or placebo. In Part C, study drug is defined as ALN-CC5.

Placebo will be administered to subjects participating in Part A and Part B of the study and will be supplied by the clinical study site as sterile normal saline 0.9% for SC injection.

7.1.1. Antibiotic Prophylaxis

Ciprofloxacin will be supplied by the clinical study sites.

7.1.2. Study-specific Vaccinations

Meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine will be supplied by the clinical study sites.

7.2. Study Drug Packaging and Labeling

All packaging, labeling, and preparation of ALN-CC5 will be in compliance with Good Manufacturing Practice (GMP) specifications, as described in The Rules Governing Medicinal Products in the European Union, Volume 4, Annex 13, Investigational Medicinal Products, and any other or local applicable regulations.

Study drug labels will include all appropriate local labeling requirements on the vial and external packaging. Sample labels will be submitted to health authorities according to local country submission requirements.

ALN-CC5 (solution for SC injection) is packaged in 2-mL glass vials with a fill volume of no less than 0.55 mL to allow for complete withdrawal of a 0.5-mL of drug product at the pharmacy. The container closure system consists of a Type I glass vial, a Teflon-faced 13-mm stopper, and a flip-off aluminum seal.

7.3. Study Drug Storage

All doses of the study drug will be stored upright and refrigerated at approximately 2 to 8°C. The vial should be stored in the carton until ready for use in the storage area of the clinical study site pharmacy, in a secure, temperature-controlled, locked environment with restricted access. Any deviation from the recommended storage conditions should be reported to Sponsor and/or the CRO and use of the study drug halted until authorization for its continued use has been provided by Sponsor or designee.

No special procedures for the safe handling of ALN-CC5 are required.

The Sponsor will be permitted, upon request, to audit the supplies, storage, dispensing procedures, and records.

7.4. Study Drug Preparation

The study drug may be dispensed only by the pharmacist. Each clinical study site will be responsible for assembly and labeling of injection syringe(s) according to procedures detailed in the Pharmacy Manual. The pharmacist will prepare the study drug using an aseptic technique. The amount (in mg) of study drug to be administered will be determined based on the assigned dose level for the cohort. On study drug dosing days, the pharmacist or designee will withdraw the required amount of study drug into one or more syringes to be administered to the subject/patient on that day. The procedure for preparing study drug and the volume to be loaded into each syringe will be provided in the Pharmacy Manual/Part C Pharmacy Manual.

7.5. Study Drug Administration

Subjects/patients will be administered study drug by SC injection(s) by qualified clinical study site staff under the supervision of the Investigator or designee and the injection site may be marked and mapped for later observation. The preferred site of injection is the abdomen and for administration of multiple injections, the injection site should be rotated. Optional additional sites are the upper arms and thighs. If a local reaction around the injection site occurs, photographs may be obtained.

In Part C, ALN-CC5 may be administered at home between visits to the clinical study center by a home healthcare provider trained in the administration of ALN-CC5.

Detailed instructions for dose administration will be included in the Drug Administration Manual.

7.5.1. Injection Site Examinations

Further details, including guidance on AE recording in relation to ISRs, will be described in the Study Manual (see Section 10.4.2.1).

7.6. Study Drug Accountability

The Investigator or designee will maintain accurate records of receipt and the condition of all study drugs, including dates of receipt. In addition, accurate records will be kept by the pharmacist of when and how much study drug is dispensed and used by each subject/patient in the study. Any reason for departure from the protocol dispensing regimen must also be recorded.

Drug accountability records and inventory will be available for verification by the Sponsor, or designee. At the completion of the study, there will be a final reconciliation of all study drugs.

Study drug must not be used for any purpose other than the present study. Study drug, which has been dispensed to a subject and returned unused must not be re-dispensed to a different subject.

Further instructions about study drug accountability will be detailed in the Pharmacy Manual.

7.7. Study Drug Handling and Disposal

Remaining study drug (all used, partially used, and unused vials) will be returned to the Sponsor or its agent or destroyed at the clinical study site according to applicable regulations and only after receipt of written authorization from the Sponsor.

8. PHARMACOKINETIC ASSESSMENTS

Blood and urine samples will be collected for assessment of ALN-CC5 PK parameters and possible metabolite analysis. The PK parameters include, but are not limited to, maximum (peak) plasma drug concentration (C_{max}), time to reach maximum plasma concentration (t_{max}), area under the plasma concentration versus time curve (AUC), and apparent terminal elimination half-life ($t_{½}$).

8.1. Blood Sample Collection

Blood samples will be collected for assessment of ALN-CC5 PK parameters and possible metabolite analysis at the time points in the Schedule of Assessments. A detailed scheduled of time points for the collection of blood samples for PK analysis are in Table 10, Table 11, Table 12, Table 13, and Table 14 in the appendices (Section 18).

8.2. Urine Sample Collection

Urine samples for determination of ALN-CC5 concentration will be obtained from the total urine sample collected at the time points in the Schedule of Assessments. A detailed scheduled of time points for the collection of urine samples for PK analysis are in Table 10, Table 11, Table 12, Table 13, and Table 14 in the appendices (Section 18). Urine samples for will be retained on behalf of the Sponsor for a maximum of 7 years following the last subject's/patient's last visit in the study.

8.3. Sample Analysis

Plasma and urine samples for determination of ALN-CC5 concentration will be analyzed by a GLP-validated liquid chromatography-mass spectroscopy method. Details regarding the collection, processing, shipping, and storage of the samples will be provided in a Laboratory Manual.

9. PHARMACODYNAMIC AND EXPLORATORY ASSESSMENTS

9.1. Pharmacodynamic Blood Sample Collection

Blood samples for PD analysis will be collected at the time points in the Schedule of Assessments.

The PD analysis will include assessment of the impact of ALN-CC5 administration on plasma levels of C5 protein levels (assessed by ELISA and/or mass spectrometry-based methods) and serum complement activity (assessed by CAP ELISA and CCP ELISA assays).

Samples will be analyzed at central laboratories. Details regarding the collection, processing, shipping, and storage of the samples will be provided in a Laboratory Manual.

9.2. Exploratory [redacted]

[redacted]

[redacted].

Exploratory assessments in Parts A, B, and C of the study include inhibition of hemolysis (assessed by sensitized sheep RBC and [redacted] Samples for these analyses will be aliquoted from the blood sample collected for complement activity.

For Part C, exploratory assessments in patients with PNH also include, but are not limited to, LDH levels, [redacted] and eculizumab levels (patients on stable doses of eculizumab only).

[redacted]

Details regarding the collection, processing, storage, and shipping of samples will be in the Laboratory Manual.

9.3. Exploratory [redacted]

[redacted] Further details regarding these assessments will be included in the Study Manual/Procedures.

9.3.1. [redacted]

[redacted].

9.3.2. [redacted]

[redacted]

9.3.3. [redacted]

[redacted]

9.3.4. [redacted]

[redacted]

10. ASSESSMENT OF SAFETY

10.1. Safety Parameters

10.1.1. Demographics and Medical History

Subject/patient demographic data (age, gender, race, and ethnicity) will be obtained during screening.

A complete medical history will be obtained at screening and will include past and present conditions of the following: general, head and neck, eyes, ears, nose and throat, chest/respiratory, heart/cardiovascular, gastrointestinal/liver, gynecological/urogenital, musculoskeletal/extremities, dermatological/skin, neurological/psychiatric, endocrine/metabolic, hematologic/lymphatic, allergies/drug sensitivities, past surgeries, substance abuse, or any other disease or disorder. The subject's/patient's medical history will be verified by either a personal physician or medical practitioner, as appropriate. For Part C only, [redacted] will be captured as part of complete medical history.

After the Screening visit, the medical history for each subject/patient will be updated with any changes during the interval since the last recording and before the first dose of the study drug. Any changes in medical history will be evaluated against the inclusion and exclusion criteria to determine the subject's/patient's continued eligibility for the study before the first dose.

10.1.2. Vital Signs

Vital signs (oral body temperature, blood pressure, heart rate, and respiration rate) will be measured at the time points in the Schedule of Assessments. Vital signs will be measured in the supine position after the subject has rested comfortably for at least 10 minutes.

10.1.3. Weight, Height, and Body Mass Index

Height will be measured in centimeters and weight in kilograms. Measurements should be obtained with the subject/patient wearing light clothing and without shoes using calibrated scales for all measurements. BMI will be calculated from the height and weight measured at time points in the Schedule of Assessments.

10.1.4. Physical Examination

Physical examinations will be performed at the time points in the Schedule of Assessments.

A full physical examination includes an assessment of the following: general appearance, skin, eyes, ears, nose, throat, thyroid/neck, lymph nodes, abdomen, chest/respiratory, heart/cardiovascular, gastrointestinal/liver, dermatological/skin, neurological/psychiatric, and musculoskeletal system/extremities.

A directed physical examination includes an assessment of the following: chest/respiratory, heart/cardiovascular, dermatological/skin, gastrointestinal/liver, musculoskeletal/extremities, and abdomen.

10.1.5. Electrocardiogram

Triplicate 12-lead ECGs will be recorded at the time points in the Schedule of Assessments. ECGs will be stored electronically on the relevant information system for the clinical study site. Only ECGs recorded electronically will be valid for any purpose other than safety assessment. ECG printouts may be filed in the eCRF for the subject/patient for medical safety reviews.

Each ECG recorder will be set up to the required technical specifications and containing the information required to identify the records. Each ECG recording will be clearly identified (subject/patient identification number, visit date, and the actual times of ECG recordings).

Triplicate 12-lead ECG recordings will be measured in the supine position after the subject/patient has rested comfortably for at least 10 minutes. Subjects/patients will avoid postural changes during the ECG recordings and clinical study site staff will ensure that subjects/patients remain awake during the ECG recording.

All recorded ECGs will be reviewed by the Investigator, or designee, and the review documented in the eCRF. Bazett-corrected QT interval (QTcB) will be automatically calculated by the clinical study site equipment and available on the ECG printout. Fridericia-corrected QT interval will only be assessed at the clinical study site if QTcB is prolonged. If a subject/patient shows an abnormal ECG, additional safety recordings (including 5- or 12-lead Holter ECG equipment) may be obtained and the abnormality followed to resolution, if required.

Details regarding ECG assessments using clinical study site-specific equipment will be in the Study Manual/Procedures.

10.1.6. Maximum Blood Volume

The maximum total blood volume that will be collected from subjects and patients participating in this study will be documented in the Study Manual/Procedures. Maximum total blood volume according to study part is as follows:

- Part A: up to 800 mL over the extended course of the study
- Part B: up to 900 mL over the course of the study
- Part C: up to 900 mL over the course of the study

10.1.7. Laboratory Assessments

10.1.7.1. Biochemistry, Hematology, Coagulation, and [redacted]

Blood samples for determination of hematology, biochemistry, and coagulation parameters will be obtained at the time points in the Schedule of Assessments. Analyses will be performed at a local laboratory, using routine methods, except where noted. Details regarding the processing, shipping, and analysis of samples will be provided in the Laboratory Manual.

Additional and repeat testing may be performed at the discretion of the Investigator. In the event of an unexplained clinically relevant abnormal laboratory test occurring after study drug administration, the test should be repeated and followed up at the discretion of the Investigator until it has returned to the normal range and/or a diagnosis is made to adequately explain the abnormality.

Biochemistry Parameters

- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Alkaline phosphatase (ALP)
- Gamma glutamyl transferase (GGT)
- Uric acid
- Bilirubin (TBIL; total and direct)
- Cholesterol
- Triglycerides
- Sodium
- Creatine phosphokinase
- Lactate dehydrogenase (LDH)
- Urea (BUN)
- Creatinine
- Potassium
- Chloride
- Glucose
- Inorganic phosphate
- Calcium
- Total protein
- Albumin
- Carbon dioxide
- C-reactive protein (CRP)

Hematology Parameters

- Hemoglobin
- Hematocrit
- Red blood cell count (erythrocytes and reticulocytes)
- Mean cell hemoglobin (MCH)
- Platelets
- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin concentration (MCHC)
- White blood cell count
- Differential blood count (absolute and %: neutrophils, lymphocytes, monocytes, eosinophils, and basophils)
- PNH (type III) cells (Part C only)

Coagulation Parameters

- Prothrombin time (PT)
- Activated partial thromboplastin (aPTT)
- International normalized ratio (INR)

- [redacted]

[redacted]

10.1.7.2. Urinalysis

Urine samples for determination of urinalysis parameters will be obtained at the time points in the Schedule of Assessments.

Urinalysis[a]

- Ketones
- Bilirubin
- Urobilinogen
- Nitrite
- Specific gravity
- Protein
- Leukocytes
- Urine microscopy
- pH
- Glucose
- Red blood cells

a Visual inspection for appearance and color will occur; urine microscopy will be performed if clinically indicated.

10.1.7.3. [redacted]

[redacted]

Details regarding the processing, shipping, and analysis of the samples will be provided in the Laboratory Manual.

10.1.7.4. Viral Serology

Serology will be performed at the time points in the Schedule of Assessments. During screening, subjects and patients will be tested for HIV-I and II antibody, HBsAg, and anti-HCV. Results of the assessments will not be entered into the study database. If a subject/patient is confirmed positive for any of these tests, the subject/patient will be referred for further examination, counseling, or treatment and is not eligible for the study.

10.1.7.5. Drugs of Abuse and Alcohol Screening (Part A and Part B only)

Urine will be tested for drugs of abuse (DOA) at the clinical study site at the time points in the Schedule of Assessments. If a subject fails the DOA screening, they will be excluded from the study. A repeat drug screen may only be performed when methodological reasons are believed to have led to a false positive. Borderline positive results, unless covered by the preceding condition, are to be considered as positive and the subject will be excluded from the study. If subjects are found to be positive due to medication (eg, flu or cold remedies) they may undergo a repeat drug screen if they continue to meet study requirements.

An alcohol test (urine and/or breathalyzer) will be performed according to local clinical study site policy at the time points in the Schedule of Assessments. If a subject tests positive then they will be excluded from the study. Details will be provided in the Study Manual/Procedures.

Drugs of Abuse (Urine)

- Amphetamines
- Barbiturates
- Benzodiazepines
- Cannabinoids
- Opiates
- Cocaine
- Methadone

10.1.7.6. Pregnancy Screening

Serum β-HCG test will be performed at the time points in the Schedule of Assessments. Any woman with a positive pregnancy test before study entry will be excluded from the study. Any woman with a positive pregnancy test during the study will be discontinued from study drug, but will continue to be followed for safety.

10.1.7.7. Follicle-Stimulating Hormone Assessment

The postmenopausal status of women will be confirmed by a follicle-stimulating hormone test at the time points in the Schedule of Assessments.

10.1.8. Study-specific Vaccinations

Meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine will be administered in accordance with the manufacturer's instructions. Further details will be included in the Study Manual/Procedures.

10.1.8.1. Vaccination Specifications for Part A and Part B

Subjects will be immunized against *Neisseria meningitides* according to the following specifications before receiving the first dose of study drug:

- Subjects who were not previously vaccinated will be vaccinated with meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine. Vaccinations should be administered within the 90 day screening period according to the following plan (Note: Vaccination day is not the same as Study Day):

  Vaccination day 1: administer meningococcal group ACWY conjugate and meningococcal group B vaccine

  Vaccination day 28: measure ACWY titer and administer meningococcal group B vaccine booster

  Vaccination day 56: assessment of ACWY titer result; if positive, vaccination program is complete; if negative, consider repeat measurement of ACWY titer

- Subjects who were previously vaccinated must have confirmed seroconversion to ACWY (laboratory documentation less than 12 months old is considered valid) before administration of the first dose of study drug. If the last meningococcal

group B injection was administered more than 12 months before the Day -1 study visit, then a booster injection of this vaccine must be administered before administration of the first dose of study drug.

- Titer measurements will be used to exclude subjects without an immune response to ACWY.

10.1.8.2. Vaccination Specifications for Part C

Patients will be immunized against *Neisseria meningitides* according to the following specifications:

- Treatment-naïve patients with PNH who have previously received meningococcal vaccinations (meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine) can start study assessments after confirming eligibility.
- To reduce the potential for vaccine-induced breakthrough hemolytic events, patients with PNH, who have not been previously vaccinated, will receive ALN-CC5 and antibiotic prophylaxis with ciprofloxacin (according to standard practice at the clinical study site). Following completion of treatment with ciprofloxacin, and within a maximum of 14 days after administration of the first dose of ALN-CC5, patients will be vaccinated with meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine (according to standard practice at the clinical study site). Subsequent prophylaxis with an appropriate antibiotic of the penicillin class can be administered at the Investigator's discretion.
- Patients with PNH who are on stable eculizumab therapy who have previously received both meningococcal vaccinations (meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine) can start study assessments after confirming eligibility. Patients who have not had both vaccinations can receive the remaining vaccination before starting treatment with ALN-CC5.

10.1.9. Prophylactic Antibiotic Administration and Compliance Check

Ciprofloxacin will be administered in accordance with the manufacturer's instructions. Antibiotic compliance checks will be performed at the time points in the Schedule of Assessments.

Subjects participating in Part A and Part B will be treated with prophylactic ciprofloxacin (according to standard practice at the clinical study sites) from start of dosing with study drug (ALN-CC5 or placebo) until serum complement activity, as assessed by CAP ELISA, returns to within the normal reference range. If an individual subject's complement functional activity as measured by CAP ELISA is within the reference range, prophylactic antibiotics will be stopped after unblinding and that subject will have completed the study. If an individual subject who received ALN-CC5 has a CAP ELISA result that has not returned to within the reference range after unblinding, then prophylactic antibiotics will continue and the subject will be required to attend follow-up visits until the CAP ELISA result returns to within the reference range or until the SRC makes a decision on a case-by-case basis to discontinue follow-up and prophylactic antibiotics, whichever is sooner (see Section 3.5.3).

Patients in Part C will receive antibiotics at the discretion of the investigator.

Details of antibiotic compliance methodology will be described in the Study Operations Manual.

10.2. Adverse and Serious Adverse Events

10.2.1. Definition of Adverse Events

10.2.1.1. Adverse Event

An AE is any untoward medical occurrence in a subject, or clinical investigational patient, administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

Therefore, an AE can be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

10.2.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose of study drug:

- Results in death;
- Is life-threatening (an event which places the subject/patient at immediate risk of death from the event as it occurred. It does not include an event that had it occurred in a more severe form might have caused death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly or birth defect;
- An important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject/patient or may require intervention to prevent one of the other outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions, or the development of drug dependency or abuse.

10.2.1.3. Suspected Unexpected Serious Adverse Reactions

A suspected unexpected serious adverse reaction (SUSAR) is any SAE where a causal relationship with the study drug is at least a reasonable possibility, but is not listed in the IB reference safety information.

10.2.1.4. Other Adverse Events

AEs of clinical interest, other than SAEs and those AEs leading to discontinuation of the subject/patient from the study, will be classified as other adverse events (OAEs). OAEs may be identified during the evaluation of safety data.

10.3. Eliciting Adverse Event Information

The subject/patient should be asked about medically relevant changes in his/her health since the last visit. The subject/patient should also be asked if he/she has been hospitalized, had any accidents, used any new medications, or changed concomitant medication routines (both prescription and OTC).

In addition to subject/patient observations, AEs will be documented from any clinically relevant laboratory findings, vital signs, physical examination findings, 12-lead ECG changes, or other documents, that are relevant to subject/patient safety.

10.4. Adverse Event Reporting

The Investigator is responsible for reporting all AEs that are observed or reported after administration of the first dose of study drug through the last postdose follow-up visit regardless of their relationship to study drug or clinical significance.

All AEs must be followed to satisfactory resolution or until the AE is deemed by the Investigator to be chronic or the patient to be stable.

SAEs will be followed until resolved or until the SAE is considered by the Investigator to be chronic or the subject/patient to be stable, whichever occurs first.

Any medical condition that is present when a subject/patient is screened and does not deteriorate is captured as medical history and should not be reported as an AE; however, if it does deteriorate at any time during the study, it may meet the definition of an AE and should be reported.

All AEs must be reported on the appropriate eCRF page and recorded in the source records at the clinical study unit. The description of the AE will include the onset time and date, duration, severity, seriousness, relationship to study drug, action obtained, and outcome (including time and date of resolution, if applicable). AEs resulting from concurrent illnesses, concomitant medications, or progression of disease states must also be reported.

10.4.1. Assessment of Causality

Causal relationship assessment to drug treatment is required for purposes of reporting AEs. To promote consistency, the following guidelines should be taken into consideration along with good clinical and scientific judgment when determining the relationship of study medication to an AE:

Definitely Related: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to the medication administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug should be clinically plausible.

Possibly Related: A clinical event, including laboratory test abnormality, with a reasonable time sequence to the medication administration, but which could also be explained by concurrent disease, or other drugs or chemicals. Information on the drug withdrawal may be lacking or unclear.

Unlikely Related: A clinical event, including laboratory test abnormality, with little or no temporal relationship to medication administration, and which other drugs, chemicals, or underlying disease provide plausible explanations.

Not Related: A clinical event, including laboratory test abnormality, that has no temporal relationship to the medication or has more likely alternative etiology.

10.4.2. Assessment of Toxicity

Standard toxicity grading according to the CTCAE (Version 4.0) will be used to grade AEs. Local laboratory normal values are to be applied. Abnormal laboratory and other tests should always be repeated before grading in order to ensure consistency and to exclude technical errors. Diurnal variations in laboratory parameters and other measurements as well as baseline status and conditions (eg, Gilbert's syndrome) should be taken into account when assessing whether abnormalities constitute a study drug-related AE and when grading, if applicable.

The CTCAE criteria and their interpretation are consistent with the standard severity grading for AEs during clinical trials: Grade I, Grade II, and Grade III AEs may constitute an SAE and/or SUSAR. Grades IV and V constitute an SAE and/or SUSAR.

The grading of the CTCAE related to off-target organ toxicities and potentially expected AEs is considered suitable for ALN-CC5, the study design, and the study populations in conjunction with the protocol suspension/stopping rules and no further qualifications are required.

Refer to CTCAE (Version 4.0) for unique clinical descriptions of severity (Grades 1 through 5) for each AE based on this general guideline:

Grade I:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade II:	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental ADL[a]
Grade III:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]
Grade IV:	Life-threatening consequences; urgent intervention indicated
Grade V:	Death related to AE

Abbreviations: ADL = Activities of Daily Living; AE = adverse event.
a Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

10.4.2.1. Injection Site Signs or Symptoms

Individual signs or symptoms (eg, erythema, swelling, etc.) at the injection site reported by a subject/patient within 4 hours following dose administration will be recorded as an AE. After 4 hours postdose, injection site signs or symptoms will be evaluated according to the CTCAE criteria of Injection Site Reaction (general disorders and administration site conditions). If, after 4 hours postdose, the ISR CTCAE criteria are met, the event is recorded as an ISR; if the criteria

are not met, individual sign(s) or symptom(s) will be recorded as AE(s) under the appropriate System Organ Class (SOC; Medical Dictionary for Regulatory Activities [MedDRA]).

10.5. Serious Adverse Event Reporting

An assessment of the seriousness of each AE will be made by the Investigator. Any AE and laboratory abnormality that meets the seriousness criteria (Section 10.2.1.2) must be reported to the Sponsor within 24 hours from the time that clinical study site personnel first learn of the event, using the SAE Report Form provided. All SAEs must be reported regardless of the relationship to study drug. The SAE must also be recorded on the standard eCRF pages.

The initial report should include at a minimum the following information:

- Subject/patient study number
- Brief description and date of onset of the event
- Event term being reported and criterion for seriousness
- Preliminary assignment of causality to study drug

Routine AE reporting will be via electronic data capture. SAE reporting will be via the paper SAE Report Form provided in the Study Manual/Procedures.

The Investigator will complete the SAE Report Form and fax the form via to Covance Pharmacovigilance and Drug Safety Services (PV and DSS) immediately (within 24 hours) of becoming aware of an SAE.

SAE Reporting Contact Information	
[redacted] PV and DSS fax:	[redacted]
[redacted] PV and DSS telephone:[a]	[redacted]

[a] Where possible, SAE information should be faxed to Covance PV and DSS before initiating telephone contact.

If follow-up is required, new information should be provided to the Sponsor as soon as it becomes available using the SAE Report Form. Copies of discharge summaries, consultant reports, autopsy reports, and any other relevant documents may also be requested.

Appropriate remedial measures should be performed by the Investigator or Sub-investigator using his/her best medical judgment to treat the SAE. These measures and the subject/patient's response to these measures should be recorded. All SAEs, regardless of relationship to study drug, will be followed by the Investigator until satisfactory resolution or the Investigator or Sub-investigator deems the SAE to be chronic or stable. Clinical, laboratory, and diagnostic measures should be employed by the Investigator or Sub-investigator as needed to adequately determine the etiology of the event.

10.6. Suspected Unexpected Serious Adverse Reactions Reporting

Covance Drug Safety Services Europe, Maidenhead, UK, is responsible for coordinating the reporting of SUSARs in accordance with the European Directive 2001/20/EC to the applicable REC.

A fatal or life-threatening SUSAR must be reported to the applicable Regulatory Authority and the relevant REC by the Sponsor, or delegate, within 7 days after the Sponsor first becomes aware of the event. If the initial report is incomplete, a complete report must be submitted within 8 days of sending the first response.

A SUSAR which is not fatal or life-threatening must be reported to the applicable Regulatory Authority and the REC within 15 days after the Sponsor first becomes aware of the event.

The Investigator may be informed by the Sponsor or its representatives of SAEs from other Investigators or clinical studies that may have relevance to this clinical trial. These SAEs should also be reported promptly to the REC that approved this study.

10.6.1. Pregnancy Reporting

A subject/patient who becomes pregnant during this study must be instructed to stop all study drug administration and will continue to be followed for safety. The Investigator or Sub-investigator must report a subject/patient or partner pregnancy to the Sponsor or its agency within 24 hours of being notified of the pregnancy. Details of the pregnancy will be reported on a Pregnancy Report Form. The subject/patient/partner shall receive any necessary counseling regarding the risks of continuing the pregnancy and the possible effects on the fetus. Safety monitoring of the subject/patient/partner will continue until the conclusion of the pregnancy, and the outcome of the pregnancy will be reported to the Sponsor.

If, in the opinion of the Investigator, knowledge of the study drug assignment is required to monitor the pregnancy for safety, then unblinding procedures detailed in Section 6.6.1 will be followed.

11. STATISTICS

11.1. Sample Size and Randomization

This is a randomized Phase 1/2 study to assess the safety and tolerability of ALN-CC5 in SAD and MAD in healthy adult subjects and will also assess the safety and tolerability of ALN-CC5 in patients with PNH. The SAD and MAD portions (Part A and Part B) will be conducted as a double-blinded, placebo-controlled study and the multiple-dose portion in patients with PNH (Part C) will enroll in an open-label fashion. The sample size was not determined based on power calculations. Up to 76 participants (60 subjects and 16 patients) are expected be enrolled in the study (including optional cohorts).

11.2. Analysis Sets

The populations (analysis sets) are defined as follows and will be identified separately for subjects in Part A and Part B, and for patients in Part C:

Safety Analysis Set:	All subjects/patients who receive at least a single dose of study drug will be included in the safety analyses.
PK Analysis Set:	All subjects/patients who receive at least a single dose of study drug, and who have at least one postdose blood sample for PK parameters, and who have evaluable PK data will be included in the PK analyses.
PD Analysis Set:	All subjects/patients who receive at least a single dose of study drug and who have at least one postdose blood sample for the determination of plasma ALN-CC5 will be included in the PD analyses.

11.3. Statistical Methodology

A SAP will be written after finalizing the protocol and before database lock. The specifications in this document will detail the implementation of all the planned statistical analyses in accordance with the principal features stated in the protocol.

Statistical analyses will be primarily descriptive; no formal hypothesis testing will be conducted. Analyses will be performed using SAS® for Windows (Version 9.2 or higher). Data from Part A, Part B, and Part C will be analyzed separately. Summary tables for Part A and Part B will include results by cohort for each dose level of ALN-CC5 and placebo, where the placebo subjects will be combined across dose cohorts. Descriptive statistics will be presented for continuous variables, and frequencies and percentages will be presented for categorical and ordinal variables. Percentages will be based on the number of nonmissing values in a dose group. All study data will be presented in by-subject/patient data listings.

In Part C, data will be analyzed by cohort for patients on the same dose and dose regimen. Additionally, analysis may be based on patients who are either naïve to eculizumab treatment or on stable doses of eculizumab (as assessed by the Investigator).

11.3.1. Baseline Evaluations

Demographics will be summarized for subjects/patients in the safety analysis set, by dose group and overall. If the PK and PD analysis sets are a different set of subjects/patients compared to those included in the safety analysis set, then demographic information will be summarized separately for those analysis sets. Descriptive statistics will be provided for age, height, weight, and BMI at screening. Frequencies and percentages will be tabulated for gender, race, and ethnicity. Demographic information for patients in Part C may include additional disease-specific information at baseline.

11.3.2. Safety Data Analysis

11.3.2.1. Safety Parameters

Safety assessments will include clinical laboratory parameters (hematology, biochemistry, coagulation, and urinalysis), vital signs (oral body temperature, blood pressure, heart rate, and respiration rate), physical examinations, 12-lead ECGs, and AE and concomitant medication monitoring.

11.3.2.2. Adverse Events

AEs will be summarized by the MedDRA SOC and Preferred Term. Separate tabulations will be produced for treatment-emergent adverse events (TEAEs), TEAEs by maximum severity, treatment-related AEs, SAEs, and discontinuation of study drug due to AEs. By-subject and by-patient listings will be provided for deaths, SAEs, and AEs leading to discontinuation of study drug.

11.3.2.3. Clinical Laboratory Safety Parameters, Vital Signs, Physical Examinations, and 12-lead Electrocardiograms

For each continuous laboratory safety parameter (including, but not limited to, hematology, biochemistry, coagulation, and urinalysis) results will be categorized as low, normal, or high based on the laboratory normal ranges. Shifts from baseline laboratory grade to the maximum laboratory grades will be examined for key safety parameters. All out-of-range and clinically significant laboratory results will be identified in data listings. Descriptive statistics will also be provided as actual value and change from baseline over time.

Descriptive statistics for vital signs, and ECG interval data will be presented by actual values and changes over time from baseline. Details of any abnormalities will be included in the data listings.

11.3.3. Pharmacokinetic Analysis

11.3.3.1. Pharmacokinetic Parameters

Blood and urine samples will be collected for assessment of PK parameters and possible metabolite analysis. The PK parameters will be derived from the relevant plasma concentration data of ALN-CC5 by noncompartmental analysis. To assess the single-dose and multiple-dose PK and the overall exposure to ALN-CC5, the PK parameters that will be derived include, but are not limited to, C_{max}, $t_{½}$, t_{max}, and AUC.

For final analysis, actual sampling times, when feasible, will be used for all calculations of the PK parameters. If there is any doubt in the actual time a sample was obtained, then the scheduled time will be used.

11.3.3.2. Analysis

The PK parameters will be calculated and listed for each subject/patient and each cohort, along with summary statistics including arithmetic and geometric means; standard deviations; minimum, maximum, and median values; and coefficients of variation.

The PK data will also be displayed graphically, as appropriate. Exploratory analyses on the PK data and their relationship to PD and safety evaluations may be investigated.

11.3.4. Pharmacodynamic Analysis

The PD parameters will be summarized using descriptive statistics for actual results and relative-to-baseline. For PD parameters, baseline levels will be defined in the SAP. Part A, Part B, and Part C will be analyzed separately. The PD evaluations will include the effect of ALN-CC5 on plasma C5 protein and on serum complement activity. Additional PD parameters are included in the exploratory analysis section.

11.3.5. Exploratory Analysis

Exploratory analyses will assess the effect of ALN-CC5 on inhibition of hemolysis and the effect of ALN-CC5 on the induction [redacted] in subjects and patients.

The remainder of the exploratory analyses are in patients with PNH and include, but are not limited to, effect of ALN-CC5on LDH levels, [redacted]

11.4. Interim Analysis

There is no formal interim analysis planned for this study.

11.5. Handling of Missing and Incomplete Data

Unrecorded values will be treated as missing. The appropriateness of the method(s) described for handling missing data may be reassessed and documented in the SAP at the data review before database lock. Depending on the extent of missing values, further investigation may be made into the sensitivity of the analysis results to the method(s) specified.

12. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

12.1. Quality Assurance and Quality Control

The Investigator(s) will permit trial-related monitoring, audits, and review by the REC, providing direct access to source data/documents. The study may be subject to audit by the Sponsor or its representatives, or external agencies. If such an audit occurs, the Investigator must agree to allow access to the required subject/patient records. In the event of an audit, the Investigator agrees to allow the Sponsor, representatives from the Sponsor, or regulatory agencies access to all study records.

12.2. Monitoring

All aspects of the study will be carefully monitored by the sponsor, or designee, for compliance with applicable government regulations with respect to GCP and current standard operating procedures.

The monitoring of this study will be performed by the Sponsor's Monitor(s) or a designee in accordance with the principles of GCP as laid out by the International Conference on Harmonisation (ICH) in the "Good Clinical Practice: Consolidated Guideline".

The clinical monitor, as a representative of the Sponsor, has an obligation to follow the study closely. In doing so, the monitor will visit the Investigator and site periodically as well as maintain frequent telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and staff.

13. STUDY REPORTING REQUIREMENTS

The Sponsor will immediately notify the Investigator of important safety data (eg, toxicology; absorption, distribution, metabolism, excretion; teratology) that becomes available during the course of this study.

The Investigator will submit reports of SAEs as outlined in this protocol. In addition, the Investigator agrees to submit progress reports to his/her REC per local reporting requirements, or at least annually and at the conclusion of the study. The reports will be made available to the Sponsor or designee.

All deviations from the protocol (including those deemed necessary to protect subject safety) should be reported to the Medical Monitor and the Sponsor within 24 hours of knowledge of the event.

Any communications from regulatory agencies in regard to inspections, other studies that impact this protocol, or the qualifications of study personnel should be promptly reported to the Sponsor.

14. ETHICS

14.1. Informed Consent

The informed consent is a process by which a subject/patient voluntarily confirms his/her willingness to participate in a clinical trial. It is the responsibility of the Investigator or delegate to obtain a written informed consent from each subject/patient participating in the trial, after explanation of the aims, methods, benefits, and potential hazards of the trial and in accordance with GCP requirement (CPMP/ICH/135/95) and Directive 2001/20/EC.

The Subject/Patient Information Sheet and ICF given to the subject/patient should be kept clear, relevant, and understandable, including those measures taken to safeguard subject privacy and the protection of personal data.

The Investigator should provide the subject/patient with sufficient time to decide whether or not to participate in the trial. The subject/patient should be also provided with a contact point where he/she may obtain further information.

If more than the ICF constitutes the materials to be used in the consenting process, the Subject/Patient Information Sheet, ICF, and/or form for the protection of personal data should be translated to the local language and adapted to local requirements (eg, in respect to data protection). Only the approved version of the ICF can be used in the center.

The signatures of the ICF and the Protection of Personal Data Form must be obtained before any trial-specific procedures are performed on the subject/patient. The Investigator must keep 1 form personally signed and dated by the subject/patient on file and a copy of it must be delivered to the subject/patient. The informed consent must be documented in the source records. The subject/patient should be informed if new information becomes available that might be relevant to the subject's/patient's willingness to continue participation in the study.

14.2. Research Ethics Committee Approval

It is the responsibility of the Investigator to submit this protocol, the ICF (approved by Sponsor), all relevant supporting information, and study-specific advertisements to the REC for review. Before the study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for subject recruitment, and any other written information regarding this study to be provided to a subject/patient or subject's/patient's legal guardian must be approved by the REC.

Before implementing changes in the study, the Sponsor and the REC must also approve any revised ICFs and substantial amendments to the protocol.

National regulations and ICH require that approval be obtained from an REC before participation of subjects/patients in research studies.

The Investigator will make all attempts to ensure that the REC is constituted and operates in accordance with ICH GCP and any local regulations.

14.3. Confidentiality

The Investigator agrees to maintain the confidentiality of the study at all times. By signing the final protocol, each Investigator agrees to keep all information and results concerning the study

and the investigational product confidential for as long as the data remain unpublished. This confidentiality obligation applies to all personnel involved at the investigational site.

The Investigator must ensure that subject anonymity will be maintained. On documents submitted to the Sponsor, subjects should not be identified by their names, but by the assigned subject number and initials. If subject names are included on copies of documents, the names (except for initials) will be obliterated and the assigned subject number added to the document before submission to the Sponsor. Documents not for submission to the Sponsor (eg, signed ICFs) should be maintained by the Investigator in strict confidence.

Following GCP principles, a subject number will be used to identify the subject in their study records. Laboratory samples and samples in storage will be labeled with only the subject number; the identity of the subject will only be known by the clinical study site. An independent numbering code and the label will not contain any other personal identification information. The numbering code associated with these labels will be held by the study CRO and the Sponsor, thereby allowing no unwarranted access to the information. When reporting results for interim safety assessment and at the end of the study, the code will be shared per standard operating procedures with the responsible member of the Biostatistical and Data Management Departments of the CRO. The numbering code will also be held for samples in storage until marketing approval in the countries where this study was conducted, or until notified that storage is no longer required.

15. DATA HANDLING AND RECORD KEEPING

15.1. Inspection of Records

The Sponsor will be allowed to conduct clinical trial site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

15.2. Retention of Records

Essential study documents should be retained for the period of time required by applicable local law. The essential documents include the signed and dated final protocol, signed and dated amendments(s), if applicable, signed and dated Curriculum Vitae of the Investigators, copies of the completed eCRFs, signed ICFs, REC approval and all related correspondence, financial agreements, regulatory approval, drug accountability, study correspondence, and subject/patient identification codes. Records will not be destroyed without informing the Sponsor in writing and giving the Sponsor the opportunity to store the records for a longer period of time at the expense of the Sponsor.

See Section 14.3 for confidentiality requirements.

16. PUBLICATION POLICY

It is intended that after completion of the study, the data are to be submitted for publication in a scientific journal and/or for reporting at a scientific meeting. A copy of any proposed manuscript must be provided and confirmed received at the Sponsor at least 30 days before its submission, and according to any additional publication details in the Investigator Agreement.

17. LIST OF REFERENCES

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18. APPENDICES

Appendix 1: Pharmacokinetic Assessment Time Points

The following tables contain detailed PK schedules for the collection of blood and urine samples for PK analysis for the SAD (Part A), MAD (Part B), and MD (Part C) phases of the study.

Table 10: Pharmacokinetic Time Points for Single-ascending Dose Cohorts (Part A)

Protocol Time (hh:mm)	PK Blood	Urine PK	Pooled Urine
Predose (-60 minutes)	X	X	
00:00 (dose)			X 00:00-06:00
00:30 (±2 mins)	X		
01:00 (±5 mins)	X		
02:00 (±15 mins)	X		
04:00 (±15 mins)	X		
06:00 (±15 mins)	X	X	X 06:00-12:00
08:00 (±15 mins)	X		
12:00 (±30 mins)	X	X	X 12:00-24:00
24:00 (±120 mins)	X	X	
48:00 (±120 mins)	X	X	

Table 11: Pharmacokinetic Time Points for Multiple-ascending Dose Cohorts (Part B) – Weekly Dosing

Study Day	Protocol Time (hh:mm)	PK Blood	Urine PK	Pooled Urine
Day 0 and Day 28	Predose (-60 minutes)	X	X	
	00:00 (dose)			X 00:00-06:00
	00:30 (±2 mins)	X		
	01:00 (±5 mins)	X		
	02:00 (±15 mins)	X		
	04:00 (±15 mins)	X		
	06:00 (±15 mins)	X	X	X 06:00-12:00
	08:00 (±15 mins)	X		
	12:00 (±30 mins)	X	X	X 12:00-24:00
Day 1 and Day 29	24:00 (±120 mins)	X	X	
Day 2 and Day 30	48:00 (±180 mins)	X	X	

Table 12: Pharmacokinetic Time Points for the Multiple-ascending Dose Phase (Part B) – Other Dosing Schedules

Study Day	Protocol Time (hh:mm)	PK Blood	Urine PK	Pooled Urine
Day 0 and Day 84	Predose (-60 minutes)	X	X	
	00:00 (dose)			X 00:00-06:00
	00:30 (±2 mins)	X		
	01:00 (±5 mins)	X		
	02:00 (±15 mins)	X		
	04:00 (±15 mins)	X		
	06:00 (±15 mins)	X	X	X 06:00-12:00
	08:00 (±15 mins)	X		
	12:00 (±30 mins)	X	X	X 12:00-24:00
Day 1 and Day 85	24:00 (±120 mins)	X	X	
Day 2 and Day 86	48:00 (±180 mins)	X	X	

Table 13: Pharmacokinetic Time Points for the Multiple Dose Phase (Part C) – 13 Weekly Doses (Cohort 1)

Study Day	Protocol Time (hh:mm)	PK Blood	Urine PK	Pooled Urine
Day 0 and Day 84	Predose (-60 minutes)	X	X	
	00:00 (dose)			X 00:00-06:00
	00:30 (±2 mins)	X		
	01:00 (±5 mins)	X		
	02:00 (±15 mins)	X		
	04:00 (±15 mins)	X		
	06:00 (±15 mins)	X	X	X 06:00-12:00
	08:00 (±15 mins)	X		
	12:00 (±30 mins)	X	X	X 12:00-24:00
Day 1 and Day 85	24:00 (±120 mins)	X	X	

Table 14: Pharmacokinetic Time Points for the Multiple Dose Phase (Part C) – 5 Weekly Doses Followed by Once Every 2 Weeks Dosing or Followed by Monthly Dosing (Cohort 2 and Cohort 3)

Study Day	Protocol Time (hh:mm)	PK Blood	Urine PK	Pooled Urine
Day 0	Predose (-60 minutes)	X	X	
	00:00 (dose)			X 00:00-06:00
	00:30 (±2 mins)	X		
	01:00 (±5 mins)	X		
	02:00 (±15 mins)	X		
	04:00 (±15 mins)	X		
	06:00 (±15 mins)	X	X	X 06:00-12:00
	08:00 (±15 mins)	X		
	12:00 (±30 mins)	X	X	X 12:00-24:00
Day 1	24:00 (±120 mins)	X	X	

Appendix 2: Schedules of Assessments for Alternative Dosing Regimens for Part B

The following tables contain additional Schedules of Assessments for alternative dosing regimens which may be investigated in Part B of the study.

Table 15: Schedule of Assessments for Multiple-ascending Dose Cohorts (Part B) – 13 Weekly Doses

Study Stage	Screening	Weekly Dosing (13 Weeks only)																	Postdose Follow-up				PD Follow-up[c]
Study Day (D)		D-1[a]	D0	D1[b]	D2	D7	D14	D21	D28	D35	D42	D49	D56	D63	D70	D77	D84	D85	D86	D98	D112	D140/ ET	
Visit Window (± Days)	D-90 to D-2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	±4	±4	±4	every 28±7 days
Informed Consent	X																						
Vaccination against *Neisseria meningitides*[d]	X																						
Vaccination titer[d]	X	X																					
Antibiotic compliance check[e]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Demography	X																						
Medical history	X																						
Inclusion/exclusion criteria	X	X																					
Full physical examination[f]	X																					X	
Directed physical examination[f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Body weight and BMI calculation	X	X				X	X	X	X	X	X	X	X	X	X	X	X						
Height	X																						
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG[h]	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X				X	
β-HCG pregnancy test	X	X							X				X				X			X	X	X	
FSH screening	X																						
Viral serology[i]	X																						
Biochemistry, hematology, and coagulation[j]	X	X	X[k]	X		X[k]	X[k]	X[k]	X[k]	X	X[k]	X	X[k]	X	X[k]	X	X[k]	X			X[k]	X	
Urinalysis[j]	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	
Urine DOA/alcohol screen	X	X																					
Randomization			X																				
Study drug administration[l]			X			X	X	X	X	X	X	X	X	X	X	X	X						

Table 15: Schedule of Assessments for Multiple-ascending Dose Cohorts (Part B) – 13 Weekly Doses

Study Stage	Screening	Weekly Dosing (13 Weeks only)																	Postdose Follow-up				PD Follow-up[c]
Study Day (D)		D-1[a]	D0	D1[b]	D2	D7	D14	D21	D28	D35	D42	D49	D56	D63	D70	D77	D84	D85	D86	D98	D112	D140/ ET	
Visit Window (± Days)	D-90 to D-2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	±4	±4	±4	every 28±7 days
Blood and urine samples for PK analysis			X[m]	X[m]	X[m]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[m]	X[m]	X[m]	X	X	X	
Plasma C5 sampling[o]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X	X
Serum complement activity[p]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X	X
[redacted]			X																			X	
[redacted]			X	X		X	X	X	X								X	X					
Concomitant medications	X																						
Review/record AEs		X[r]																					

Abbreviations: ACWY = *Neisseria meningitides* serogroups A, C, W-135, and Y; AE adverse event; β-HCG = beta-human chorionic gonadotropin; BMI = body mass index; C5 = complement 5; CAP ELISA = complement alternative pathway enzyme-linked immunosorbent assay; CCP = complement classic pathway; D = Day; DOA = drugs of abuse; ECG = electrocardiogram; ET = early termination; FSH = follicle-stimulating hormone; ISR = injection site reaction; PK = pharmacokinetic; SC = subcutaneous.

NOTE: On days when study drug is administered, assessments are performed predose only, unless otherwise noted; during postdose follow-up, assessments will be performed at any time during the visit, unless otherwise noted.

a. Subjects will be admitted to the clinical study site for assessments and study drug administration.
b. Subjects will be discharged from the clinical study unit following the completion of 24 hour postdose assessments.
c. For subjects with serum complement activity below normal range at the last postdose follow-up study visit, monitoring visits will occur until serum complement activity is within the normal reference range as assessed by CAP ELISA or until the SRC makes a decision on a case-by-case basis to discontinue follow-up, whichever is sooner (see Section 3.5.3).
d. Subjects will be vaccinated against *Neisseria meningitides* with meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine, and have a positive titer for ACWY before receiving the first dose of study drug. The vaccination program can take place at any time within the screening window. See Section 10.1.8 for vaccination program requirements.
e. Subjects will be treated with prophylactic ciprofloxacin from the first dose of study drug until serum complement activity returns to within the normal reference range as assessed by CAP ELISA or until the SRC makes a decision on a case-by-case basis to discontinue follow-up and antibiotic prophylaxis, whichever is sooner (see Section 10.1.9 and Section 3.5.3).
f. See Section 10.1.4 for assessments to be performed during a full and directed medical examination.
g. Vital signs include blood pressure, heart rate, oral body temperature, and respiratory rate. Vital signs will be measured in the supine position after the subject has rested comfortably for 10 minutes. On Day 0, vital signs should be collected predose (-60 minutes); and 30±5 minutes and 4 hours (±15 minutes) postdose. After Day 0, vital signs should be collected predose (-60 minutes); and up to 12 hours postdose on days when study drug is administered.

h. 12-lead ECGs will be measured in the supine position after the subject has rested comfortably for 10 minutes. On Day 0, the ECG should be performed predose (-60 minutes); and ±4 hours postdose . After Day 0, the ECG should be performed predose (-60 minutes); and up to 12 hours postdose on days when study drug is administered.
i. See Section 10.1.7.4 for viral serology parameters.
j. Biochemistry, hematology, coagulation, and urinalysis parameters to be measured are described in Section 10.1.7.
k. Collect blood samples for biochemistry and hematology only.
l. SC injection of study drug per the Study Drug Administration Manual.
m. Details regarding time points for collection of blood and urine samples for full PK analysis are outlined in Table 11 in the appendix (Section 18).
n. Collect blood samples for PK analysis predose (-60 minutes); and 60±30 minutes postdose only. Collect urine samples for PK analysis predose (-60 minutes) only.
o. C5 levels will be measured by ELISA and/or mass spectrophotometry in a central laboratory.
p. Serum complement activity includes: CAP ELISA and CCP ELISA.
q. [redacted]
r. See Section 10.4.2.1 for handling of ISRs.

Table 16: Schedule of Assessments for Multiple-ascending Dose Cohorts (Part B) – Once Every 2 Weeks Dosing

Study Stage	Screening	Once Every 2 Weeks Dosing													Postdose Follow-up				PD Follow-up[c]
Study Day (D)		D-1[a]	D0	D1[b]	D2	D7	D14	D21	D28	D42	D56	D70	D84	D85	D86	D98	D112	D140/ET	
Visit Window (±Days)	D-90 to D-2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	±4	±4	±4	every 28±7days
Informed Consent	X																		
Vaccination against *Neisseria meningitideses*[d]	X																		
Vaccination titer[d]	X	X																	
Antibiotic compliance check[e]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Demography	X																		
Medical history	X																		
Inclusion/exclusion criteria	X	X																	
Full physical examination[f]	X																	X	
Directed physical examination[f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Body weight and BMI calculation	X	X				X	X	X	X	X	X	X	X						
Height	X																		
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECGs[h]	X	X	X	X		X	X	X	X	X	X	X	X	X				X	
β-HCG pregnancy test	X	X							X		X		X			X	X	X	
FSH screening	X																		
Viral serology[i]	X																		
Biochemistry, hematology, and coagulation[j]	X	X	X[k]	X		X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X			X[k]	X	
Urinalysis[j]	X	X	X	X		X	X	X	X	X	X	X	X	X			X	X	
Urine DOA/alcohol screen	X	X																	

Table 16: Schedule of Assessments for Multiple-ascending Dose Cohorts (Part B) – Once Every 2 Weeks Dosing

Study Stage	Screening	Once Every 2 Weeks Dosing													Postdose Follow-up				PD Follow-up[c]
Study Day (D)		D-1[a]	D0	D1[b]	D2	D7	D14	D21	D28	D42	D56	D70	D84	D85	D86	D98	D112	D140/ET	
Visit Window (±Days)	D-90 to D-2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	±4	±4	±4	every 28±7days
Randomization			X																
Study drug administration[l]			X				X		X	X	X	X	X						
Blood and urine samples for PK analysis			X[m]	X[m]	X[m]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[m]	X[m]	X[m]	X	X	X	
Plasma C5 sampling[o]	X	X	X		X	X	X	X	X	X	X	X	X			X	X	X	X
Serum complement activity[p]	X	X	X		X	X	X	X	X	X	X	X	X			X	X	X	X
[redacted]			X															X	
[redacted]			X	X		X	X	X	X	X	X	X	X	X					
Concomitant medications	X																		
Review/record AEs			X[r]																

Abbreviations: ACWY = *Neisseria meningitides* serogroups A, C, W-135, and Y; AE adverse event; β-HCG = beta-human chorionic gonadotropin; BMI = body mass index; C5 = complement 5; CAP ELISA = complement alternative pathway enzyme-linked immunosorbent assay; CCP = complement classic pathway DOA = drugs of abuse; ET = early termination; ECG = electrocardiogram; FSH = follicle-stimulating hormone; LDH = lactate dehydrogenase; PK = pharmacokinetic; [redacted] SC = subcutaneous.

NOTE: On days when study drug is administered, assessments are performed predose only, unless otherwise noted; during postdose follow-up, assessments will be performed at any time during the visit, unless otherwise noted.

a. Subjects will be admitted to the clinical study site for assessments and study drug administration.
b. Subjects will be discharged from the clinical study unit following the completion of 24 hour postdose assessments.
c. For subjects with serum complement activity below normal range at the last postdose follow-up study visit, monitoring visits will occur until serum complement activity is within the normal reference range as assessed by CAP ELISA or until the SRC makes a decision on a case-by-case basis to discontinue follow-up, whichever is sooner (see Section 3.5.3).
d. Subjects will be vaccinated against *Neisseria meningitides* with meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine, and have a positive titer for ACWY before receiving the first dose of study drug. The vaccination program can take place at any time within the screening window. See Section 10.1.8 for vaccination program requirements.

e. Subjects will be treated with prophylactic ciprofloxacin from the first dose of study drug until serum complement activity returns to within the normal reference range as assessed by CAP ELISA or until the SRC makes a decision on a case-by-case basis to discontinue follow-up and antibiotic prophylaxis, whichever is sooner (see Section 10.1.9 and Section 3.5.3).
f. See Section 10.1.4 for assessments to be performed during a full and directed medical examination.
g. Vital signs include blood pressure, heart rate, oral body temperature, and respiratory rate. Vital signs will be measured in the supine position after the subject has rested comfortably for 10 minutes. On Day 0, vital signs should be collected predose (-60 minutes); and 30±5 minutes and 4 hours (±15 minutes) postdose. After Day 0, vital signs should be collected predose (-60 minutes); and up to 12 hours postdose on days when study drug is administered.
h. 12-lead ECGs will be measured in the supine position after the subject has rested comfortably for 10 minutes. On Day 0, the ECG should be performed predose (-60 minutes); and ±4 hours postdose. After Day 0, the ECG should be performed predose (-60 minutes); and up to 12 hours postdose on days when study drug is administered.
i. See Section 10.1.7.4 for viral serology parameters.
j. Biochemistry, hematology, coagulation, and urinalysis parameters to be measured are described in Section 10.1.7.
k. Collect blood samples for biochemistry and hematology only.
l. SC injection of study drug per the Study Drug Administration Manual.
m. Details regarding time points for collection of blood and urine samples for full PK analysis are outlined in Table 11 in the appendix (Section 18).
n. Collect blood samples for PK analysis predose (-60 minutes) and 60±30 minutes postdose only. Collect urine samples PK analysis predose (-60 minutes) only.
o. C5 levels will be measured by ELISA and/or mass spectrophotometry in a central laboratory.
p. Serum complement activity includes: CAP ELISA and CCP ELISA.
q. [redacted].
r. See Section 10.4.2.1 for handling of ISRs.

Table 17: Schedule of Assessments for Multiple-ascending Dose Cohorts (Part B) – Monthly Dosing

Study Stage	Screening	Monthly Dosing													Postdose Follow-up				PD Follow-up[e]
Study Day (D)		D-1[a]	D0	D1[b]	D2	D7	D14	D21	D28	D42	D56	D70	D84	D85	D86	D98	D112	D140/ET	
Visit Window (±Days)	D-90 to D-2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	±4	±4	±4	every 28±7days
Informed Consent	X																		
Vaccination against *Neisseria meningitides*[d]	X																		
Vaccination titer[d]	X	X																	
Antibiotic compliance check[e]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Demography	X																		
Medical history	X																		
Inclusion/exclusion criteria	X	X																	
Full physical examination[f]	X																	X	
Directed physical examination[f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Body weight and BMI calculation	X	X				X	X	X	X	X	X	X	X						
Height	X																		
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECGs[h]	X	X	X	X		X	X	X	X	X	X	X	X	X				X	
β-HCG pregnancy test	X	X							X		X		X			X	X	X	
FSH screening	X																		
Viral serology[i]	X																		
Biochemistry, hematology, and coagulation[j]	X	X	X[k]	X		X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X			X[k]	X	
Urinalysis	X	X	X	X		X	X	X	X	X	X	X	X	X			X	X	
Urine DOA/alcohol screen	X	X																	
Randomization			X																

Table 17: Schedule of Assessments for Multiple-ascending Dose Cohorts (Part B) – Monthly Dosing

Study Stage	Screening	Monthly Dosing													Postdose Follow-up				PD Follow-up[s]
Study Day (D)		D-1[a]	D0	D1[b]	D2	D7	D14	D21	D28	D42	D56	D70	D84	D85	D86	D98	D112	D140/ET	
Visit Window (±Days)	D-90 to D-2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	±4	±4	±4	every 28±7days
Study drug administration[l]			X						X		X		X						
Blood and urine samples for PK analysis			X[m]	X[m]	X[m]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[m]	X[m]	X[m]		X	X	
Plasma C5 sampling[o]	X	X	X		X	X	X	X	X	X	X	X	X			X	X	X	X
Serum complement activity[p]	X	X	X		X	X	X	X	X	X	X	X	X			X	X	X	X
[redacted]			X															X	
[redacted]			X	X			X	X	X	X	X	X	X	X					
Concomitant medications	X																		
Review/record AEs			X[r]																

Abbreviations: ACWY = *Neisseria meningitides* serogroups A, C, W-135, and Y; AE adverse event; β-HCG = beta-human chorionic gonadotropin; BMI = body mass index; C5 = complement 5; CAP ELISA = complement alternative pathway enzyme-linked immunosorbent assay; CCP = complement classic pathway DOA = drugs of abuse; ET = early termination; ECG = electrocardiogram; FSH = follicle-stimulating hormone; LDH = lactate dehydrogenase; PK = pharmacokinetic; [redacted]; SC = subcutaneous.

NOTE: On days when study drug is administered, assessments are performed predose only, unless otherwise noted; during postdose follow-up, assessments will be performed at any time during the visit, unless otherwise noted.

a. Subjects will be admitted to the clinical study site for assessments and study drug administration.
b. Subjects will be discharged from the clinical study unit following the completion of 24 hour postdose assessments.
c. For subjects with serum complement activity below normal range at the last postdose follow-up study visit, monitoring visits will occur until serum complement activity is within the normal reference range as assessed by CAP ELISA or until the SRC makes a decision on a case-by-case basis to discontinue follow-up, whichever is sooner (see Section 3.5.3).
d. Subjects will be vaccinated against *Neisseria meningitides* with meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine, and have a positive titer for ACWY before receiving the first dose of study drug. The vaccination program can take place at any time within the screening window. See Section 10.1.8 for vaccination program requirements.
e. Subjects will be treated with prophylactic ciprofloxacin from the first dose of study drug until serum complement activity returns to within the normal reference range as assessed by CAP ELISA or until the SRC makes a decision on a case-by-case basis to discontinue follow-up and antibiotic prophylaxis, whichever is sooner (see Section 10.1.9 and Section 3.5.3).
f. See Section 10.1.4 for assessments to be performed during a full and directed medical examination.

g. Vital signs include blood pressure, heart rate, oral body temperature, and respiratory rate. Vital signs will be measured in the supine position after the subject has rested comfortably for 10 minutes. On Day 0, vital signs should be collected predose (-60 minutes); and 30±5 minutes and 4 hours (±15 minutes) postdose. After Day 0, vital signs should be collected predose (-60 minutes); and up to 12 hours postdose on days when study drug is administered.
h. 12-lead ECGs will be measured in the supine position after the subject has rested comfortably for 10 minutes. On Day 0, the ECG should be performed predose (-60 minutes); and ±4 hours postdose . After Day 0, the ECG should be performed predose (-60 minutes); and up to 12 hours postdose on days when study drug is administered.
i. See Section 10.1.7.4 for viral serology parameters.
j. Biochemistry, hematology, coagulation, and urinalysis parameters to be measured are described in Section 10.1.7.
k. Collect blood samples for biochemistry and hematology only.
l. SC injection of study drug per the Study Drug Administration Manual.
m. Details regarding time points for collection of blood and urine samples for full PK analysis are outlined in Table 11 in the appendix (Section 18).
n. Collect blood samples for PK analysis predose (-60 minutes) and 60±30 minutes postdose only. Collect urine samples PK analysis predose (-60 minutes) only.
o. C5 levels will be measured by ELISA and/or mass spectrophotometry in a central laboratory.
p. Serum complement activity includes: CAP ELISA and CCP ELISA.
q. [redacted]
r. See Section 10.4.2.1 for handling of ISRs.

Table 18: Schedule of Assessments for Multiple-ascending Dose Cohorts (Part B) – 5 Weekly Doses Followed by Once Every 2 Weeks Dosing

Study Stage	Screening	5 Weekly Doses Followed by Once Every 2 Weeks Dosing													Postdose Follow-up				PD Follow-up[c]
Study Day (D)		D-1[a]	D0	D1[b]	D2	D7	D14	D21	D28	D42	D56	D70	D84	D85	D86	D98	D112	D140/ ET	
Visit Window (± Days)	D-90 to D-2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	±4	±4	±4	every 28±7 days
Informed Consent	X																		
Vaccination against *Neisseria meningitides*[d]	X																		
Vaccination titer[d]	X	X																	
Antibiotic compliance check[e]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Demography	X																		
Medical history	X																		
Inclusion/exclusion criteria	X	X																	
Full physical examination[f]	X																	X	
Directed physical examination[f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Body weight and BMI calculation	X	X				X	X	X	X	X	X	X	X						
Height	X																		
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECGs[h]	X	X	X	X		X	X	X	X	X	X	X	X	X				X	
β-HCG pregnancy test	X	X							X		X		X			X	X	X	
FSH screening	X																		
Viral serology[i]	X																		
Biochemistry, hematology, and coagulation[j]	X	X	X[k]	X		X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X			X[k]	X	
Urinalysis[j]	X	X	X	X		X	X	X	X	X	X	X	X	X			X	X	
Urine DOA/alcohol screen	X	X																	
Randomization			X																

Table 18: Schedule of Assessments for Multiple-ascending Dose Cohorts (Part B) – 5 Weekly Doses Followed by Once Every 2 Weeks Dosing

Study Stage	Screening	5 Weekly Doses Followed by Once Every 2 Weeks Dosing													Postdose Follow-up				PD Follow-up[e]
Study Day (D)		D-1[a]	D0	D1[b]	D2	D7	D14	D21	D28	D42	D56	D70	D84	D85	D86	D98	D112	D140/ ET	
Visit Window (± Days)	D-90 to D-2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	±4	±4	±4	every 28±7 days
Study drug administration[l]			X			X	X	X	X	X	X	X	X						
Blood and urine samples for PK analysis			X[m]	X[m]	X[m]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[m]	X[m]	X[m]	X	X	X	
Plasma C5 sampling[o]	X	X	X		X	X	X	X	X	X	X	X	X			X	X	X	X
Serum complement activity[p]	X	X	X		X	X	X	X	X	X	X	X	X			X	X	X	X
[redacted]			X															X	
[redacted]			X	X		X	X	X	X	X	X	X	X	X					
Concomitant medications	X																		
Review/record AEs			X[r]																

Abbreviations: ACWY = *Neisseria meningitides* serogroups A, C, W-135, and Y; AE adverse event; β-HCG = beta-human chorionic gonadotropin; BMI = body mass index; C5 = complement 5; CAP ELISA = complement alternative pathway enzyme-linked immunosorbent assay; CCP = complement classic pathway DOA = drugs of abuse; ET = early termination; ECG = electrocardiogram; FSH = follicle-stimulating hormone; LDH = lactate dehydrogenase; PK = pharmacokinetic; [redacted]; SC = subcutaneous.

NOTE: On days when study drug is administered, assessments are performed predose only, unless otherwise noted; during postdose follow-up, assessments will be performed at any time during the visit, unless otherwise noted.

a. Subjects will be admitted to the clinical study site for assessments and study drug administration.
b. Subjects will be discharged from the clinical study unit following the completion of 24 hour postdose assessments.
c. For subjects with serum complement activity below normal range at the last postdose follow-up study visit, monitoring visits will occur until serum complement activity is within the normal reference range as assessed by CAP ELISA or until the SRC makes a decision on a case-by-case basis to discontinue follow-up, whichever is sooner (see Section 3.5.3).
d. Subjects will be vaccinated against *Neisseria meningitides* with meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine, and have a positive titer for ACWY before receiving the first dose of study drug. The vaccination program can take place at any time within the screening window. See Section 10.1.8 for vaccination program requirements.
e. Subjects will be treated with prophylactic ciprofloxacin from the first dose of study drug until serum complement activity returns to within the normal reference range as assessed by CAP ELISA or until the SRC makes a decision on a case-by-case basis to discontinue follow-up and antibiotic prophylaxis (see Section 10.1.9 and Section 3.5.3).
f. See Section 10.1.4 for assessments to be performed during a full and directed medical examination.

g. Vital signs include blood pressure, heart rate, oral body temperature, and respiratory rate. Vital signs will be measured in the supine position after the subject has rested comfortably for 10 minutes. On Day 0, vital signs should be collected predose (-60 minutes); and 30±5 minutes and 4 hours (±15 minutes) postdose. After Day 0, vital signs should be collected predose (-60 minutes); and up to 12 hours postdose on days when study drug is administered.
h. 12-lead ECGs will be measured in the supine position after the subject has rested comfortably for 10 minutes. On Day 0, the ECG should be performed predose (-60 minutes); and ±4 hours postdose . After Day 0, the ECG should be performed predose (-60 minutes); and up to 12 hours postdose on days when study drug is administered.
i. See Section 10.1.7.4 for viral serology parameters.
j. Biochemistry, hematology, coagulation, and urinalysis parameters to be measured are described in Section 10.1.7.
k. Collect blood samples for biochemistry and hematology only.
l. SC injection of study drug per the Study Drug Administration Manual.
m. Details regarding time points for collection of blood and urine samples for full PK analysis are outlined in Table 11 in the appendix (Section 18).
n. Collect blood samples for PK analysis predose (-60 minutes) and 60±30 minutes postdose only. Collect urine samples PK analysis predose (-60 minutes) only.
o. C5 levels will be measured by ELISA and/or mass spectrophotometry in a central laboratory.
p. Serum complement activity includes: CAP ELISA and CCP ELISA.
q. [redacted].
r. See Section 10.4.2.1 for handling of ISRs.

Table 19: Schedule of Assessments for Multiple-ascending Dose Cohorts (Part B) – 5 Weekly Doses Followed by Monthly Dosing

Study Stage	Screening	5 Weekly Doses Followed by Monthly Dosing											Postdose Follow-up				PD Follow-up[c]
Study Day (D)		D-1[a]	D0	D1[b]	D2	D7	D14	D21	D28	D56	D84	D85	D86	D98	D112	D140/ET	
Visit Window (± Days)	D-90 to D-2	-	-	-	-	-	-	-	-	-	-	-	-	±4	±4	±4	every 28±7 days
Informed Consent	X																
Vaccination against Neisseria *meningitides*[d]	X																
Vaccination titer[d]	X	X															
Antibiotic compliance check[e]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Demography	X																
Medical history	X																
Inclusion/exclusion criteria	X	X															
Full physical examination[f]	X															X	
Directed physical examination[f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Body weight and BMI calculation	X	X				X	X	X	X	X	X						
Height	X																
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECGs[h]	X	X	X	X		X	X	X	X	X	X	X				X	
β-HCG pregnancy test	X	X							X	X	X			X	X	X	
FSH screening	X																
Viral serology[i]	X																
Biochemistry, hematology, and coagulation[j]	X	X	X[k]	X		X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X			X[k]	X	
Urinalysis	X	X	X	X		X	X	X	X	X	X	X			X	X	
Urine DOA/alcohol screen	X	X															
Randomization			X														

Table 19: Schedule of Assessments for Multiple-ascending Dose Cohorts (Part B) – 5 Weekly Doses Followed by Monthly Dosing

Study Stage	Screening	5 Weekly Doses Followed by Monthly Dosing											Postdose Follow-up				PD Follow-up[c]
Study Day (D)		D-1[a]	D0	D1[b]	D2	D7	D14	D21	D28	D56	D84	D85	D86	D98	D112	D140/ET	
Visit Window (± Days)	D-90 to D-2	-	-	-	-	-	-	-	-	-	-	-	-	±4	±4	±4	every 28±7 days
Study drug administration[l]			X			X	X	X	X	X	X						
Blood and urine samples for PK analysis			X[m]	X[m]	X[m]	X[n]	X[n]	X[n]	X[n]	X[n]	X[m]	X[m]	X[m]	X	X	X	
Plasma C5 sampling[o]	X	X	X		X	X	X	X	X	X	X			X	X	X	X
Serum complement activity[p]	X	X	X		X	X	X	X	X	X	X			X	X	X	X
[redacted]			X													X	
[redacted]			X	X		X	X	X	X	X	X	X					
Concomitant medications	X																
Review/record AEs			X[r]														

Abbreviations: ACWY = *Neisseria meningitides* serogroups A, C, W-135, and Y; AE adverse event; β-HCG = beta-human chorionic gonadotropin; BMI = body mass index; C5 = complement 5; CAP ELISA = complement alternative pathway enzyme-linked immunosorbent assay; CCP = complement classic pathway DOA = drugs of abuse; ET = early termination; ECG = electrocardiogram; FSH = follicle-stimulating hormone; LDH = lactate dehydrogenase; PK = pharmacokinetic; [redacted] SC = subcutaneous.

NOTE: On days when study drug is administered, assessments are performed predose only, unless otherwise noted; during postdose follow-up, assessments will be performed at any time during the visit, unless otherwise noted.

a. Subjects will be admitted to the clinical study site for assessments and study drug administration.
b. Subjects will be discharged from the clinical study unit following the completion of 24 hour postdose assessments.
c. For subjects with serum complement activity below normal range at the last postdose follow-up study visit, monitoring visits will occur until serum complement activity is within the normal reference range as assessed by CAP ELISA or until the SRC makes a decision on a case-by-case basis to discontinue follow-up, whichever is sooner (see Section 3.5.3).
d. Subjects will be vaccinated against *Neisseria meningitides* with meningococcal group ACWY conjugate vaccine and meningococcal group B vaccine, and have a positive titer for ACWY before receiving the first dose of study drug. The vaccination program can take place at any time within the screening window. See Section 10.1.8 for vaccination program requirements.
e. Subjects will be treated with prophylactic ciprofloxacin from the first dose of study drug until serum complement activity returns to within the normal reference range as assessed by CAP ELISA or until the SRC makes a decision on a case-by-case basis to discontinue follow-up and antibiotic prophylaxis, whichever is sooner (see Section 10.1.9 and Section 3.5.3).
f. See Section 10.1.4 for assessments to be performed during a full and directed medical examination.

g. Vital signs include blood pressure, heart rate, oral body temperature, and respiratory rate. Vital signs will be measured in the supine position after the subject has rested comfortably for 10 minutes. On Day 0, vital signs should be collected predose (-60 minutes); and 30±5 minutes and 4 hours (±15 minutes) postdose. After Day 0, vital signs should be collected predose (-60 minutes); and up to 12 hours postdose on days when study drug is administered.
h. 12-lead ECGs will be measured in the supine position after the subject has rested comfortably for 10 minutes. On Day 0, the ECG should be performed predose (-60 minutes); and ±4 hours postdose. After Day 0, the ECG should be performed predose (-60 minutes); and up to 12 hours postdose on days when study drug is administered.
i. See Section 10.1.7.4 for viral serology parameters.
j. Biochemistry, hematology, coagulation, and urinalysis parameters to be measured are described in Section 10.1.7.
k. Collect blood samples for biochemistry and hematology only.
l. SC injection of study drug per the Study Drug Administration Manual.
m. Details regarding time points for collection of blood and urine samples for full PK analysis are outlined in Table 11 in the appendix (Section 18).
n. Collect blood samples for PK analysis predose (-60 minutes) and 60±30 minutes postdose only. Collect urine samples PK analysis predose -60 minutes) only.
o. C5 levels will be measured by ELISA and/or mass spectrophotometry in a central laboratory.
p. Serum complement activity includes: CAP ELISA and CCP ELISA.
q. [redacted]
r. See Section 10.4.2.1 for handling of ISRs.

Appendix 3: Schedules of Assessments for Alternative Dosing Regimens for Part C

The following tables contain additional Schedules of Assessments for alternative dosing regimens which may be investigated in Part C of the study.

Table 20: Schedule of Assessments for Multiple-dose Cohorts (Part C) – 5 Weekly Doses Followed by Once Every 2 Weeks Dosing (Cohort 2 and Cohort 3)

Study Stage	Screening	Consul-tation	Dosing Period									
			Weekly Dosing						Once Every 2 Weeks Dosing			
Study Day (D)		D-1[b]	D0	D1[c]	D7	D14	D21	D28	D42	D56	D70	D84
Visit Window (± Days)	D-90 to D-2	-	-	-	-	-	-	-	-	-	-	-
Informed Consent	X											
Vaccination against *Neisseria meningitides*[d]	X					X						
Demography	X											
Medical history	X											
Inclusion/ exclusion criteria	X	X										
Full physical examination[e]	X	X										
Directed physical examination[e]			X	X						X		X
Body weight and BMI calculation	X	X										
Height	X											
Vital signs[f]	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECGs[g]	X	X	X	X						X		X
β-HCG pregnancy test	X	X						X		X		X
FSH screening	X											
Viral serology[h]	X											
Biochemistry, hematology, and coagulation[i]	X	X	X	X	X[r]	X	X[r]	X	X	X	X	X
Urinalysis[i]	X	X	X	X	X	X	X	X	X	X	X	X

Table 20: Schedule of Assessments for Multiple-dose Cohorts (Part C) – 5 Weekly Doses Followed by Once Every 2 Weeks Dosing (Cohort 2 and Cohort 3)

Study Stage	Screening	Consul-tation	Dosing Period									
			Weekly Dosing						Once Every 2 Weeks Dosing			
Study Day (D)		D-1[b]	D0	D1[c]	D7	D14	D21	D28	D42	D56	D70	D84
Visit Window (± Days)	D-90 to D-2	-	-	-	-	-	-	-	-	-	-	-
Blood sample for eculizumab level[j]	X		X									
Study drug administration[k]			X		X	X	X	X	X	X	X	X
Blood and urine samples for PK analysis			X[l]	X[l]				X[m]		X[m]		X[m]
Plasma C5 sampling[n]	X	X	X		X	X	X	X	X	X	X	X
Serum complement activity[o]	X	X	X		X	X	X	X	X	X	X	X
LDH	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]		X		X	X	X	X	X	X	X	X	X
[redacted]		X		X	X	X	X	X	X	X	X	X
[redacted]		X					X			X		X
[redacted]			X					X				
[redacted]		X										X
[redacted]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X											
Review/record AEs			X[q]									

Table 20: Schedule of Assessments for Multiple-dose Cohorts (Part C) – 5 Weekly Doses Followed by Once Every 2 Weeks Dosing (Cohort 2 and Cohort 3)

Study Stage	Screening	Consul-tation	Dosing Period									
			Weekly Dosing						Once Every 2 Weeks Dosing			
Study Day (D)		D-1[b]	D0	D1[c]	D7	D14	D21	D28	D42	D56	D70	D84
Visit Window (± Days)	D-90 to D-2	-	-	-	-	-	-	-	-	-	-	-

Abbreviations: ACWY = *Neisseria meningitides* serogroups A, C, W-135, and Y; AE = adverse event; β-HCG = beta-human chorionic gonadotropin; BMI = body mass index; C5 = complement 5; CAP ELISA = complement alternative pathway enzyme-linked immunosorbent assay; CCP = complement classic pathway DOA = drugs of abuse; ET = early termination; ECG = electrocardiogram; FSH = follicle-stimulating hormone; LDH = lactate dehydrogenase; PK = pharmacokinetic[redacted]; SC = subcutaneous.

NOTE: On days when study drug is administered, assessments are performed predose only, unless otherwise noted; during postdose follow-up, assessments will be performed at any time during the visit, unless otherwise noted.

a. Patients may continue ALN-CC5 administration at the same or at a modified dose and dosing regimen (eg, from weekly to once every 2 weeks, or monthly, or continuation of weekly dosing).
b. Patients will be admitted to the clinical study site on Day -1 for assessments and study drug administration.
c. Patients will be discharged from the clinical study site on Day 1 following completion of 24 hour postdose assessments.
d. Patients will have been or will be vaccinated against *Neisseria meningitides* (see Section 10.1.8 for vaccination specifications).
e. See Section 10.1.4 for assessments to be performed during a full and directed medical examination.
f. Vital signs include blood pressure, heart rate, oral body temperature, and respiratory rate. Vital signs will be measured in the supine position after the subject has rested comfortably for 60 minutes. On Day 0, vital signs should be collected predose (-60 minutes); and 30±5 minutes and 4 hours (±15 minutes) postdose. After Day 0, vital signs should be collected predose (-60 minutes); and up to 12 hours postdose on days when study drug is administered.
g. 12-lead ECGs will be measured in the supine position after the subject has rested comfortably for 10 minutes. On Day 0, the ECG should be performed predose (-60 minutes); and ±4 hours postdose. After Day 0, the ECG should be performed predose (-60 minutes); and up to 12 hours postdose on days when study drug is administered.
h. See Section 10.1.7.4 for viral serology parameters.
i. Biochemistry, hematology, coagulation, and urinalysis parameters to be measured are described in Section 10.1.7.
j. For patients receiving treatment with eculizumab, a blood sample for the measurement of eculizumab levels will be collected before and 60±30 minutes after each treatment with eculizumab. Single weekly samples will be taken on the weeks between eculizumab treatments on the days that ALN-CC5 is administered. If eculizumab treatment is stopped, weekly samples will be taken, thereafter.
k. SC injection of study drug per the Study Drug Administration Manual. Patients on stable doses of eculizumab will continue receiving treatment concomitantly with ALN-CC5; patients will receive their last dose of eculizumab when at least 2 consecutive measurements of C5 levels demonstrate a degree of suppression consistent with complement inhibition. Patients who are naïve to eculizumab treatment may begin ALN-CC5 administration. ALN-CC5 may be administered at home between visits to the clinical study center by a home healthcare provider trained in the administration of ALN-CC5.
l. Details regarding time points for collection of blood and urine samples for full PK analysis are outlined in Table 14 in the appendix (Section 18).
m. Collect a blood and urine sample for PK analysis at any time during the visit.
n. C5 levels will be measured by ELISA and/or mass spectrophotometry in a central laboratory.

o. Serum complement activity includes: CAP ELISA and CCP ELISA.
p. Exploratory [redacted] are described in Section 9.3 .
q. See Section 10.4.2.1 for handling of ISRs.
r. Collect blood samples for biochemistry and hematology only.

Table 21: Schedule of Assessments for Multiple-dose Cohorts (Part C) – 5 Weekly Doses Followed by Monthly Dosing (Cohort 2 and Cohort 3)

Study Stage	Screening[a]	Consultation	Dosing Period									
			Weekly Dosing						Monthly Dosing			
Study Day (D)		D-1[b]	D0	D1[c]	D7	D14	D21	D28	D42	D56	D70	D84
Visit Window (± Days)	D-90 to D-2	-	-	-	-	-	-	-	-	-	-	-
Informed Consent	X											
Vaccination against *Neisseria meningitides*[d]	X					X						
Demography	X											
Medical history	X											
Inclusion/ exclusion criteria	X	X										
Full physical examination[e]	X	X										
Directed physical examination[e]			X	X						X		X
Body weight and BMI calculation	X	X										
Height	X											
Vital signs[f]	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECGs[g]	X	X	X	X						X		X
β-HCG pregnancy test	X	X						X		X		X
FSH screening	X											
Viral serology[h]	X											
Biochemistry, hematology, and coagulation[i]	X	X	X	X	X[r]	X	X[r]	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for eculizumab level[j]	X		X									
Study drug administration[k]			X		X	X	X	X		X		X
Blood and urine samples for PK analysis			X[l]	X[l]				X[m]		X[m]		X[m]
Plasma C5 sampling[n]	X	X	X		X	X	X	X	X	X	X	X

Table 21: Schedule of Assessments for Multiple-dose Cohorts (Part C) – 5 Weekly Doses Followed by Monthly Dosing (Cohort 2 and Cohort 3)

Study Stage	Screening[a]	Consultation	Dosing Period: Weekly Dosing						Monthly Dosing			
Study Day (D)		D-1[b]	D0	D1[c]	D7	D14	D21	D28	D42	D56	D70	D84
Visit Window (± Days)	D-90 to D-2	-	-	-	-	-	-	-	-	-	-	-
Serum complement activity[o]	X	X	X		X	X	X	X	X	X	X	X
LDH	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]		X		X	X	X	X	X	X	X	X	X
[redacted]		X					X			X		X
[redacted]			X					X				
[redacted]		X										X
[redacted]		X	X	X	X	X	X	X	X	X	X	X
[redacted]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X											
Review/record AEs			X[q]									

Abbreviations: ACWY = *Neisseria meningitides* serogroups A, C, W-135, and Y; AE adverse event; β-HCG = beta-human chorionic gonadotropin; BMI = body mass index; C5 = complement 5; CAP ELISA = complement alternative pathway enzyme-linked immunosorbent assay; CCP = complement classic pathway DOA = drugs of abuse; ET = early termination; ECG = electrocardiogram; FSH = follicle-stimulating hormone; LDH = lactate dehydrogenase; PK = pharmacokinetic[redacted]; SC = subcutaneous.

NOTE: On days when study drug is administered, assessments are performed predose only, unless otherwise noted; during postdose follow-up, assessments will be performed at any time during the visit, unless otherwise noted.

a. Patients may continue ALN-CC5-001 administration at the same or at a modified dose and dosing regimen (weekly, once every 2 weeks, or monthly dosing).
b. Patients will be admitted to the clinical study site on Day -1 for assessments and study drug administration.
c. Patients will be discharged from the clinical study site on Day 1 following completion of 24 hour postdose assessments.
d. Patients will have been or will be vaccinated against *Neisseria meningitides* (see Section 10.1.8 for vaccination specifications).
e. See Section 10.1.4 for assessments to be performed during a full and directed medical examination.
f. Vital signs include blood pressure, heart rate, oral body temperature, and respiratory rate. Vital signs will be measured in the supine position after the subject has rested comfortably for 10 minutes. On Day 0, vital signs should be collected predose (-60 minutes); and 30±5 minutes and 4 hours (±15 minutes) postdose. After Day 0, vital signs should be collected predose (-60 minutes); and up to 12 hours postdose on days when study drug is administered.

g. 12-lead ECGs will be measured in the supine position after the subject has rested comfortably for 10 minutes. On Day 0, the ECG should be performed predose (-60 minutes); and ±4 hours postdose. After Day 0, the ECG should be performed predose (-60 minutes); and up to 12 hours postdose on days when study drug is administered.
h. See Section 10.1.7.4 for viral serology parameters.
i. Biochemistry, hematology, coagulation, and urinalysis parameters to be measured are described in Section 10.1.7.
j. For patients receiving treatment with eculizumab, a blood sample for the measurement of eculizumab levels will be collected before and 60±30 minutes after each treatment with eculizumab. Single weekly samples will be taken on the weeks between eculizumab treatments on the days that ALN-CC5 is administered. If eculizumab treatment is stopped, weekly samples will be taken, thereafter.
k. SC injection of study drug per the Study Drug Administration Manual. Patients on stable doses of eculizumab will continue receiving treatment concomitantly with ALN-CC5; patients will receive their last dose of eculizumab when at least 2 consecutive measurements of C5 levels demonstrate a degree of suppression consistent with complement inhibition. Patients who are naïve to eculizumab treatment may begin ALN-CC5 administration. ALN-CC5 may be administered at home between visits to the clinical study center by a home healthcare provider trained in the administration of ALN-CC5.
l. Details regarding time points for collection of blood and urine samples for full PK analysis are outlined in Table 14 in the appendix (Section 18).
m. Collect a blood and urine sample for PK analysis at any time during the visit.
n. C5 levels will be measured by ELISA and/or mass spectrophotometry in a central laboratory.
o. Serum complement activity includes: CAP ELISA and CCP ELISA.
p. Exploratory [redacted] are described in Section 9.3.
q. See Section 10.4.2.1 for handling of ISRs.
r. Collect blood samples for biochemistry and hematology only.

Table 22: Schedule of Assessments for Multiple-dose Cohorts (Part C) – All Cohorts (Day 91 through PD Follow-up)

Study Stage	Weekly, Once Every 2 Weeks, or Monthly Dosing																										Postdose Follow-up				PD Follow-up[c]
Study Day (D)	D91[a]	D98[a]	D105	D112[a]	D119	D126	D133	D140	D147	D154[b]	D161[b]	D168	D175[b]	D182	D189	D196	D203	D210	D217	D224	D231	D238	D245	D252	D259	D266	D273	D280	D308	D336	D364/ET	
Visit Window (± Days)	+21 days	+14 days	-	+7 days	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	±4	±4	±4	±4	every 28±7 days
Full physical examination[d]																															X	
Directed physical examination[d]	X	X[e]	X	X[e,f]	X	X[e]	X	X[e,f]	X	X[e]	X	X[e,f]	X	X[e]	X	X[e,f]	X	X[e]	X	X[e,f]	X	X[e]	X	X[e,f]	X	X[e]	X	X	X	X		
Body weight and BMI calculation				X								X								X							X			X	
Vital signs[g]	X	X[e]	X	X[e,f]	X	X[e]	X	X[e,f]	X	X[e]	X	X[e,f]	X	X[e]	X	X[e,f]	X	X[e]	X	X[e,f]	X	X[e]	X	X[e,f]	X	X[e]	X	X	X	X	X	X
12-lead ECGs[h]				X				X				X				X				X				X				X			X	
β-HCG pregnancy test				X				X				X				X				X				X				X			X	
Biochemistry, hematology, and coagulation[i]				X				X				X				X				X				X				X			X	
Urinalysis[i]				X				X				X				X				X				X				X			X	
[redacted] level[j]	X																															

Table 22: Schedule of Assessments for Multiple-dose Cohorts (Part C) – All Cohorts (Day 91 through PD Follow-up)

Study Stage	Weekly, Once Every 2 Weeks, or Monthly Dosing																										Postdose Follow-up				PD Follow-up[c]
Study Day (D)	D91[a]	D98[a]	D105	D112[a]	D119	D126	D133	D140	D147	D154[b]	D161[b]	D168	D175[b]	D182	D189	D196	D203	D210	D217	D224	D231	D238	D245	D252	D259	D266	D273	D280	D308	D336	D364/ET	
Visit Window (± Days)	+21 days	+14 days	-	+7 days	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	±4	±4	±4	±4	every 28±7 days
Weekly study drug administration[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Once every 2 weeks study drug administration[k]		X		X		X		X		X		X		X		X		X		X		X		X		X					
Monthly study drug administration[k]				X				X				X				X				X				X								
Blood and urine samples for PK analysis[l]				X				X				X				X				X				X							X	
Plasma C5 sampling[m]				X				X				X				X				X				X				X	X	X	X	X
Serum complement activity[n]				X				X				X				X				X				X				X	X	X	X	X
LDH				X				X				X				X				X				X				X	X	X	X	X
[redacted]				X				X				X				X				X				X				X	X	X	X	
[redacted]				X				X				X				X				X				X				X			X	
[redacted]								X																							X	
[redacted]																								X								

Table 22: Schedule of Assessments for Multiple-dose Cohorts (Part C) – All Cohorts (Day 91 through PD Follow-up)

Study Stage	Weekly, Once Every 2 Weeks, or Monthly Dosing																											Postdose Follow-up				PD Follow-up[c]
Study Day (D)	D91[a]	D98[a]	D105	D112[a]	D119	D126	D133	D140	D147	D154[b]	D161[b]	D168	D175[b]	D182	D189	D196	D203	D210	D217	D224	D231	D238	D245	D252	D259	D266	D273	D280	D308	D336	D364/ET	
Visit Window (± Days)	+21 days	+14 days	-	+7 days	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	±4	±4	±4	±4	every 28±7 days
[redacted]	X	X[e]	X	X[e,f]	X	X[e]	X	X[e,f]	X	X[e]	X	X[e,f]	X	X[e]	X	X[e,f]	X	X[e]	X	X[e,f]	X	X[e]	X	X[e,f]	X	X[e]	X	X	X	X	X	X
[redacted]	X	X[e]	X	X[e,f]	X	X[e]	X	X[e,f]	X	X[e]	X	X[e,f]	X	X[e]	X	X[e,f]	X	X[e]	X	X[e,f]	X	X[e]	X	X[e,f]	X	X[e]	X	X	X	X	X	X
Concomitant medications	X																															
Review/record AEs	X[p]																															

Abbreviations: ACWY = *Neisseria meningitides* serogroups A, C, W-135, and Y; AE adverse event; β-HCG = beta-human chorionic gonadotropin; BMI = body mass index; C5 = complement 5; CAP ELISA = complement alternative pathway enzyme-linked immunosorbent assay; CCP = complement classic pathway DOA = drugs of abuse; ET = early termination; ECG = electrocardiogram; FSH = follicle-stimulating hormone; LDH = lactate dehydrogenase; PK = pharmacokinetic[redacted]; SC = subcutaneous.

NOTE: On days when study drug is administered, assessments are performed predose only, unless otherwise noted; during postdose follow-up, assessments will be performed at any time during the visit, unless otherwise noted.

a. After completing the 13 week dosing period, patients may transition to extended dosing on a modified regimen provided the Day 140/ET study visit has not been completed; these patients will resume ALN-CC5 administration at a dose and regimen recommended by the SRC (Day 91 for weekly dosing; Day 98 for every 2 week dosing; or Day 112 for monthly dosing).
b. Patients may transition to a modified dosing regimen (eg, from weekly to once every 2 weeks, or monthly, or continuation of weekly dosing).
c. For patients with serum complement activity below normal range at the last postdose follow-up visit, monitoring visits will occur until serum complement activity is within the normal reference range as assessed by CAP ELISA or until the SRC makes a decision on a case-by-case basis to discontinue follow-up, whichever is sooner (see Section 3.5.3).
d. See Section 10.1.4 for assessments to be performed during a full and directed medical examination.
e. Perform study assessment on days when ALN-CC5 is administered according to an every 2 week dosing schedule.
f. Perform study assessments on days when ALN-CC5 is administered according to a monthly dosing schedule.
g. Vital signs include blood pressure, heart rate, oral body temperature, and respiratory rate. Vital signs will be measured in the supine position after the subject has rested comfortably for 10 minutes. Vital signs should be collected predose (-60 minutes); and up to 12 hours postdose on days when study drug is administered.
h. 12-lead ECGs will be measured in the supine position after the subject has rested comfortably for 10 minutes. The ECG should be performed predose (-60 minutes); and up to 12 hours postdose on days when study drug is administered.
i. Biochemistry, hematology, coagulation, and urinalysis parameters to be measured are described in Section 10.1.7.

j. For patients receiving treatment with eculizumab, a blood sample for the measurement of eculizumab levels will be collected before and 60±30 minutes after each treatment with eculizumab. Single samples will be collected on the weeks between eculizumab treatments on the days that ALN-CC5 is administered. If eculizumab treatment is stopped, samples will be collected, thereafter, according to the dosing regimen administered.
k. SC injection of study drug per the Study Drug Administration Manual. Patients on stable doses of eculizumab will continue receiving treatment concomitantly with ALN-CC5; patients will receive their last dose of eculizumab when at least 2 consecutive measurements of C5 levels demonstrate a degree of suppression consistent with complement inhibition. Patients who are naïve to eculizumab treatment may begin ALN-CC5 administration.
Patients will return to the study center on days when study drug is administered. Assessments will be performed according to the dosing regimen administered.
ALN-CC5 may be administered at home between visits to the clinical study center by a home healthcare provider trained in the administration of ALN-CC5.
l. Collect a blood and urine sample for PK analysis at any time during the visit.
m. C5 levels will be measured by ELISA and/or mass spectrophotometry in a central laboratory.
n. Serum complement activity includes: CAP ELISA and CCP ELISA.
o. Exploratory [redacted] are described in Section 9.3.
p. See Section 10.4.2.1 for handling of ISRs.