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

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STATISTICAL ANALYSIS PLAN

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

Statistical Analysis Plan Status: Final Version 2
Statistical Analysis Plan Date: 18 NOV 2016

Study Drug: ALN-CC5

Sponsor Reference No.: ALN-CC5-001

Clinical Phase I/II

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Telephone:[Redacted]
1. **STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURES**

By signing this page when the Statistical Analysis Plan (SAP) is considered final, the signatories agree to the statistical analyses to be performed for this study, and to the basic format of the tables, figures, and listings (TFLs). Once the SAP has been signed, programming of the TFLs based upon this document can proceed. Any modifications to the SAP and TFLs made after signing may result in a work-scope change.

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**Covance approval:**

Statistician: [Redacted]

Date: 18 Nov 2016

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**Sponsor approval:**

[Redacted]

Date: 18 Nov 2016

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[Redacted]
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### 3. ABBREVIATIONS

Abbreviations pertain to the SAP only (not the TFLs).

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADaM</td>
<td>Analysis Data Model</td>
</tr>
<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomic Therapeutic Class</td>
</tr>
<tr>
<td>C5</td>
<td>component 5</td>
</tr>
<tr>
<td>CAP</td>
<td>complement alternative pathway</td>
</tr>
<tr>
<td>CCP</td>
<td>complement classical pathway</td>
</tr>
<tr>
<td>CDISC</td>
<td>Clinical Data Interchange Standards Consortium</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CSR</td>
<td>clinical study report</td>
</tr>
<tr>
<td>CTCAE</td>
<td>Common Terminology Criteria for Adverse Events</td>
</tr>
<tr>
<td>CV%</td>
<td>coefficient of variation</td>
</tr>
<tr>
<td>ECB</td>
<td>Early Clinical Biometrics</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>ELISA</td>
<td>enzyme-linked immunosorbent assay</td>
</tr>
<tr>
<td>EORTC</td>
<td>European Organization for Research and Treatment of Cancer</td>
</tr>
<tr>
<td>FACIT</td>
<td>Functional Assessment of Chronic Illness Therapy</td>
</tr>
<tr>
<td>FSH</td>
<td>Follicle-Stimulating Hormone</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
</tr>
<tr>
<td>ISR</td>
<td>Injection Site Reaction</td>
</tr>
<tr>
<td>LDH</td>
<td>lactate dehydrogenase</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>MAD</td>
<td>Multiple ascending doses</td>
</tr>
<tr>
<td>PD</td>
<td>pharmacodynamic</td>
</tr>
<tr>
<td>PK</td>
<td>pharmacokinetic</td>
</tr>
<tr>
<td>PNH</td>
<td>paroxysmal nocturnal hemoglobinuria</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>QTcB</td>
<td>QT interval corrected using Bazett’s formula</td>
</tr>
<tr>
<td>QTcF</td>
<td>QT interval corrected using Fridericia’s formula</td>
</tr>
<tr>
<td>SAD</td>
<td>single-ascending dose</td>
</tr>
<tr>
<td>SAP</td>
<td>Statistical Analysis Plan</td>
</tr>
<tr>
<td>SEM</td>
<td>standard error of the mean</td>
</tr>
<tr>
<td>SOC</td>
<td>System Organ Class</td>
</tr>
<tr>
<td>SRC</td>
<td>Safety Review Committee</td>
</tr>
<tr>
<td>TEAE</td>
<td>treatment-emergent adverse event</td>
</tr>
<tr>
<td>TFLs</td>
<td>tables, figures, and listings</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
</tbody>
</table>
4. INTRODUCTION

This SAP has been developed after review of the clinical study protocol (final version dated 21 November 2014), protocol amendment no. 1 (final version dated 08 December 2014), protocol amendment no. 1 (final version dated 16 June 2015), protocol amendment no. 3 (final version dated 13 November 2015) and protocol amendment no. 4 (final version dated 16 August 2016).

This SAP describes the planned analysis of the safety, tolerability and pharmacodynamic (PD) data from this study. A detailed description of the planned TFLs to be presented in the clinical study report (CSR) is provided in the accompanying TFL shell document. The Pharmacokinetic (PK) analysis and report will be provided by Alnylam Pharmaceuticals, Inc. under a separate PK analysis plan.

The intent of this document is to provide guidance for the statistical analyses of the safety, tolerability, and PD data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement between Alnylam Pharmaceuticals, Inc. and A limited amount of information concerning this study (eg, objectives, study design) is given to help the reader’s interpretation. This SAP must be finalised prior to the lock of the clinical database for this study. When the SAP and TFL shells are agreed upon and finalized, they will serve as the template for this study’s CSR.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon between Alnylam Pharmaceuticals, Inc. and and identified in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 guideline entitled, “Guidance for Industry: Statistical Principles for Clinical Trials” and the ICH E3 guideline entitled, “Guidance for Industry: Structure and Content of Clinical Study Reports.”1,2

5. STUDY OBJECTIVES

Primary Objective

- 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 Objectives

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

- To assess the PD effect of ALN-CC5 on inhibition of hemolysis in healthy adult subjects and in patients with PNH

- To explore the PD effect of ALN-CC5 on lactate dehydrogenase (LDH) levels in patients with PNH

6. 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. 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 3 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 eculizumab treatment or on stable doses 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 hours 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).

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 hours safety follow-up. The second sentinel subject in each cohort will then receive study drug (ALN-CC5 or placebo) followed by an approximately 24 hours 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 ALN-CC5 or placebo
- Cohort 3: 400 mg ALN-CC5 or placebo
- Cohort 4: 600 mg ALN-CC5 or placebo
- Cohort 5: 900 mg ALN-CC5 or placebo

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

The study design for Part A is illustrated in Figure 1.

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

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 hours 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.

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 ALN-CC5 or placebo
- Cohort 2: 200 mg ALN-CC5 or placebo
- Cohort 3: 400 mg ALN-CC5 or placebo
- Cohort 4: 600 mg ALN-CC5 or placebo

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

The study design for Part B is illustrated in Figure 2.

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

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.

The study design for Part C is illustrated in Figure 3.

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

**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.

7. TREATMENTS

The following is a list of the study treatment abbreviations that will be used in the TFLs.

<table>
<thead>
<tr>
<th>Study Part</th>
<th>Study Treatment Name</th>
<th>Treatment order on TFL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part A</td>
<td>Placebo*</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>50 mg ALN-CC5</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>50 mg ALN-CC5 (Japanese)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>200 mg ALN-CC5</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>200 mg ALN-CC5 (Japanese)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>400 mg ALN-CC5</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>600 mg ALN-CC5</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>600 mg ALN-CC5 (Japanese)</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>900 mg ALN-CC5</td>
<td>9</td>
</tr>
<tr>
<td>Part B</td>
<td>Placebo*</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>100 mg ALN-CC5 weekly</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>200 mg ALN-CC5 weekly</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>400 mg ALN-CC5 weekly</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>200 mg ALN-CC5 weekly/biweekly</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>600 mg ALN-CC5 biweekly</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>200 mg ALN-CC5 weekly/monthly</td>
<td>7</td>
</tr>
<tr>
<td>Part C#</td>
<td>Eculizumab treated</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Eculizumab naive</td>
<td>2</td>
</tr>
</tbody>
</table>

*Placebo will be pooled separately for Part A and Part B.  
# ALN-CC5 doses will be pooled within Eculizumab groups for Part C.

Part A, Part B and Part C will be reported separately.

8. SAMPLE SIZE JUSTIFICATION

The sample size was not determined based on power calculations. Up to 76 participants (60 subjects and 16 patients) are expected to be enrolled in the study (including optional cohorts).

9. DEFINITION OF ANALYSIS POPULATIONS

The Safety Population will consist of all subjects/patients who received at least 1 dose of study drug (ALN-CC5, placebo). The safety population will be used for all analyses of demographics, baseline characteristics, disposition and safety data.
The **PD Population** will consist of all subjects/patients who received at least 1 dose of study drug (ALN-CC5, placebo) and have at least one postdose blood sample for the determination of plasma ALN-CC5.

### 10. STATISTICAL METHODOLOGY

#### 10.1 General

Data listings will be provided for all subjects/patients. Summary statistics and statistical analysis will only be presented for data where detailed in this SAP. For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation, standard error of the mean [SEM], median, quartiles, minimum, maximum and number; for log-normal data, the geometric mean and geometric coefficient of variation (CV%) will also be presented. For categorical data, frequency counts, percentages and number will be presented. Data listings will be provided for all subjects/patients up to the point of withdrawal, with any subjects/patients excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for subjects/patients included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

For PD assessments (C5 protein levels, serum complement activity, hemolysis) baseline is defined as the average of all measurements collected before the first dose/time of study drug (scheduled and any unscheduled visits between screening and dosing).

For PD assessment (LDH) baseline is defined as the average of all measurements collected before the first dose/time of study drug (scheduled and any unscheduled visits between screening and dosing). For patients entering the trial on stable doses of eculizumab, a supplementary baseline definition will be considered. This baseline will be defined as the average of historical LDH values (including the LDH at study screening).

For safety assessment baseline is defined as the average of all measurements collected before the first dose/time of study drug (scheduled and any unscheduled visits between screening and dosing).

For vital sign, serum biochemistry, hematology, coagulation, urinalysis, and high-sensitivity C-reactive protein (hs-CRP) data; baseline is defined as the last observed value prior to the first dose of study drug.
For ECG data baseline is defined as last observed value (mean of triplicate) prior to the first dose of study drug.

For other data baseline is defined as the last observed value prior to the first dose of study drug.

Mean change from baseline is the mean of all individual subjects’/patients’ change from baseline values. Each individual change from baseline will be calculated by subtracting the individual subject’s/patient’s baseline value from the value at the time point. The individual subject’s change from baseline values will be used to calculate the mean change from baseline using a SAS® procedure such as Proc Univariate.

Mean percent change from baseline is the mean of all individual subjects’/patients’ percent change from baseline values. Each percent change from baseline will be calculated by subtracting the individual subject’s/patient’s baseline value from the value at the desired timepoint and then dividing this calculated value by the individual subject’s/patient’s baseline value and multiplying by 100. These individual subjects’/patient’s percent changes from baseline values will be used to calculate the mean percent change from baseline using a SAS® procedure such as Proc Univariate.

Relative change from baseline will be calculated as the actual value divided by baseline.

Onset times postdose are calculated from the last dose administered. For Part B, onset times are also calculated from the first dose administered.

Missing values will not be imputed.

Data analysis will be performed using SAS® Version 9.3.

Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) Analysis Data Model Version 2.1, and CDISC ADaM Implementation Guide Version 1.0. OpenCDISC Version 1.5 will be utilised to ensure compliance with CDISC standards

10.1.1 Repeat and Unscheduled Readings

Repeat readings occur when the original result requires confirmation. Repeat readings are labelled as ‘Repeat’ in the listings and replace the original readings in all summaries and changes from baseline presentations and calculations. Prior to dosing, all readings taken in addition to the original reading are defined as pre-dose repeats. Postdose repeat readings are defined as readings collected within 15 minutes of the actual time of the original reading. Where results are taken in triplicate and repeated the last 3 readings are used in all subsequent calculations.

With the exception of pre-dose results described above, at all other timepoints unscheduled readings are defined as readings collected >15 minutes from the actual time of the original reading. Where results are taken in triplicate the original reading is defined as the first reading of
the triplicate. Unscheduled readings are labelled as ‘Unscheduled’ in the listings. As unscheduled readings are not associated with any scheduled timepoint they are excluded from all summaries.

10.1.2 Data captured after unblinding.

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 followup visits until the CAP ELISA result returns to within the reference range.

Parts A and B will be unblinded after the last subject of Part B has reached the 9 months time point after last dose of study drug. An interim analysis of Parts A and B will be performed at unblinding. At the end of the study, analysis will be completed for the final complete set of data and also repeated for the data captured up to the cut-off date of the original interim analysis prior to the unblinding.

10.2 Demographics and Subject/Patient Disposition

Subject/patient disposition will be summarised and listed by dose group and overall for subjects in the safety analysis set. If the PD analysis set differs to the safety analysis set then subject/patient disposition will be summarised separately. The demographic variables age, sex, race, ethnicity, body weight, height and body mass index will be summarised and listed. 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.

Disposition of Parts A and B will be summarized for the double-blind treatment period and entire treatment period separately.

10.3 Baseline Characteristics

Medical history, drugs of abuse/alcohol screen (Part A and Part B only), β-HCG pregnancy test, Follicle-Stimulating Hormone (FSH) screening (postmenopausal women only) and viral serology data will be listed.
10.4 Pharmacodynamic Assessment

10.4.1 Pharmacodynamic Analysis

PD assessments will include 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 in CAP ELISA and complement classical pathway [CCP] ELISA assays).

By default any values that are below the limit of quantification should be set to half the limit of quantification.

10.4.2 Pharmacodynamic Statistical Methodology

PD assessments will be summarized by study phase, treatment and scheduled time point using the PD analysis set.

For Part A (SAD) and Part B (MAD), the data will be tabulated for each cohort. Data will be pooled for active subjects by dose and placebo.

For Part C (patients with PNH), the data will be tabulated based on treatment experience (naïve to eculizumab treatment and stable doses of eculizumab) and dose level if required.

Relative change from baseline for plasma levels of C5 protein levels and serum complement activity will be calculated as the actual value divided by baseline. Percentage change from baseline (“knockdown”) for will also be calculated as described in section 10.1 above. Baseline is defined as the average of all measurements collected before the first dose/time of study drug (scheduled and any unscheduled visits between screening and dosing).

Plasma levels of C5 protein levels and serum complement activity actual values, relative, and percentage change from baseline will be summarized. Mean (± SEM) relative and percentage changes at each scheduled time point will be plotted.

Individual nadir values (defined as the lowest postdose C5 protein level and serum complement activity percent change from baseline values per subject) and group nadir values (defined as the postdose C5 protein level and serum complement activity relative to baseline values at the timepoint where group [i.e. treatment group] mean relative to baseline value is minimized) will be plotted and summarized. Mean, maximum, and SEM knockdown at individual and group nadirs will be displayed with visit date of group nadirs.

Analysis 1: PD differences over time among treatment groups

Differences in PD parameters (plasma levels of C5 protein levels and serum complement activity) between treatment groups (active dose groups versus pooled placebo) will be explored separately in the study phases via repeated-measures analysis of covariance (ANCOVA). The analysis will use an autoregressive first order covariance structure (ar(1)). Ln (PD parameter relative to baseline) will be the dependent variable in the model. Ln (PD parameter at baseline)
will be a covariate; factors will be Treatment group (dose levels versus pooled placebo), Residential or Outpatient Follow-up timepoint (Day), and Treatment by Day interaction. Only measurements collected at scheduled time points will be considered:

$$\text{Ln (PD parameter relative to BL)} = \text{Ln (PD parameter at BL)} + \text{Subject} + \text{Treatment} \times \text{Day}$$

If the Treatment * Day interaction term is statistically significant ($p<0.05$), then nominal p-values will be used to examine pairwise comparisons of least square means (LSMs) among treatments per visit day (significance at $p<0.05$, no further adjustment).

If the Treatment * Day interaction was not statistically significant (i.e., trends in the PD effect are parallel across visits between treatment groups), then the interaction term from the model will be removed and whether the main effect of Treatment is statistically significant ($p<0.05$) will be tested. If treatment is significant under the simplified model, nominal p-values will be reported per visit day as above.

**Analysis 2: PD differences in Area Under the Curve among treatment groups**

Plasma levels of C5 protein levels and serum complement activity Area Under the effect Curve (AUCe) will be calculated using C5 protein levels and serum complement activity concentrations and the method of trapezoids, beginning with baseline and extending to the last scheduled time point containing data for all members of groups being compared (e.g. cohorts, pooled placebo and active). Only scheduled assessments will be considered when calculating the AUC. Differences in AUCe between placebo and active will be examined via ANCOVA, with Treatment group as the sole factor and PD parameter at baseline as a covariate:

$$\text{AUCe} = \text{Ln (Baseline)} + \text{Treatment}$$

The relationships between C5 protein and serum complement activity AUCe will be explored using Pearson’s correlation coefficient (if normality assumption holds) or Spearman correlation coefficient (if normality does not hold). A correlation plot will be provided along with the r-squared value and corresponding p-value.

The relationships between C5 protein and serum complement activity will be explored by comparing distributions of serum complement activity collected at time points where knockdown of C5 protein was either low or high (i.e. KD<50% vs. KD≥ 50%).

**Analyses for Exploratory Objectives:**

*Exploratory PD Parameter: hemolysis*

PD assessments will examine the impact of ALN-CC5 on hemolysis (assessed by sensitized sheep red blood cells [RBC] and PNH RBC lysis assays) in subjects and patients.
The descriptive summaries outlined in the Pharmacodynamic Statistical Methodology (above) will be performed in the same manner for the Exploratory PD parameters using the PD Analysis set as above.

Given that these parameters will not be collected for all of the cohorts, the analyses will be descriptive in nature and the Analysis 1 and Analysis 2 (above) will not be performed for these parameters.

*Exploratory PD Parameter: LDH*

PD assessments will examine the impact of ALN-CC5 on LDH levels in patients with PNH.

The descriptive summaries outlined in the Pharmacodynamic Statistical Methodology (above) will be performed in the same manner for LDH for actual values, change from baseline and percentage change from baseline as above separately based on treatment experience (naïve to eculizumab treatment and stable doses of eculizumab) and dose level if required.

Additional analysis will be conducted for patients on stable doses of eculizumab at study entry. The descriptive summaries outlined in the Pharmacodynamic Statistical Methodology (above) will be performed in the same manner for LDH for actual values, change from baseline and percentage change from baseline as above during the timeframe when the patient is receiving only ALN-CC5 for patients on stable doses of eculizumab at study entry.

*Exploratory safety parameter: Number of transfusions*

For the patients on stable doses of eculizumab at study entry, 3 time points will be displayed (before treatment, treatment with ALN-CC5+eculizumab, and treatment with ALN-CC5 only). Given that the duration of treatment of ALN-CC5+eculizumab and ALN-CC5 (alone) will vary per patient, descriptive statistic of duration of treatment at each time point will also be provided.

For patients who are naïve to eculizumab, descriptive statistics of transfusions will be displayed by 2 time points (before treatment and during treatment).
10.5 Safety and Tolerability Assessments

10.5.1 Adverse Events

A baseline sign and symptom is defined as an adverse event (AE) that starts after the subject/patient has provided written informed consent and resolves prior to the first dosing occasion or an AE that starts prior to the first dosing occasion and does not increase in severity after dosing. A treatment-emergent adverse event (TEAE) is defined as an AE that occurs postdose or that is present pre-dose and becomes more severe postdose.

Adverse events (AEs) will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) (Version 17.1). AEs will be graded using the Common Terminology Criteria for Adverse Events (CTCAE; Version 4.0). Where changes in grading are recorded in the CRF, each separate grading of the AE will be reported in the tables and listings.

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 [ISR] (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).

All AEs will be listed. TEAEs will be summarised by study part and treatment, maximum severity (CTCAE grade), and relationship to the study drug. The frequency (the number of TEAEs, the number of subjects/patients experiencing a TEAE, and the percentage of subjects/patients experiencing a TEAE) of TEAEs will be summarised by treatment, Medical Dictionary for Regulatory Activities system organ class, and preferred term. A frequency summary will be presented by day of onset across the multiple dosing period. The summary and frequency TEAE tables will be presented for all causalities and for those considered related to the study drug (those that have a relationship of definitely or possibly related). Any serious AEs and AEs leading to discontinuation of treatment will be listed. Any deaths will be listed.

Injection site reactions will be listed and summarized by study part and treatment.

10.5.2 Concomitant Medication

Concomitant medications will be coded using the World Health Organisation (WHO) drug dictionary (September 2014). Concomitant medications will be tabulated by Anatomic Therapeutic Class (ATC) and Preferred Term and by overall decreasing frequency of subjects/patients who took the medications. Concomitant medications and prior medications will be listed.

10.5.3 Clinical Laboratory Parameters

**Serum biochemistry, hematology, coagulation and urinalysis data**

Absolute values and change from baseline will be summarised by study part and treatment. Shift
tables from baseline (last observed value prior to the first dose of the study drug) to both maximum and minimum post baseline levels will be presented by study part, parameter and treatment with high, low and normal as defined by the laboratory ranges for hematology, serum chemistry, coagulation and urinalysis data.

Mean laboratory parameters will be plotted over time by study part and treatment.

For key safety parameters, shift tables will be produced summarising the maximum shift from baseline in laboratory grade according to the CTCAE for adverse events (version 4.0).

In addition, all serum biochemistry, hematology, and urinalysis data outside the clinical reference ranges will be listed by parameter and treatment.

Any clinically significant results and any serum biochemistry, hematology, coagulation and urinalysis values outside the clinical reference ranges will be flagged on the individual subject/patient data listings.

10.5.4 Vital signs
Changes from baseline will be calculated, where baseline is defined as last observed value prior to the first dose of study drug.

Vital sign values outside the clinical reference ranges will be flagged on the individual subject/patient data listings.

The vital signs data will be summarized by study part and treatment, together with changes from baseline.

10.5.5 Electrocardiogram
The electrocardiogram (ECG) data will be obtained directly from the 12-lead ECG traces. These data include the PR, QT, QT interval corrected using Bazett’s formula (QTcB) intervals; QRS duration; and heart rate (also RR interval and QRS Axis for Part A). For Parts B and C QT interval corrected using Frederica’s formula (QTcF) will only be assessed at the clinical study site if QTcB is prolonged. Part A, both QTcB and QTcF will be presented.

Where ECGs are measured in triplicate (at approximately 2 minute intervals), the mean value will be used in all subsequent calculations. Changes from baseline will be calculated, baseline is defined as the last value prior to dosing on Day 0.
Values for ECG parameters outside the clinical reference ranges will be flagged on the individual subject/patient data listings.

The ECG data will be summarised by treatment, together with changes from baseline. Assessed QTcF data will be listed.

For purposes of the final analysis of the study a single interpretation derived from each triplicate will be provided, and will use the convention that if any of the 3 ECG’s are “abnormal” that the overall interpretation will be abnormal (and CS or NCS as the case may be). All 3 interpretations will be included in the listings.

10.5.6 Other Assessments

Abnormal physical examination findings will be listed.

Vaccination against Neisseria meningitides will be listed.

10.5.7 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

11. INTERIM ANALYSES

Parts A and B will be unblinded after the last subject of Part B has reached the 9 months time point after last dose of study drug. An interim analysis of Parts A and B will be performed at unblinding.

12. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

13. DATA PRESENTATION

13.1 Insufficient Data for Presentation

Some of the TFLs will not have sufficient numbers of subjects/patients or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, “No serious adverse events occurred for this study.”

14. REFERENCES
