A Phase 3, Randomized, Parallel-Group, Multicenter, Open-Label, Pharmacokinetic, Noninferiority Study of Ravulizumab Administered Subcutaneously Versus Intravenously in Adult Patients With Paroxysmal Nocturnal Hemoglobinuria Currently Treated With Eculizumab

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Alexion Pharmaceuticals, Inc.

STATISTICAL ANALYSIS PLAN

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Author: PPD

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1. APPROVAL SIGNATURES

PPD Covance — Date dd Mmm yyyy

PPD Alexion Pharmaceuticals — Date dd Mmm yyyy

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PPD Alexion Pharmaceuticals — Date dd Mmm yyyy

STATISTICAL ANALYSIS PLAN SUMMARY OF CHANGES

Section/Table	Description of Change	Version
Section 4 (Figure 1 and Table 2) and Section 4.1.3	Updated Figure 1, Table 2 and Table 6 to reflect the extended Extension Period.	2.0
Section 4, 5.3, 7.4, 7.5.1 and 9.5.4	Removed the single exploratory endpoint (PPQ).	2.0
Section 5.5.2, 5.5.3, 7.5.3 and 7.5.3.5	Updated definitions of overdose for ravulizumab administered via IV infusion and via OBDS	2.0
Section 9.5.4	Modified the estimate statement in the mixed model so the estimate is calculated as a difference of logs (SC-IV)	2.0
Section 4.2, 6, 6.6 and 6.8	Added modified safety and full analysis sets to include patients from site 0657 who have clinical trial data that has been flagged as part of a for-cause clinical investigator site audit.	2.0
Section 5.4.2	Added verbiage to the definition of an ADE around partial or no dose administrations.	2.0
Section 6.2	Modified the definition of the PK analysis set to include the dose and PK windowing set forth in Protocol Amendment 4.	2.0
Section 7.2.3.1	Defined baseline age as age at informed consent	2.0
Section 7.2.3.2	Removed age at PNH diagnosis and age at first eculizumab infusion as summarized parameters	2.0
Section 7.5.1	Added verbiage around the definition of dose interruptions, time under treatment effect and treatment compliance.	2.0
Section 7.5.3.5	Changed the section title from “ADEs not classified as AEs” to “Medication Error ADEs” and defined a medication error.	2.0
Section 9.3.2	Added imputation rules for partial medication dates	2.0
Section 4.0	Removed “ Noninferiority will be claimed, if after 71 days of treatment, the lower boundary of the two-sided 90% CI of the geometric mean ratio C_{trough} SC:C_{trough} IV is greater than 0.8.” as the claim will be based on the combined z-score.	3.0
Section 7.3.1	Revised analysis such that the noninferiority claim will be based on the log-transformed parameters although the ratio scale will be presented.	3.0
Section 7.3.1.1.1	Added the pre-specified CHW weights and removed the formula for calculating the weights.	3.0
Section 4	Added references to the administrative change letters indicating changes to length of extension period.	4.0
Section 4.1	Added sentence indicating COVID-19 analyses will be specified in a separate SAP Addendum.	4.0
Section 4.1.3	Modified the section to include the 12-month snapshot time point.	4.0
Section 4.2	Added all changes from any analyses specified in PA4.	4.0
Section 4.3.1, 4.3.2 and 4.3.3	Formatted section to include changes from each previous version of the SAP (v1, v2 and v3).	4.0

Section 5.2.1	Added a reference for the EORTC Scale.	4.0
Section 5.2.2	Removed "From Baseline to Day 183" from all secondary efficacy endpoints.	4.0
Section 5.3	Changed C_{trough} to concentration.	4.0
Table 5	Changed SOM to SOP.	4.0
Section 4.2, 6.7, 6.8, 6.11, 6.12	Added SC Treated Safety Analysis Set, Modified SC Treated Safety Analysis Set, SC Treated Full Analysis Set and Modified SC Treated Full Analysis Set.	4.0
Section 7	Added details regarding the exclusion of clinical laboratory data that is impacted by Table Top Hemolysis.	4.0
Section 7.1	Removed presentation by group totals across all Day 71 summaries.	4.0
Section 7.1	Added subsection 7.1.4 "Data Collected but not Analyzed" and subsection 7.1.5 "Analysis of Subgroups".	4.0
Section 7.1.2	Changed the title of Table 6 from "Exposure Difference to SC Treatment by Study Day at the Start of the Extension Period" to " Study Visits" and modified the days since first SC treatment.	4.0
Section 7.2.2	Clarified that important protocol deviations will be presented using group totals.	4.0
Section 7.2.3.1	Removed presentation by extension period for patient demographics.	4.0
Section 7.2.3.3	Added sorting rule for medical history summaries.	4.0
Section 7.2.4	Added presentation by group totals and added sorting rule for medication summaries.	
Section 7.4	Added SCF and mSCF populations to secondary analyses.	4.0
Section 7.4.1, 7.4.2, 7.4.3, 7.4.4 and 7.4.5	Added six month and one year time point analyses as well as rules for patients who withdrawal from the study due to lack of efficacy.	4.0
Section 7.4.5	Added additional analyses for shift summaries as well as descriptive statistics for each PNH symptom shown.	4.0
Section 7.4.6	Removed FAS as the single population referenced.	4.0
Section 7.4.6.2 and 7.5	Added the SC related populations for analysis along with listings being produced for titer values.	4.0
Section 7.4.7.1 and 7.4.7.2	Added 'Subscale Score' to the section heading.	4.0
Section 7.5.1	Modified summaries based on on-site dose administrations and added data cutoff rule for treatment duration.	4.0
Section 7.5.2	Added verbiage to indicate which treatment AEs are attributed to at the time of treatment switch (Day 15 and Day 71).	4.0
Section 7.5.2	Added verbiage to indicate that AEs will be analyzed in 6 month intervals and defined the number of days that equal 1 month.	4.0
Section 7.5.2	Added subsection 7.5.2.8 describing the additional analysis of AEs using a rate of AEs in patient years.	4.0
Section 7.5.2.2	Added analyses for ADEs that are or are not product issues and added AESIs	4.0
Section 7.6	Removed subsection 7.6.1.5 – Medication Errors	4.0
Section 7.5.3.1	Removed reference to scatter plots.	4.0
Section 7.6	Moved device performance to section 7.6 and added analyses based on product complaints.	4.0

2. TABLE OF CONTENTS AND LIST OF TABLES

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and acronyms are used in this SAP.

Table 1: Abbreviations and Acronyms

Abbreviation or acronym	Explanation
ADA	antidrug antibody
ADE	adverse device effect
AE	adverse event
AESI	adverse events of special interest
ANC	absolute neutrophil count
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BP	blood pressure
C	Celsius
C5	complement component 5
CI	confidence interval
cm	centimeters
CS	clinically significant
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variance
ECG	electrocardiogram
F	Fahrenheit
FCS	fully conditional specification
eCRF	Electronic Case Report Form
EOI	end of infusion
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 scale
ER	emergency room
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	full analysis set
FDA	Food and Drug Administration
HLT	high level term
HR	heart rate
HRQoL	Health-Related Quality of Life
IFU	instructions for use
IV	intravenous(ly)
ISAP	Interim Statistical Analysis Plan
kg	kilogram
LDH	lactate dehydrogenase
MAVE	major adverse vascular event
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified full analysis set
mg	milligram
mmHG	millimeters mercury
mSCF	modified sc treated full analysis set
mSCS	modified sc treated safety analysis set
mSS	modified safety set
NIM	noninferiority margin

Abbreviation or acronym	Explanation
OBDS	On-Body Delivery System
PCHG	percent change
PD	pharmacodynamic
PK	pharmacokinetic
PNH	paroxysmal nocturnal hemoglobinuria
PPS	per protocol set
PT	preferred term (MedDRA)
PTAEs	pre-treatment adverse events
PY	patient years
qw	once every week
QLQ-C30	Quality of Life Questionnaire-Core 30 Scale
QoL	quality of life
QTcF	qt interval corrected using fridericia's formula
RBC	red blood cell
RR	respiration rate
SADE	serious adverse device effect
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis Software®
SC	sub-cutaneous
SCF	sc treated full analysis set
SCS	sc treated safety analysis set
SD	standard deviation
SMQ	standardized MedDRA queries
SOA	schedule of activities
SOC	system organ class (MedDRA)
SOP	Standard Operating Procedure
SS	safety set
TA	transfusion avoidance
TASQ	Treatment Administration Satisfaction Questionnaire
TEAEs	treatment-emergent adverse events
TTH	table top hemolysis
µL	micro liters
ULN	upper limit of normal
WHO-DRUG	World Health Organization Drug Dictionary

4. DESCRIPTION OF THE PROTOCOL

ALXN1210-PNH-303 is a Phase 3, randomized, open-label, parallel-group, multicenter study to evaluate pharmacokinetic (PK) noninferiority of ravulizumab subcutaneously (SC) administered via an on-body delivery system (OBDS) compared with intravenously (IV) administered ravulizumab in adult patients with paroxysmal nocturnal hemoglobinuria (PNH) who are clinically stable and have been previously treated with eculizumab for at least 3 months prior to study entry. This study is planned to be conducted at up to 60 centers globally.

As per the Administrative Change Letter #2, 26-May-2020, applicable to Protocol Amendment 3.0 dated 17-May2019 or Protocol Amendment 4.0 dated 19-Nov-2010, the study will consist of an up to 30-day Screening Period, a 10-week Randomized Treatment Period, and a 172-week Extension Period (or until the product is registered or approved, whichever occurs first). Study entry is defined as the date when signed informed consent is provided by the patient. Patients will be stratified by weight groups (≥ 40 to < 60 kg and ≥ 60 to < 100 kg) and then randomized in a 2:1 ratio to receive either ravulizumab SC or ravulizumab IV.

Ravulizumab IV dosing during the Randomized Treatment Period will be administered in the clinic by a trained member of the site study team. Day 1 of study treatment will occur 12 to 16 days from the patient's last dose of eculizumab. Timing for study drug administration and predose PK sample collection is critical to ensure adequate numbers of patients with evaluable PK data (Table 2). The time for the start of the dose administered on Day 1 is the nominal time for all subsequent doses and PK/PD sample collections. Specifically, all subsequent doses during the Randomized Treatment Period are expected to be administered at the same time of the day that the dose was administered on Day 1. The PK samples are expected to be drawn as close as possible to the administration of the dose (or from the nominal time from the start of the Day 1 dose on non-dosing days). The PK analysis set population is defined in Section 6.2.

The study will enroll at least 105 patients (70 patients in the ravulizumab SC group; 35 patients in the ravulizumab IV group). An interim analysis for sample size re-estimation will be conducted and the sample size may be increased to a maximum of 144 patients (Section 4.1.1).

Ravulizumab OBDS will be supplied in a kit, comprising 245 mg of ravulizumab SC in a sterile, single-use, prefilled cartridge assembly co-packaged with a single-use injector. Two kits will be used to deliver the full 490 mg dose of ravulizumab SC.

Ravulizumab IV loading and maintenance doses will be based on patient body weight at the last recorded study visit.

Patients randomly assigned to the ravulizumab SC group will receive a loading dose of ravulizumab IV on Day 1 followed by maintenance doses of ravulizumab SC on Day 15 and qw thereafter for a total of 10 weeks of study treatment. Two ravulizumab OBDS kits will be used to deliver the full maintenance dose of ravulizumab SC. Patients randomly assigned to the ravulizumab IV group will receive a loading dose of ravulizumab IV on Day 1 followed by a maintenance dose of ravulizumab IV on Day 15 (Table 2).

On Day 15, patients who randomized to the ravulizumab SC group will self-administer ravulizumab SC in the clinic with oversight by trained study site personnel as part of the required training program for at-home self-administration. Once training has been completed, the patient will be able to self-administer ravulizumab SC. On Days 29, 43, 57, and 64, patients can

self-administer ravulizumab SC in the clinic with oversight by trained study site personnel. On Days 22, 36, and 50, ravulizumab SC can be self-administered by the patient at home. With approval from the Sponsor, the patient can self-administer ravulizumab SC at the clinic on dosing days that are not scheduled in-clinic visits. On days that ravulizumab SC is self-administered at home, the site will contact the patient via telephone at scheduled times to ensure patient is queried about study drug dose administration and device condition.

Table 2: Ravulizumab Study Drug Dosing

Treatment Group	Randomized Treatment Period (10 weeks)		Extension Period (up to 172 weeks)
Ravulizumab SC	**Loading Dose on Day 1:** Ravulizumab IV 2400 mg[a or] Ravulizumab IV 2700 mg[b]	**SC Doses on Days 15, 22, 29, 36, 43, 50, 57, and 64:** Ravulizumab SC 490 mg[c] (2 ravulizumab OBDS kits per weekly dose)	**Maintenance Doses on Day 71 and qw through Day 1275:** Ravulizumab SC 490 mg[d] (2 ravulizumab OBDS kits per weekly dose)
Ravulizumab IV		**Maintenance Dose on Day 15:** Ravulizumab IV 3000 mg[a] or Ravulizumab IV 3300 mg[b]	

[a] Weight group ≥ 40 to < 60 kg.
[b] Weight group ≥ 60 to < 100 kg.
[c] On Day 15, patients who randomized to the ravulizumab SC group will self-administer ravulizumab SC in the clinic with oversight by trained study site personnel as part of the required training program for at-home self-administration. On Days 29, 43, 57, and 64, ravulizumab SC will be self-administered by the patient in the clinic with oversight by trained study site personnel. On Days 22, 36, and 50, ravulizumab dosing can be self-administered by the patient at home. With approval from the Sponsor, the patient can self-administer ravulizumab SC at the clinic at these visits.
[d] Self-administered by the patient at home or self-administered in the clinic with oversight by trained study site personnel on scheduled visit days. With approval from the Sponsor, the patient can self-administer ravulizumab SC at the clinic on dosing days that are not scheduled in-clinic visits. On Day 71, patients who had been randomized to the ravulizumab IV group will self-administer ravulizumab SC in the clinic with oversight by trained study site personnel as part of the required training program for at-home self-administration.
Abbreviations: IV = intravenous; OBDS = on-body delivery system; qw = every week; SC = subcutaneous.

Day 71 is the end of the Randomized Treatment Period and the beginning of the Extension Period. All Day 71 assessments completed prior to dosing are considered part of the Randomized Treatment Period. Dosing on Day 71 is the start of the Extension Period. During the Extension Period:

- Patients who had been randomized to the ravulizumab SC group will continue to receive 490 mg of ravulizumab SC using 2 OBDS kits on Day 71 and qw thereafter through the end of the Extension Period (up to Day 1275)
- Patients who had been randomized to the ravulizumab IV group will switch to 490 mg of ravulizumab SC using 2 OBDS kits on Day 71 and qw thereafter through the end of the Extension Period (up to Day 1275)

Ravulizumab SC dosing during the Extension Period will be self-administered by the patient at home with the following exceptions where ravulizumab SC must be administered in the clinic:

- For patients who had been randomized to the ravulizumab IV group, ravulizumab SC 490 mg dose on Day 71 will be self-administered by the patient in the clinic with oversight by trained study site personnel as part of the required training program for at-home self-administration.
- For all patients, doses that coincide with study visits specified in the Schedule of Activities (SoA) listed in the protocol, will be self-administered by the patient in the clinic with oversight by trained study site personnel.

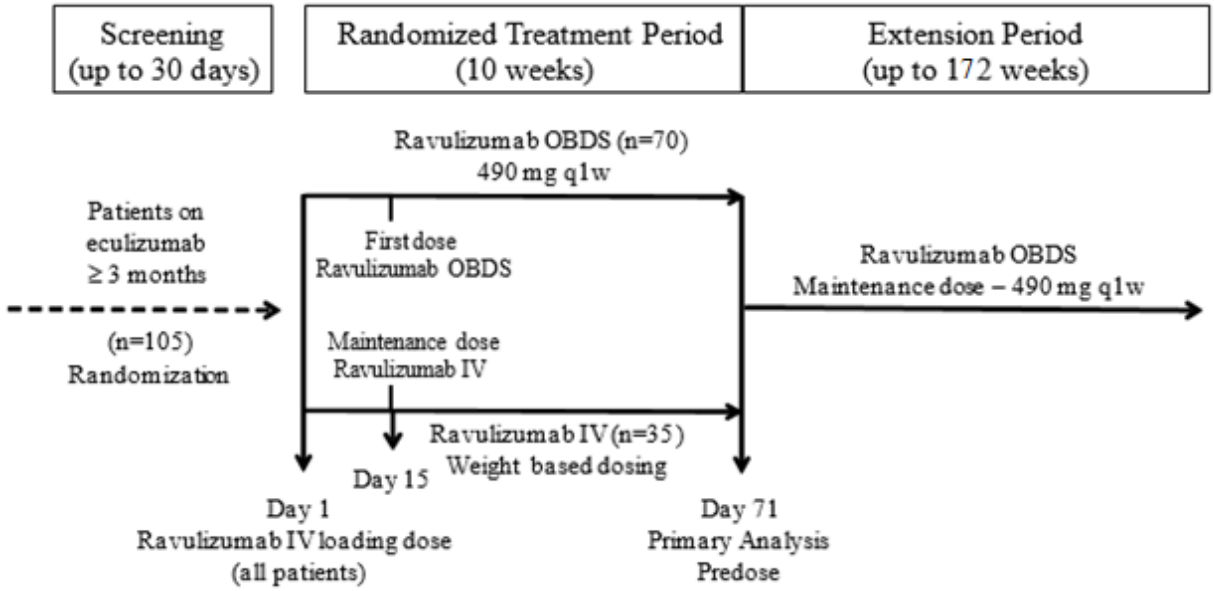
- With approval from the Sponsor, the patient can self-administer ravulizumab SC at the clinic on dosing days that are not scheduled in-clinic visits (with oversight by trained study site personnel).

- An additional follow-up phone call will occur 30 days following the last dose of ravulizumab (SC or IV) and is limited to AE and concomitant medication monitoring.

  The end of the study for each patient occurs when the safety follow-up is completed. The safety follow-up consists of a phone call 30 days after the last dose. Data collection during the safety follow-up is limited to reporting adverse events and concomitant medications. If a patient discontinues treatment, but not from the study, the end of study for such a patient will be their last visit as long as that visit is more than 30 days from their last dose. The end of the study is defined as the date of the last patient visit or safety follow up, whichever occurs later.

  Figure 1 illustrates the study design.

Figure 1: Study Design Schematic for Clinical Protocol ALXN1210-PNH-303



The primary objective is to assess noninferiority in serum C_{trough} of ravulizumab SC compared with ravulizumab IV after all patients have completed all protocol-required assessments in the Randomized Treatment Period.

The secondary objectives of the study are to assess the following:

- To characterize the pharmacokinetics (PK) of ravulizumab SC
- To characterize the pharmacodynamics (PD) of ravulizumab SC
- To characterize the immunogenicity of ravulizumab SC
- To evaluate health-related quality of life (HRQoL) and treatment satisfaction on ravulizumab SC
- To evaluate the safety of ravulizumab SC and ravulizumab OBDS

- To evaluate the efficacy of ravulizumab SC
- To assess performance of ravulizumab OBDS

A final clinical study report (CSR) will be produced at study completion and will include data on all patients in the study through the end of the Extension Period.

4.1. Planned Analyses

A separate SAP Addendum will contain the planned analyses for all COVID-19 related summaries and listings.

4.1.1. Interim Analysis for Sample Size Re-estimation

A single interim analysis to evaluate futility and assess sample size re-estimation will be performed when approximately 50% of the planned patients (n = 105) have been assessed for the primary endpoint (ie, 34 patients in the ravulizumab SC group and 17 patients in the ravulizumab IV comparison group). This is expected to yield at least 45 patients who meet the criteria for inclusion in the PK analysis set. Patient demography and disposition will also be presented.

The initial part of the analysis will be to assess futility in order to allow the Sponsor to stop the study early if it is unlikely to lead to a significant final result. This will conserve resources and not expose additional patients to the study drug in the event that noninferiority appears very unlikely.

Following the futility assessment, but using the same set of patients and data, an interim sample size re-estimation analysis to reassess the required size of the study based on estimation of the primary endpoint will also be performed. This sample size re-estimation may lead to an increase of up to 144 patients (up to 96 patients in the ravulizumab SC group and 48 patients in the ravulizumab IV comparison group).

The interim analysis will be performed by an independent statistical center that is not involved with study conduct or final analysis of study data. The interim analysis will be conducted following the approach explained in Mehta and Pocock (Mehta, 2011). The interim result (parameter estimate) will be kept blinded from all study team members and only the sample size adjustment (if any) will be communicated to selected individuals at the Sponsor. The actual adjustment will be kept blinded to all study team members directly involved with study conduct, statistical analysis and/or programming.

More information on this interim analysis along with details of confidentiality are provided in the Interim Analysis Statistical Analysis Plan (ISAP). No interim analyses are planned for secondary or efficacy endpoints.

4.1.2. Analysis of the Randomized Treatment Period

When all patients have completed the Randomized Treatment Period (Day 71) an analysis of the primary endpoint and supporting sensitivity analyses will be conducted. All secondary and exploratory endpoints will be summarized as well as all safety data, through Day 71 (predose).

4.1.3. Analysis of the Extension Period

All secondary, exploratory and safety endpoints will be analyzed from the start of subcutaneous treatment which is Day 15 for the SC group and the beginning of the Extension Period for the IV group. A 12-month data snapshot will be analyzed for submission purposes along with a 12-month CSR.

4.2. Changes from Analyses Specified in the Protocol

The definition of the Safety Analysis Set was changed from "Patients will be analyzed according to the study drug they actually received" to "Patients will be analyzed according to the treatment they actually received during the Randomized Treatment Period".

The disease related efficacy endpoints (breakthrough hemolysis, transfusion avoidance and stabilized hemoglobin) were changed to include the verbiage "from baseline to Day 183" in the SAP v1.0.

PNH symptomology was inadvertently excluded from the protocol as an endpoint and was added to version 1.0 of the SAP.

To ensure the integrity of the analyses, a modified FAS and SS have been added and are defined Section 6. Additional 'SC-Treated' populations have been added in order to define separate analysis sets for use when analyzing data since the administration of the first SC treatment and are defined in Section 6.

Section 9.4.1 of the clinical protocol states that "The ratio of the geometric mean Ctrough from the ravulizumab SC group over the geometric mean Ctrough from ravulizumab IV group with a 2-sided 90% CI will be calculated. If the lower bound of the 90% CI for the ratio of the geometric means (ravulizumab SC/ravulizumab IV) is greater than the NIB of 80%, then the ravulizumab SC treatment will be concluded to be noninferior to the ravulizumab IV treatment."

Although the planned statistical methodology to be used is not being changed, the language is being adjusted to clarify that the primary analysis must account for the effect of the interim analysis on the final analysis and therefore will be conducted on the log-scale, and that the claim of noninferiority will be made based on a weighted combination z-score and p-value for significance rather than a confidence interval.

4.3. Changes from Analyses Specified in the Previous Version of the SAP

4.3.1. Changes from Analyses Specified in Version 1.0 of the SAP

The Patient Preference Questionnaire (PPQ) exploratory analysis has been removed. Additionally, the Extension Period was increased from 52 weeks to up to 172 weeks.

The definitions of the full and safety analysis sets were changed to exclude patients from site 0657 due to critical audit findings. Additionally, modified full and modified safety analysis sets to include patients from site -0657 who have clinical trial data were added.

Modified the definition of the PK analysis set to include dosing and PK windowing times.

Removed age at PNH diagnosis and age at first eculizumab infusion as summarized parameters.

Added date imputation rules for partial and missing medication dates.

4.3.2. Changes from Analyses Specified in Version 2.0 of the SAP

The language in Section 7.3.1 indicating what a claim of noninferiority would be based on was adjusted to clarify that such a claim would result from the analysis described in Section 7.3.1.1.1 based on a weighted z-score approach.

4.3.3. Changes from Analyses Specified in Version 3.0 of the SAP

None of the changes made from Version 3.0 of the SAP, impact the Day 71 Interim Analysis that was conducted on the locked data dated 15-Jun-2010.

There was one subject in the IV treatment group who discontinued the study during the Randomized Treatment Period and never received an SC treatment. Therefore, analyses that summarize data from the start of SC treatment will use the SC Treated Full (Section 6.7) and SC Treated Safety Analysis Sets (Section 6.11) as opposed to the Full and Safety Analysis Sets to exclude that subject. Similarly, modified SC Treated Full Analysis Set (Section 6.8) and modified SC Treated Safety Analysis Set (Section 6.12) are created for the modified populations to summarize the data from the start of the SC treatment.

Patients who consented to the study under Protocol Amendment 4 prior to the applicable study visit have questionnaire data at Day 127 through Day 351 and a few other assessments such as Laboratory, Immunogenicity, PK and PD, and Vital Signs at Day 351 and ECG and Physical Exam data at Day 365 and these assessments were not required under amendment 4. These data are collected and reported in the analysis datasets but will not appear in the analysis outputs such as tables, listings or figures with the exception of Protocol Deviations.

Additional subgroup analyses based on stratified weight group (40 to <60 kg and 60 to < 100 kg) were added to the secondary efficacy endpoints and are described in Section 7.1.5.

Adverse events will be analyzed using 6-month time intervals in addition to the analyses described in version 3.0 and are described in Section 7.5.3. Additional analyses of non-serious adverse events occurring at a rate of at least 5% were added.

Summaries for Adverse Device Effects were added for patients that had events considered product issues. Product issues were related to medication errors so the definition for medication errors was removed as they are not summarized. Additionally, more detailed analyses were added for the OBDS device performance which include product complaints which are collected by the Investigations Group.

Scatter plots of the worst laboratory value post first study drug versus baseline were removed during the pre-database lock dry run for the Day 71 primary analysis. However, they were inadvertently left in the SAP and thus, the sentence has been removed.

The patient reported PNH Symptomology efficacy endpoint was changed to “Change in clinical manifestations of PNH” as the symptoms are not patient reported. The analysis of PNH symptomology was modified to include the counts for the number of symptoms experienced at each visit along with summary statistics for the number of symptoms shown at each visit. Additionally, shift from baseline analyses were added.

To match the protocol wording, the disease related secondary efficacy endpoints were modified to be summarized over time as opposed to over time and through Day 183. There is no change in the planned analysis due to this change in the endpoint wording.

The immunogenicity analysis of the proportion of patients ever ADA-positive and the proportion of patients always ADA-negative was removed.

Presentation by group totals were removed from the Randomized Treatment Period and Extension Period during the pre-database lock dry run for the Day 71 primary analysis. This was inadvertently left in the SAP, however, totals will only be presented where specified, not generally across all summaries.

During the conduct of the study, it has been observed that some of the central laboratory chemistry samples undergo in vitro erythrocyte lysis or table top hemolysis (TTH) caused by sample mishandling. This is unrelated to hemolysis due to PNH. The reasons for TTH vary and include delayed or improper centrifugation and traumatic blood draws. In addition, PIGA deficient erythrocytes from patients with PNH are more susceptible to mechanical lysis than non-PNH erythrocytes (Smith, 1985). Hemolysis results in release of RBC contents including LDH, potassium and AST. In contrast to hemolysis in patients with PNH, in which serum potassium is normal, for samples affected by TTH both potassium and LDH are markedly and proportionally increased (Goyal and Schmotzer, 2015; Ostendorp 2006). Marked hyperkalemia (defined as >6mmol/L) seen in TTH, but not PNH hemolysis, differentiates TTH (in vitro) from PNH hemolysis (in vivo), and is not clinically significant (Hollander-Rodriguez 2006; Kovesdy 2014). Due to the artefactual increase in LDH in samples affected by TTH, the potassium, ALT, AST, and LDH values in samples affected by TTH will not be used in the analysis of any efficacy or safety endpoints, with the exception that the LDH value will be used for the qualification of breakthrough hemolysis events. Breakthrough hemolysis is captured on a separate form and central lab LDH, in addition to new or worsening symptoms as specified in the protocol, are used by the principal investigator or designee to qualify patients with breakthrough hemolysis. TTH samples from the central lab will be defined as having serum potassium ≥ 6 mmol/L and LDH ≥ 2x ULN, and will be excluded from analyses as described above.

5. DEFINITIONS

5.1. Primary Endpoint

The primary endpoint of the study is serum ravulizumab trough concentration (C_{trough}) at Day 71.

5.2. Secondary Endpoints

5.2.1. HRQoL and Treatment Satisfaction Endpoints

1. Change in quality of life (QoL) assessed via the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale, Version 4, from Baseline to Day 183.
2. Change in the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (Aaronson, 1993) Scale (QLQ-C30), Version 3.0, from Baseline to Day 183.
3. Reported treatment satisfaction and patient preference as reported by the Treatment Administration Satisfaction Questionnaire (TASQ) at Baseline and Day 183.

5.2.2. Efficacy Endpoints

1. Change in lactate dehydrogenase (LDH) and the following other disease related laboratory parameters over time:
   - Reticulocyte count
   - Paroxysmal nocturnal hemoglobinuria RBC clone size evaluated by high-sensitivity flow cytometry (Borowitz, 2010)
   - Estimated glomerular filtration rate (calculated using the Modification of Diet in Renal Disease formula)
2. Proportion of patients with breakthrough hemolysis over time, defined as at least 1 new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin < 10 g/dL], major adverse vascular event (MAVE) including thrombosis, dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2 × upper limit of normal (ULN) as assessed by the central laboratory.
3. Transfusion avoidance (TA), defined as the proportion of patients who remain transfusion-free and do not require a transfusion as per protocol-specified guidelines over time.
4. Proportion of patients with stabilized hemoglobin, defined as avoidance of a ≥ 2 g/dL decrease in hemoglobin level from Baseline in the absence of transfusion over time.
5. Change in clinical manifestations of PNH (fatigue, hemoglobinuria, abdominal pain, shortness of breath, anemia, dysphagia, and erectile dysfunction) over time.

5.2.3. Device Performance Endpoint

The OBDS device performance endpoint for this study is:

1. Reported outcomes of the attempted full dose administration (including device failure/malfunction) per the requirements in the instruction for use.

5.3. Pharmacokinetic and Pharmacodynamic Endpoints

Assessments for PK/PD are as follows:

1. Serum ravulizumab concentration over time
2. Free serum C5 concentrations over time

5.4. Safety Endpoints

The safety and tolerability of ravulizumab SC and ravulizumab OBDS endpoints are:

1. Change in physical examinations, vital signs, electrocardiograms, and laboratory assessments over time.
2. Incidence and severity of adverse events (AEs) and serious adverse events (SAEs) over time.
3. Incidence of adverse device effects (ADEs) and serious adverse device effects (SADEs) over time.

5.4.1. Adverse Events

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable or 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.

Situations in which an untoward medical occurrence did not occur (eg, hospitalization for elective surgery if planned before the start of the study, admissions for social reasons or for convenience), and anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen are not AEs.

The severity of AEs will be graded using Common Terminology Criteria for Adverse Events (CTCAE) v4.03 or higher. The following grading scale is used to assess each AE term.

1. Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2. Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3. Grade 3: Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4. Grade 4: Life-threatening consequences; urgent intervention indicated
5. Grade 5: Death related to AE

Adverse events are further defined in Protocol Section 8.3.

5.4.2. Adverse Device Effects

An AE deemed associated to the investigational medical device and/or the use of the device is classified as an ADE. This includes any AE resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the installation, the operation, or any malfunction of the investigational medical device. Partial or no dose SC administrations using OBDS will be collected as ADEs at the individual kit level.

A SADE is an ADE that has resulted in any of the consequences characteristic of an SAE. The ADEs and SADEs will be determined by the Investigator or qualified designee. Adverse device effects are further described in Protocol Section 8.3.

5.4.3. Infusion Evaluation

Subcutaneous or IV infusion site evaluations will be performed at the time points specified in the SoA.

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

Local and systemic reactions are a potential risk with the use of monoclonal antibodies, these are immune and non-immune mediated, and incidence may vary with different routes of administration. Table 3 details these infusion reactions.

Table 3: Infusion Reactions - Definitions

Infusion-site reactions	AEs (IV) and ADEs (SC) localized to the site of IP administration
Infusion-associated reactions	Systemic AEs occurring during or within 24 hours of the start of infusion that are considered to be possible, probable or definitely related to IP (e.g.: fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea, nausea, vomiting, diarrhea, generalized skin rashes)
Hypersensitivity/Allergic reactions	AEs with preferred terms in the narrow SMQ of Anaphylactic reaction and the narrow SMQ of Hypersensitivity

5.4.4. Vital Signs

Vital signs will include assessments of systolic and diastolic blood pressure (BP), temperature, respiration rate (RR) and heart rate (HR). Systolic and diastolic BPs will be documented in millimeters of mercury (ie, mmHg). Temperature will be obtained in degrees Celsius (°C) or Fahrenheit (°F). Heart rate will be documented in beats per minute. Respiration rate will be documented in breaths per minute.

5.4.5. Laboratory Assessments

Samples for analysis of postmenopausal or pregnancy status, hematology, chemistry, coagulation, virus serology and urinalysis will be collected (See Appendix 2 of Study ALXN1210-PNH-303 protocol for a listing of all clinical laboratory parameters). If a suspected

event of breakthrough hemolysis occurs, an unscheduled visit must take place at which time a sample is collected for analysis of LDH, PK, PD, and anti-drug antibodies (ADA) by the central laboratory or bioanalytical laboratory. A central laboratory will be used to evaluate all laboratory assessments.

5.4.6. Electrocardiograms (ECGs)

A single 12-lead electrocardiogram (ECG) will be conducted according to the SoA in the protocol. Heart rate (HR), PR, QRS, and QT will be measured. The QT interval will be corrected for HR using Fridericia's formula (QTcF) and inter beat (RR) interval will be calculated.

5.4.7. Physical Examination

A physical examination will be performed assessing general appearance; skin; head, eyes, ears, nose, and throat; neck; lymph nodes; chest; heart; abdominal cavity; limbs; central nervous system; and musculoskeletal system. An abbreviated physical examination will be performed consisting of a body system relevant examination based upon Investigator judgment and patient symptoms.

5.4.8. Immunogenicity

Blood samples will be collected to test for presence of ADAs to ravulizumab in serum prior to study drug administration. Further characterization of antibody responses may be conducted as appropriate, including binding and neutralizing antibodies, PK/PD, safety, and activity of ravulizumab. Serum samples will be screened for antibodies binding to ravulizumab and the titer of confirmed positive samples will be reported.

6. DATA SETS ANALYZED (STUDY POPULATIONS)

In addition to definitions below, patients from site 0657 will be excluded from the primary PK, Full and Safety analysis sets. This decision was made based on a For-Cause Clinical Investigator Site audit conducted on November 14 and 15 of 2019. This audit of site 0657 resulted in 2 critical findings related to deficiencies in source documentation and principal investigator oversight, as well 4 major findings. These findings put in question the integrity of all data collected at the site, including date and time of doses and PK sample collection; 2 crucial components for inclusion in the PK analysis set. This will be reflected with the reporting of important protocol deviations that should result in exclusion from the aforementioned analysis sets. Hence, modified analysis sets are defined in order to preserve the integrity of the primary populations and allow for the analysis of data considering these patients.

6.1. Enrolled Analysis Set

The enrolled analysis set includes those patients who have signed informed consent and who are randomized. The enrolled analysis set will be used for the disposition summaries and important protocol deviations. Selected listings will also utilize the enrolled analysis set.

6.2. Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) analysis set includes all patients who have evaluable PK data for whom:

1. All doses up to Day 64 are compliant with the planned dose and the protocol-specified dosing time windows (Table 4):

Table 4: Dosing/Pharmacokinetic Analysis Set Window Requirements for Inclusion in the Pharmacokinetic Analysis Set

Study Day	15	22	29	36	43	50	57	64
Window for dosing to be compliant for inclusion in the PK analysis set (nominal time in hours from the start of the first dose on Day 1)	± 3	± 6	± 6	± 6	± 6	± 6	± 3	± 3

2. The predose PK sample on Day 71 has been collected within ± 3 hours from the nominal time of the first dose on Day 1.

Evaluable PK data is defined as non-missing results generated from samples that comply with sample integrity requirements during sample collection, storage, shipment, and bioanalysis including but not limited to the requirements in Table 5. The PK analysis set will be used for the primary analysis.

Table 5: PK Sample Integrity Requirements

Sample Integrity	Requirements
Collection	• Sample should be processed according to the SOP specified procedure
Storage	• Sample should be frozen within the defined time window after collection

Shipment	• No temperature excursion during sample storage and shipment
Bioanalysis	• Proper volume available for analysis • If repeat analysis is required, the sample should pass the acceptance criteria defined in the standard operating procedure

6.3. Pharmacodynamic Analysis Set

The PD analysis set consists of all patients who receive at least 1 dose of ravulizumab and who have evaluable PD data. The PD analysis set will be used for all PD analyses.

6.4. Per Protocol Analysis Set

The per protocol set (PPS) will consist of all patients in the PK set who also satisfy all of the following criteria:

- Met the following inclusion criteria:
  - #2: Treated with eculizumab according to the labeled dosing recommendation for PNH (900 mg every 14 days ± 2 days) for at least 3 months prior to study entry with no missed doses within 2 months prior to study entry and no more than 2 doses outside of the visit window.
  - #3: Lactate dehydrogenase levels ≤ 1.5 × ULN, according to central laboratory, at Screening. Sample must be obtained within 24 hours of or immediately prior to a scheduled eculizumab dose administration (ie, at trough eculizumab level).
  - #4: Documented diagnosis of PNH confirmed by high-sensitivity flow cytometry evaluation (Borowitz, 2010).
  - #6: Body weight ≥ 40 to < 100 kg, and in the opinion of the Investigator, are likely to remain within this body weight range for the duration of the study.
  - #8: Patients must be willing and able to give written informed consent and to comply with all study visits and procedures, including self-administration of ravulizumab SC doses, and the use of any data collection device(s) to directly record patient data.
- Did not meet any of the following exclusion criteria:
  - #1: More than 1 LDH value > 2 × ULN within the 3 months prior to study entry.
  - #2: MAVE in the 6 months prior to study entry.
  - #3: Platelet count < 30,000/mm^3 (30×10^9/L) at Screening.
  - #4: Absolute neutrophil count < 500/μL (0.5×10^9/L) at Screening.

Sensitivity analyses will be performed by repeating the primary analysis on the PPS patients.

6.5. Full Analysis Set

The full analysis set (FAS) will consist of all patients (except those from site 0657 as mentioned in Section 6) in the enrolled analysis set who received at least 1 dose of ravulizumab.

The primary population for assessment of the secondary efficacy endpoints is the FAS. Patients will be assessed for efficacy according to the treatment they were randomized to receive, regardless of the treatment they actually received. Additional sensitivity analyses will be performed by repeating the primary analysis on the FAS patients.

6.6. Modified Full Analysis Set

The modified full analysis set (mFAS) consists of all patients in the FAS but will also include patients from site 0657 with at least 1 dose of ravulizumab. Patients will be assessed for efficacy according to the treatment they were randomized to receive.

6.7. SC Treated Full Analysis Set

The SC treated full analysis set (SCF) consists of all patients in the FAS (excluding patients from site 0657) who received at least 1 dose of SC ravulizumab. Patients will be analyzed according to the treatment they were randomized to receive during the Randomized Treatment Period.

All efficacy and PK serum concentration analyses that start from the first exposure to SC treatment will use the SCF analysis set.

6.8. Modified SC Treated Full Analysis Set

The modified SC treated full analysis set (mSCF) consists of all patients in the SCF but will also include patients from site 0657 who received at least 1 dose of ravulizumab. Patients will be analyzed according to the treatment they were randomized to receive during the Randomized Treatment Period.

6.9. Safety Set

The safety set (SS) will consist of all patients who receive at least 1 dose of ravulizumab (except those from site 0657 as mentioned in Section 6). Patients will be analyzed according to the treatment they actually received during the Randomized Treatment Period. For a patient to be analyzed according to the treatment they actually received and not according to the randomization schedule, they would have to receive that treatment for all of their treatment administration visits. Safety analyses will be performed on the SS.

6.10. Modified Safety Set

The modified safety set (mSS) consists of all patients in the SS but will also include patients from site 0657 who received at least 1 dose of ravulizumab. Patients will be analyzed according to the treatment they actually received during the Randomized Treatment Period.

6.11. SC Treated Safety Analysis Set

The SC treated safety analysis set (SCS) consists of all patients in the SS (excluding patients from site 0657) who received at least 1 dose of SC ravulizumab. Patients will be analyzed according to the treatment they actually received during the Randomized Treatment Period.

All safety and PD analyses that start from the first exposure to SC treatment will use the SCS analysis set.

6.12. Modified SC Treated Safety Analysis Set

The Modified SC treated safety analysis set (mSCS) consists of all patients in the SCS but will also include patients from site 0657 who received at least 1 dose of SC ravulizumab. Patients will be analyzed according to the treatment they actually received during the Randomized Treatment Period.

7. STATISTICAL ANALYSIS

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

Clinical central laboratory samples that meet the definition of TTH will be identified and all potassium, ALT, AST and LDH samples affected by TTH will be excluded from analysis of all efficacy and safety endpoints, with the exception that the LDH values will be used for the qualification of breakthrough hemolysis. TTH samples from the central lab will be defined as having serum potassium ≥ 6 mmol/L and LDH ≥ 2x ULN.

7.1. General

7.1.1. Data Presentation for the Randomized Treatment Period

Data summaries will be presented by randomized treatment group. Baseline is defined as the last value prior to the start of study drug. All assessments at Day 71 will be performed prior to dosing. Dosing on Day 71 is the start of the Extension Period.

7.1.2. Data Presentation for the Extension Period

Data summaries will be presented by randomized treatment group. For each patient, their baseline will be defined as the last value prior to their initial exposure to SC treatment. For example, summaries of data over time while all patients are receiving SC administration of ravulizumab during the Extension Period, will be based on time since first exposure to ravulizumab SC. At the start of the Extension Period, it will have been 56 days since their first dose of ravulizumab SC for patients randomized to the SC group, while patients initially randomized to the IV group will be getting their first dose of ravulizumab SC. This exposure difference will be taken into account (Table 6) and, as an example, a summary for SC Day169/(Day 183 as mentioned in the protocol) will use study Day 183 data from patients randomized to the SC group and study Day 239 data from patients randomized to the IV group since it will have been 168 days since first exposure to SC treatment for each treatment group.

Table 6: SC Study Visits Since the Start of SC Treatment by Study Day

Study Day	Day 15	Day 29	Day 43	Day 57	Day 71	Day 78	Day 85	Day 99
IV					SC Baseline	SC Day 8	SC Day 15	SC Day 29
SC	SC Baseline	SC Day 15	SC Day 29	SC Day 43	SC Day 57	SC Day 64	SC Day 71	SC Day 85

Study Day	Day 127	Day 183	Day 239	Day 295	Day 365	Day 421	Day 477	Day 533
IV	SC Day 57	SC Day 113	SC Day 169	SC Day 225	SC Day 295	SC Day 351	SC Day 407	SC Day 463
SC	SC Day 113	SC Day 169	SC Day 225	SC Day 281	SC Day 351	SC Day 407	SC Day 463	SC Day 519

Study Day	Day 589	Day 645	Day 701	Day 757	Day 813	Day 869	Day 925	Day 981
IV	SC Day 519	SC Day 575	SC Day 631	SC Day 687	SC Day 743	SC Day 799	SC Day 855	SC Day 911
SC	SC Day 575	SC Day 631	SC Day 687	SC Day 743	SC Day 799	SC Day 855	SC Day 911	SC Day 967

Study Day	Day 1037	Day 1093	Day 1149	Day 1205	Day 1275
IV	SC Day 967	SC Day 1023	SC Day 1079	SC Day 1135	SC Day 1205
SC	SC Day 1023	SC Day 1079	SC Day 1135	SC Day 1191	SC Day 1261

7.1.3. Handling of Dropouts or Missing Data

For the primary endpoint of Day 71 serum ravulizumab C_{trough}, missing PK assessments for a particular patient will be imputed for a sensitivity analysis (Section 7.1.7).

Missing data for QoL instruments will be handled as specified in the instructions for each instrument (see Section 9.4).

Missing data for secondary endpoints will be handled as specified in Section 7.4.

Missing data for adverse events will be handled as specified in Section 9.3.8.

7.1.4. Data Collected but not Analyzed

Patients who consented to the study under Protocol Amendment 4 prior to the applicable study visit have questionnaire data at Day 127 through Day 351 and a few other assessments such as Laboratory, Immunogenicity, PK and PD, and Vital Signs at Day 351 and ECG and Physical Exam data at Day 365 and these assessments were not required under amendment 4. These data are collected and reported in the analysis datasets but will not appear in the analysis outputs such as tables, listings or figures with the exception of Protocol Deviations.

7.1.5. Analysis of Subgroups

All secondary endpoint efficacy analyses, PK serum concentration and select PD endpoints will be analyzed by stratified weight group (40 to <60 kg and 60 to <100kg).

7.1.6. Multicenter Studies

While this is a multicenter study, a very small number of patients are anticipated at some study sites. As such, center will not be used as an explanatory factor in the efficacy analyses.

7.1.7. Sensitivity Analyses

Since poor adherence to the protocol could have the potential to bias results towards a conclusion of noninferiority, the following sensitivity analyses will be produced to confirm the results from the primary analysis set (PK):

1. The primary noninferiority analysis, including the pre-specified CHW weights, as described in Section 7.3, will be repeated using the PP set. Analysis of the PP set will use the same windowing schema as the PK analysis set (Table 4).
2. The primary noninferiority analysis, including the pre-specified CHW weights, as described in Section 7.3, will be conducted using the mFAS/FAS. Non-missing Day 71 C_{trough} values that were excluded from the PK/PP analysis sets will be included for analysis. Patients with missing Day 71 C_{trough} values will be excluded from this analysis.
3. The primary noninferiority analysis, including the pre-specified CHW weights, as described in Section 7.3, will be repeated again using the mFAS/FAS set. For this analysis, non-missing Day 71 C_{trough} values that were excluded from the PK/PP analysis sets will be included. Missing C_{trough} values will be imputed using the fully conditional specification (FCS), a type of multiple imputation using chained equations, implemented with SAS 9.4's PROC MI under the FCS option. C_{trough} values that are missing, will be multiply imputed, under the assumption that the data have a joint distribution and are missing at random. For this multiple imputation regression modeling, treatment and weight (stratification variables) will be categorical covariates, and pre-dose ravulizumab serum concentration values will be continuous covariates. Non-missing C_{trough} values that were excluded from the PK/PP analysis sets will not be included in the imputation so that invalid PK values do not influence the imputation model. A minimum of 10 imputed datasets will be created for the analysis. The PROC MI SAS procedure with the FCS option will be used with a defined seed number. The number of burn-in iterations will be set to 200, the default value. If the model does not converge under 200 iterations, the number may be adjusted. The Day 71 C_{trough} will then be calculated for each of the multiply imputed datasets from the imputed components. Results will be combined using the MIANALYZE SAS procedure using Rubin's rules (Rubin, 1987). The sample SAS code for the imputation and analysis is listed in Section 9.4.5.

Table 7: Criteria for the Sensitivity Analyses

Sensitivity Analysis	Population	Criteria
1	PP	Repeat primary noninferiority analysis.
2	mFAS/FAS	Repeat primary noninferiority analysis including C_{trough} data that were non-missing but excluded from the primary analysis (PK set).
3	mFAS/FAS	Repeat primary noninferiority analysis including C_{trough} data that were non-missing but excluded from the primary analysis, by imputing missing C_{trough} values. Only valid C_{trough} data (PK set) will be used in the imputation model.

7.2. Study Patients

7.2.1. Disposition of Patients

A summary of patient disposition will be presented and will include the number and percentage of screened patients, screen failures, randomized patients, and treated patients for the Randomized Treatment and Extension Periods. Patient disposition for all randomized patients will be presented by treatment group and total. The number and percentage of patients who were treated, discontinued treatment (along with reason for treatment discontinuation), completed the study or discontinued/withdrew from the study, along with the primary reason for discontinuation/withdrawal, will be presented.

The number and percentage of patients in each analysis set will be tabulated.

By-patient data listings with disposition will be provided as well as a listing of patients who did not satisfy the inclusion/exclusion criteria.

7.2.2. Protocol Deviations

Protocol deviations will be determined per the standard operating procedure (SOP) "Identification, Handling, and Documentation of Protocol Deviations" (SOP-G-CL-0044). The number and percent of patients with important protocol deviations will be summarized for all enrolled patients by treatment group and by total as well as separately for the Randomized Treatment Period and Extension Period.

To ensure completeness of the list of protocol deviations, the following will be identified programmatically from the database:

1. Patients from whom informed consent was not obtained
2. Patients who violated any inclusion/exclusion criteria
3. Patients who took prohibited medications or underwent any prohibited procedure
4. Patients who received less than 100% of the protocol specified number of doses of study drug

A by-patient listing of inclusion/exclusion criteria, as well as all protocol deviations will be presented separately.

7.2.3. Demographics, Disease Characteristics, and History

All demographic and baseline characteristics will be summarized using the FAS, mFAS, SS, mSS and PK analysis set. Summary statistics will be presented by treatment group and overall. By-patient listings of demographic information, disease characteristics, and PNH medical history will be produced.

7.2.3.1. Demographics

The following demographic variables will be summarized:

- Sex
- Race including number (%) of patients of Japanese descent
- Ethnicity
- Age at Informed Consent (years): descriptive statistics (n, mean, median, standard deviation (SD), minimum, maximum) and by frequency of patients in each age category: 18 to 65 years and >65 years
- Baseline weight (kg): descriptive statistics (n, mean, median, SD, minimum, maximum) and frequency of patients in the following categories: ≥ 40 kg to < 60 kg, ≥ 60 kg to <100 kg
- Baseline height (cm)
- Observed weight stratification (≥ 40 kg to < 60 kg, ≥ 60 kg to <100 kg)

7.2.3.2. Disease Characteristics and PNH Medical History

The following PNH disease characteristics will be summarized:

- Method of PNH diagnosis
- Years from PNH diagnosis to informed consent
- PNH clone size (red blood cell (RBC) and granulocyte/monocyte) at screening
- Packed RBC transfusion requirements in the year prior to receiving study drug including number of transfusion episodes and units transfused
- All PNH symptoms experienced at any time prior to informed consent
- All PNH-associated conditions that were diagnosed at any time prior to informed consent
- History of any MAVE, including the number of patients (n, %) with any history of MAVE and within a particular MAVE category (eg, thrombophlebitis/deep vein thrombosis, pulmonary embolus, myocardial infarction, etc)

By-patient listings of hemoglobin values within 60 days of informed consent and most recent PNH clone test prior to informed consent will be produced.

7.2.3.3. Medical / Surgical History and Baseline Physical Examination

Medical history will be classified by System Organ Class (SOC) and Preferred Term (PT) using the latest available version of standardized MedDRA and will be reported by treatment group and overall for the SS. Likewise, baseline physical examination information will be summarized for the SS by treatment group and by total. By-patient listings of medical / surgical history and physical examinations will be produced. Tables will be sorted by descending frequency of SOC and by descending frequency of Preferred Term within an SOC.

7.2.4. Prior and Concomitant Medications / Nonpharmacologic Therapies and Procedures

Prior and concomitant medications (including vitamins and herbal preparations) and nonpharmacologic therapies and procedures, will be summarized using the SS by treatment group and by total. Prior medications or procedures are defined as medications or procedures taken prior to the first study drug infusion and include all medications taken within 28 days prior to informed consent as well as all *Neisseria meningitidis* vaccinations administered within 3 years of dosing with ravulizumab.

Concomitant medications or procedures are defined as medications or procedures received by the patients on or after the first study drug infusion through 30 days after the patient's last dose of study drug, unless the patient transitions to an alternate treatment for PNH. Medications will be coded using the World Health Organization Drug Dictionary version in use by Alexion at the time of the analysis while nonpharmacologic therapies and procedures (any therapeutic intervention, such as surgery/biopsy or physical therapy) will be coded using MedDRA.

Medication summaries by treatment group (ie, number [%]) of patients using prior and concomitant medications will be presented by WHO-DRUG Anatomical Therapeutic Chemical (ATC) Level 3 and by WHO-DRUG generic name. Procedures will be summarized similarly, but by MedDRA Class and preferred term. Protocol required vaccinations will be summarized similarly and will also be presented separately.

By-patient listings of these data will be provided separately. Tables will be sorted by descending frequency of ATC level and by descending frequency of generic name within an ATC.

7.3. Primary Analysis

The primary analysis will be performed using the PK analysis set and sensitivity analyses will be performed using the FAS and PPS after all patients have completed the Randomized Treatment Period.

7.3.1. Primary Analysis: Hypothesis and Methodology

The null and alternative hypotheses for the primary analysis are as follows:

$$H_0: \mu_{SC}/\mu_{IV} \leq \delta \text{ vs. } H_A: \mu_{SC}/\mu_{IV} > \delta$$

where μ_{SC} is the geometric mean of the Day 71 C_{trough} concentration of patients treated with ravulizumab SC, μ_{IV} is the geometric mean of the Day 71 C_{trough} concentration of patients treated with ravulizumab IV, and δ is the noninferiority margin, 0.8. The primary analysis will evaluate noninferiority in serum C_{trough} of ravulizumab SC compared with ravulizumab IV, and will be

conducted after all patients have completed all protocol-required assessments in the Randomized Treatment Period.

The primary endpoint is the Day 71 serum ravulizumab C_{trough}. Descriptive statistics including the arithmetic mean, SD, minimum, maximum, and arithmetic coefficient of variation (CV)% will be calculated at Day 71 for serum ravulizumab C_{trough}. In addition, the geometric mean and geometric CV% will be calculated.

The ratio of the geometric mean Day 71 C_{trough} from the ravulizumab SC group over the geometric mean Day 71 C_{trough} from ravulizumab IV group with a 2-sided 90% confidence interval (CI) will be calculated for stage 1 and stage 2. Noninferiority will be claimed based on the 90% CI that is calculated from combination z-score that takes into effect the interim analysis (Section 7.3.1.1.1).

The difference in means will be obtained using Analysis of variance (ANOVA) where the ANOVA model (Section 9.4.4) includes treatment and stratified weight group as fixed effects. The data will be transformed prior to analysis using a logarithmic transformation.

The point estimates and CIs will be calculated and constructed for the mean difference of log-transformed parameters. These results will be exponentiated in order to present the point estimates and CIs on the ratio scale.

7.3.1.1. Effect of Interim Analysis on the Primary Endpoint

Since the sample size may be increased in a data-dependent manner after the interim analysis, use of the conventional Z-statistic at the final analysis may lead to inflation of type 1 error as demonstrated by Cui et al. (1999). These authors have shown that one way to control for such type 1 error inflation is to use a weighted combination test, in which the independent increments of the Z-statistics of the 2 stages are combined by pre-specified weights that are computed based on the planned stage 1 and stage 2 sample sizes (with or without sample size increase). This weighted combination test is henceforth referred to as the CHW test.

7.3.1.1.1. CHW Test Statistic

Let $t_1 = \frac{\hat{\delta}_1}{SE(\hat{\delta}_1)}$ and $t_2 = \frac{\hat{\delta}_2}{SE(\hat{\delta}_2)}$ denote the Wald statistics computed based on stage 1 and stage 2 data, respectively, where $\hat{\delta}_k$ is the difference between the means of the log transformed data from the SC arm and the IV arm computed based on stage k data, $k = 1,2$.

Let δ_0 denote the pre-specified noninferiority margin on the mean difference scale (ln(0.8) or -0.223). Then the Z-statistics based on stage 1 and stage 2 data are:

$$z_1 = t_1 - \frac{\delta_0}{SE(\hat{\delta}_1)} \text{ and } z_2 = t_2 - \frac{\delta_0}{SE(\hat{\delta}_2)}.$$

The final CHW test statistic is:

$$Z_{CHW} = \sqrt{w_1} Z_1 + \sqrt{w_2} Z_2.$$

where w_1 and w_2 are pre-specified weights that are computed based on the planned stage 1 and stage 2 sample sizes, n_1 and n_2 (with or without sample size increase):

$w_1 = .5$ for stage 1 and $w_2 = .5$ for stage 2.

Statistical significance is reached (p-value for noninferiority ≤ .05) at the final analysis if $Z_{CHW} > c$, where c is the efficacy boundary at final analysis, 1.645.

To calculate the CI based on the CHW statistic at the final analysis, the following formula will be used:

$$\left(\frac{Z_{CHW} - 1.645}{\frac{\sqrt{w_1}}{SE(\hat{\delta}_1)} + \frac{\sqrt{w_2}}{SE(\hat{\delta}_2)}}, \frac{Z_{CHW} + 1.645}{\frac{\sqrt{w_1}}{SE(\hat{\delta}_1)} + \frac{\sqrt{w_2}}{SE(\hat{\delta}_2)}}\right)$$

This CI is for the difference of means on the log transformed data minus the noninferiority bound on the log scale (-0.223).

If the lower bound of the 90% CI for the ratio of geometric means between ravulizumab SC and ravulizumab IV groups is greater than the noninferiority margin (δ) of 0.8 (i.e., equivalent to -0.2231 noninferiority margin for the difference of the log transformed means, ravulizumab SC-ravulizumab IV), then the ravulizumab SC treatment will be concluded to be noninferior to the ravulizumab IV treatment.

7.4. Secondary Analyses

Unless otherwise specified, all secondary analyses will be performed using the FAS and mFAS for the RTP and the SCF and mSCF for the analyses from first SC treatment and will be summarized through the extension period. When applicable, results from the Randomized Treatment Period will be presented in parallel by treatment group, but no formal comparisons will be performed. Baseline values used for the Randomized Treatment Period are different from baseline values used for the Extension Period and are defined in Section 9.3.4.

7.4.1. Change Over Time in Disease Related Laboratory Parameters

LDH and other disease related laboratory parameters (Section 5.2.2) will be summarized by treatment group at baseline and each applicable postbaseline time point using descriptive statistics for continuous variables, for the observed value as well as the change from baseline and percent change from baseline. Additionally, these parameters will be summarized for the six month and one-year time points which correspond to SC Day 169 (study day 183 for the SC group and study day 239 for the IV group and SC Day 351 (study day 365 for the SC group and study day 421 for the IV group). Total columns and 95% confidence intervals will be presented for summaries for SC Day 169 and SC Day 351.

7.4.2. Incidence of Breakthrough Hemolysis

Breakthrough hemolysis is defined as at least 1 new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin < 10 g/dL], MAVE including thrombosis, dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2 × ULN as assessed by the central laboratory.

Patients who withdraw from the study for any reason, their data up to the time of withdrawal will be used to assess breakthrough hemolysis.

Patients are included in the denominator for a visit only if they have data for that visit. For through Day 71, through SC Day 169, and through SC Day 351, patients having at least one data for a visit will be included in the denominator.

For through Day 71, through SC Day 169, and through SC Day 351, only visits with data will be used to assess BTH.

The number and proportion of patients with breakthrough hemolysis will be summarized by treatment group over time by presenting the number and proportion of patients with a breakthrough along with a 2-sided 95% CI for each applicable postbaseline time point. Additionally, this proportion will be summarized through Day 71, through SC Day 169, and through SC Day 351 for each treatment group). Total columns and 95% CIs will be presented for summaries through SC Day 169 and SC Day 351.

7.4.3. Achievement of Transfusion Avoidance

Transfusion avoidance is defined as patients who remained transfusion free and did not require a transfusion after the first dose of study drug.

Patients are included in the denominator for a visit only if they have data for that visit. For through Day 71, through SC Day 169, and through SC Day 351, patients having at least one data for a visit will be included in the denominator. For Through Day 71, through SC Day 169, and through SC Day 351, only visits with data will be used to assess transfusion avoidance. Those patients who withdraw due to a lack of efficacy will be counted as needing transfusion.

The number and proportion of patients who do not require a transfusion will be summarized by treatment group over time by presenting the number and proportion of patients who remained transfusion free after the first dose of study drug along with a 2-sided 95% CI for each applicable postbaseline time point. Additionally, this proportion will be summarized through Day 71, through SC Day 169, and through SC Day 351 for each treatment group. Total columns and 95% CIs will be presented for summaries through SC Day 169 and through SC Day 351.

7.4.4. Achievement of Stabilized Hemoglobin

Stabilized hemoglobin is defined as the avoidance of a $\geq$ 2 g/dL decrease in hemoglobin level from Baseline in the absence of transfusion from Baseline to the end of the period of interest.

Patients are included in the denominator for a visit only if they have data for that visit. For through Day 71, through SC Day 169, and through SC Day 351, patients having at least one data for a visit will be included in the denominator. For Through Day 71, through SC Day 169, and through SC Day 351, only visits with data will be used to assess stabilized hemoglobin. Those patients who withdraw due to lack of efficacy will be counted as not maintaining stabilized hemoglobin.

The number and proportion of patients with stabilized hemoglobin will be summarized by treatment group over time by presenting the number and proportion of patients with stabilized hemoglobin after the first dose of study drug along with a 2-sided 95% CI for each applicable postbaseline time point. Additionally, this proportion will be summarized through Day 71, through SC Day 169, and through SC Day 351 for each treatment group. Total columns and 95% CIs will be presented for summaries through SC Day 169 and through SC Day 351.

7.4.5. Clinical Manifestations of Paroxysmal Nocturnal Hemoglobinuria

The Investigator or designee will assess each patient for signs and symptoms of PNH, which may include the following: fatigue, chest pain, abdominal pain, dyspnea, dysphagia, erectile dysfunction, and red/dark urine or hemoglobinuria. Summaries will be presented for the number and percentage of each PNH symptom along with descriptive statistics for the number of PNH symptoms per patient by treatment group.

The number and percentage of clinical manifestations of PNH will be summarized at baseline and for each applicable postbaseline study visit. Additionally, this proportion will be summarized through Day 71, through SC Day 169, and through SC Day 351. Total columns and 95% CIs will be presented for summaries through SC Day 169 and through SC Day 351.

Additionally, shifts from baseline in clinical manifestations of PNH (fatigue, chest pain, abdominal pain, dyspnea, dysphagia, hemoglobinuria, and erectile dysfunction) will be summarized by treatment group and at the study visits where these assessments are collected. These shifts will be presented at each applicable post baseline visits as well as through Day 71, through SC Day 169, and through SC Day 351. Total columns will be presented for summaries through SC Day 169, and through SC Day 351.

A by-patient listing of available patient-reported PNH symptoms will be produced.

7.4.6. Pharmacokinetic, Pharmacodynamic and Immunogenicity Analyses

Pharmacokinetic analyses will be performed for all patients who have evaluable PK data, as described for the PK analysis set in Table 5. Since this is a multicenter patient study, censoring of PK or PD data may be considered when a sample collection or handling error is inferred.

Pharmacodynamic analyses will be performed for all patients from the PD analysis set who have evaluable PD data.

7.4.6.1. Serum Concentration Over Time

Serum SC ravulizumab concentrations will be summarized over time using the descriptive statistics: number of patients, mean, SD, CV, median, minimum, and maximum. Mean serum SC ravulizumab concentrations versus nominal time will be graphically presented on both linear and semi-logarithmic scales.

Summary statistics of the absolute values and changes and percentage changes from Baseline in free C5 serum concentrations will be presented over time by treatment group using the PD analysis set.

Serum Concentration summaries will use the PKS, PDS, and FAS for the RTP and the SCF for the since first SC treatment summaries.

7.4.6.2. Incidence of Treatment-emergent Anti-drug Antibodies

All immunogenicity analyses will be conducted on the SS, mSS, PKS, PDS and mSS for the RTP and the SCS and mSCS for the summaries since first SC treatment. The number and percentage of patients developing ADAs and anti-drug neutralizing antibodies, where applicable, will be summarized by treatment group. Additionally, a by-patient listing will be produced and will list actual titer values.

7.4.7. Quality of Life and Treatment Satisfaction Analyses

7.4.7.1. Change in FACIT-Fatigue SubScale Score

Absolute levels, change and percent change in FACIT-Fatigue subscale scores (Theodore-Oklota, 2001) will be summarized by treatment group at baseline and each applicable postbaseline time point using descriptive statistics for the observed values. Additionally, these values will be summarized for the six month and one-year time points which correspond to SC Day 169 and SC Day 351 and total columns and 95% CIs will be presented. Refer to Section 9.4.1 for a more detailed description of the FACIT-Fatigue calculations and the scoring methods.

At each post baseline study visit, the proportion of patients who showed an improvement of at least 3 points for the FACIT-Fatigue subscale scores will be summarized by treatment group.

7.4.7.2. Change in EORTC QLQ-C30 Subscale Score

Absolute and changes from Baseline in EORTC-QLQ-C30 subscale scores (Fayers, 2001) will be summarized by domain and by treatment group at baseline and each applicable postbaseline time point using descriptive statistics for the observed values. Additionally, these values will be summarized for the six month and one-year time points which correspond to SC Day 169 and SC Day 351 and total columns and 95% confidence intervals will be presented. Refer to Section 9.4.2 for a more detailed description of the EORTC QLQ-C30 and the scoring methods.

7.4.7.3. Treatment Satisfaction

Patient satisfaction with treatment will be evaluated using TASQ scores. These data will be summarized by domain and by treatment group at baseline and for SC Day 169 and SC Day 351, each applicable postbaseline time point using descriptive statistics for the observed values. Additionally, these values will be summarized for the six month and one-year time points which correspond to SC Day 169 and SC Day 351 and total columns and 95% confidence intervals will be presented. Refer to Section 9.4.3 for scoring methods and a more detailed description of the TASQ.

7.5. Safety Analyses

Unless otherwise specified, all safety analysis will be conducted on the SS and mSS for the RTP and the SCS and mSCS for the analyses from first SC treatment. All safety data available from the time of informed consent to the follow-up contact period will be provided in by-patient listings. Safety analyses will be separated by the two periods (Randomized Treatment Period vs. Extension Period). Baseline values used for the Randomized Treatment Periods are different from baseline values used for the Extension Period and are defined in Section 9.3.4.

7.5.1. Duration of Treatment Effect, Treatment Compliance, and Exposure

Duration under study treatment effect is defined as the time a patient is “at risk” of reporting a treatment emergent adverse event. It is the time from first dose of study drug through the end of the study and will be summarized at the conclusion of the study. Treatment compliance will be analyzed separately for IV and SC patients during the Randomized Treatment Period. Patients will be analyzed together for summaries since first SC treatment. Summary statistics (mean, standard deviation, median, minimum, and maximum) will be produced for the following data:

- Number of patients receiving 2400 mg and 2700 mg ravulizumab IV loading/induction doses and 3000 mg and 3300 mg maintenance doses during the Randomized Treatment Period along with summary statistics for the total dose (mg) and total volume (mL) administered.
- Total number of patients with a dose administration interruption, as well as total number of infusions interrupted from Day 1 to Day 70
    - Dose administration interruption time will not be included in the infusion duration calculation. Therefore, the calculation (mins) will be (End Time of infusion – Start time of infusion – Interruption duration).
- Number of SC dose administration attempts during the RTP.
- Number of SC dose administration attempts since first SC treatment
- Primary reasons for missed doses during the RTP and since first SC treatment (for dose administrations that take place at the site)
- Total SC infusion time during the RTP and since first SC Treatment (for dose administrations that take place at the site)
- Infusion location for SC administrations during the RTP and since first SC treatment.
- Total time under study treatment effect (days):
    - Total time under study treatment effect is the time a patient is "at risk" of reporting a treatment emergent adverse event and is defined as time from the first dose of study drug to the end of the study (when the safety follow-up is completed). The safety follow-up is completed 30 days after the last dose (Time under treatment effect = last study drug infusion date – first study drug infusion date + 30), where 30 days is censored at the data cut-off date for each analysis.
        - The minimum time under treatment effect given a patient receives the Day 1 IV loading dose is 56 days.
        - For cases where a patient would discontinue after only receiving IV treatment (during the Randomized Treatment Phase), the time under study treatment effect will be calculated under a 56-day follow-up period (time under treatment effect = last IV infusion – first IV infusion + 56 days).
        - For the analysis of the primary endpoint at Day 71, the above calculations apply, however, the Day 71 visit date is the cut-off as opposed to the end of study date.
- The frequency and percentage of patients who had a percentage of drug compliance range by increments of 10% (ie ≥ 90% to ≤ 100%; ≥ 80% to < 90%; etc) will also be included. This will be calculated as follows:
    - Percent compliance for the analysis after the Randomized Treatment Period is calculated as the total number of study drug infusions taken from Day 1 to end of Randomized Treatment Period (excluding Day 71 study drug infusion) / total number of expected infusions to end of Randomized Treatment Period (excluding Day 71 study drug infusion). Percent compliance for the analysis after the Extension Period is calculated as the total number of drug infusions taken from Day 71 to the end of the

Extension Period for the IV group and is calculated as the total number of drug infusions taken from Day 15 to the end of the Extension Period for the SC group.

- A study drug infusion is defined as an infusion that results in the full amount of drug administered to the patient from that kit. Any infusion that results in a partial or incomplete drug administration is not counted as a study drug infusion.
- Should a patient discontinue prior to the completion of the study or Day 71, percent compliance is calculated as the total number of infusions taken / the total expected infusions through the date of discontinuation. For example, if a patient randomized to SC treatment discontinues on Day 35 they are expected to have taken 7 total infusions (1 on day 1 and 2 on Days 15, 22, and 29).

By-patient listings will be produced for study duration, treatment compliance, and exposure.

By-patient listings will be produced for all device issues and will include a description of the complaint.

7.5.2. Adverse Events and Adverse Device Effects

The following definitions will be used for AEs and ADEs:

- Pretreatment AEs: Any AE that starts after providing informed consent, but before the first infusion of study drug
- Treatment-emergent AE: Any AE that starts during or after the first infusion of study drug.
- All ADEs are by definition occurring during or after the start of the first SC administration.

Each AE will be attributed to the last treatment (ravulizumab SC or ravulizumab IV) prior to the AE. AEs started on the day of treatment change (Day 15 for the SC group and Day 71 for the IV group), will be assigned to the new treatment except when the data show AE start time is prior to the dosing time. An AE that worsens after treatment change is considered a new AE and will be attributed to the new treatment.

The incidence of TEAEs will be summarized by SOC and PT overall, by severity (CTCAE Grade 1 – Grade 5), by relationship (related or not related) to treatment and by incidence rate of non-serious TEAEs greater than or equal 5%. The incidence of SAEs will also be summarized. The incidence of ADEs and SADEs will be summarized similarly by SOC and Preferred Term and by severity. All AEs and ADEs will be coded using Medical Dictionary for Regulatory Activities. ADEs will be coded appropriately according to device usage.

Analyses of treatment-emergent AEs (TEAEs) through Day 71 (Week 10) will be tabulated and presented separately. Patients having multiple AEs within a category (eg, overall, SOC, Preferred Term) will be counted once in that category. For severity/relationship tables, the patient's highest grade/most related event within a category will be counted. Percentages will be based on the number of treated patients in the SS within a treatment group and overall. Tables will be sorted by descending frequency of SOC and by descending frequency of Preferred Term within an SOC.

AEs will be summarized by 6-month time intervals (0-6 months, 7-12 months and 13-18 months) after exposure to study drug on Day 1 where a month = 30.4375 days.

By-patient listings will be provided for all TEAEs, SAEs, AEs leading to study drug discontinuation and PTAEs for the mSS.

AEs will include the displays described in the following subsections.

7.5.2.1. Summary of Pre-Treatment Adverse Events

Analyses of Pre-treatment AEs (PTAEs) will be tabulated and presented separately using the mSS. Patients having multiple PTAEs within a category (eg, overall, SOC, Preferred Term) will be counted once in that category. Percentages will be based on the number of treated patients in the mSS within a treatment group and overall. Tables will be sorted by descending frequency of SOC and by descending frequency of Preferred Term within an SOC.

7.5.2.2. Overall Summary of Adverse Events and Adverse Device Effects

An overall summary table of TEAEs and ADEs (defined as treatment emergent) will be presented using summary statistics (n, %). The number of events (n) and number and percentage of patients with events (n, %) will be displayed for the following events subcategories:

- TEAEs/ADEs
- ADEs that are associated with product issues
- ADEs that are not associated with product issues
- Related to study treatment TEAEs
- Not related to study treatment TEAEs
- AESIs
- Not Associated with the device/device use TEAEs
- Related to the device TEAEs
- Not related to the device TEAEs
- Grade 1 TEAEs
- Grade 2 TEAEs
- Grade 3 TEAEs
- Grade 4 TEAEs
- Grade 5 TEAEs

The number and percentage of patients who have any TEAE leading to study treatment or study discontinuation, or who died on study will be presented. These statistics will be prepared separately for SAEs (with the exception of severity grading and AESIs) and SADEs.

7.5.2.3. AEs, SAEs, ADEs and SADEs by System Organ Class and Preferred Term

The number of AEs/ADEs and the number and percentage of patients with events will be presented by SOC and Preferred Term (PT). Patients are counted once in each SOC and Preferred Term. Percentages will be based on the total number of treated patients in the treatment group. Serious adverse events and SADEs will be summarized similarly. Serious adverse device effects will be further classified as anticipated or unanticipated events.

7.5.2.4. AEs, SAEs, ADEs and SADEs by System Organ Class, Preferred Term, and Relationship

The number of AEs/ADEs and the number and percentage of patients with events will be presented by SOC and PT as described above by relationship (related, not related for both the usual definition of related/not related and the Japanese definition of related/not related). If a patient has more than one occurrence of an AE, the strongest relationship to study treatment will be used in the summary table. Serious adverse events will be summarized similarly. Serious adverse device effects will be further classified as anticipated or unanticipated events.

7.5.2.5. AEs and ADEs by System Organ Class, Preferred Term, and Severity

The number of TEAEs/ADEs and the number and percentage of patients with events will be presented by SOC and Preferred Term as described above by severity (Grade 1, Grade 2, Grade 3, Grade 4, and Grade 5). If a patient has more than one occurrence of an AE, the highest grade will be used in the summary table.

7.5.2.6. Infusion-associated AEs

The eCRF does not include a question on whether or not an AE is deemed associated with an infusion. Therefore, based on the definition in Section 5.4.3, these AEs will be presented separately.

7.5.2.7. Deaths and Other Significant Adverse Events

A listing of patient deaths will be produced.

Adverse events of special interest (AESIs) include infusion reactions, malignancies, hematologic abnormalities, serious infections, antidrug antibodies, serious hemolysis after drug discontinuation and meningococcal infections. These will be identified through medical review of the collected AE data. AESIs will be summarized by treatment group in tabular form.

7.5.2.8. Adverse Event Incidence Rates

The rate of AEs (including ADEs) adjusted by patient years (PY) of exposure is the number of events per 100 patient years and defined as [(number of events)*100/Total PY]. Total PY will be summed across all individual PY of exposure (i.e. treatment duration as described in Section 7.5.1). Therefore, Total PY = (sum of individual treatment exposure across a treatment group)/365.25.

Adverse event incidence rates adjusted by PY of exposure will be summarized for the time since first SC treatment along with the summary of AEs, SAEs, Infusion-associated AEs and AESIs by SOC and PT described above.

7.5.3. Other Safety

7.5.3.1. Analyses for Laboratory Tests

Absolute values and changes from baseline in central laboratory parameter (continuous variables) will be summarized descriptively at each visit, by treatment group. Baseline is defined as the last non-missing assessment value prior to the first study drug infusion. Shift tables over time will be presented for all central laboratory values, where applicable, using normal, low, or high based on normal range values. For purposes of analyses, laboratory results based upon standardized units will be used. Box plots will be presented for the following central lab parameters by visit: hemoglobin, LDH, bilirubin (total and direct), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase, absolute neutrophil count (ANC) and platelets.

All central and local laboratory data will be presented in by-patient listings.

7.5.3.2. Vital Signs and Physical Examination

Absolute values and changes from baseline in vital signs (BP, HR, RR, and temperature) will be summarized descriptively at each visit, by treatment group. Baseline is defined as the last non-missing assessment value prior to the first study drug infusion. A listing of vital signs will be presented.

Absolutes values and changes from baseline in weight will be summarized by visit and treatment group. A by-patient listing of weight will be produced.

Adverse changes from baseline in physical examination findings will be classified as AEs and analyzed accordingly.

7.5.3.3. Electrocardiograms (ECG)

Descriptive statistics by visit and treatment group will be presented for each ECG parameter (including PR, QRS, QT, and QTcF) values and for change from baseline values. An outlier analysis will be performed that will summarize the frequency and percentage of patients who meet any of the following outlier criteria:

- QT, QTcF interval > 450 msec
- QT, QTcF interval > 480 msec
- QT, QTcF interval > 500 msec
- QT, QTcF interval increases from baseline > 30 msec
- QT, QTcF interval increases from baseline > 60 msec

A by-patient listing of ECG results will be presented.

7.5.3.4. Non-Drug Therapies and Procedures

By-patient listings of non-drug therapies and procedures will be produced.

7.6. Device Performance Assessment

Device performance will be assessed using the reported outcome of attempted full dose administration (including device failure/malfunction) per the requirements in the instructions for use.

Device issues are reported if no drug is administered from the OBDS, the full volume of the drug is not administered from the OBDS or other issues are reported that affect the delivery of the drug. The following outcomes will be summarized on the SS and mSS for the RTP and SCS and mSCS for the analyses from the first SC treatment:

- The number and percentage of full dose administrations
    - Total number and percentage of devices used to achieve full dose
    - Total number and percentage of devices used when full dose was not achieved
- The number and percentage of devices which delivered its full volume
- The number and percentage of devices with a reported complaint (See 21 CFR 820.3 for definition of complaint), including categories for each reported complaint
    - The number and percentage of devices with a confirmed technical defect, including categories for each confirmed technical defect.
    - The number and percentage of devices with a use error, including categories for each use error
    - The number and percentage of devices with other/unconfirmed defects, including categories for each other/unconfirmed defect.

A confirmed technical defect refers to any confirmed device defect or malfunction not attributed to use error, whether or not dose delivery was affected. Use error refers to user action/lack of user action while using the device that leads to a different result than intended by the manufacturer or expected by the user. Other/unconfirmed defect refers to everything else other than a confirmed technical defect or a use error.

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9. APPENDICES

9.1. Protocol Schedule of events

Refer to the section 1.3 of the protocol for a schedule of events.

9.2. Sample Size, Power, and Randomization

Assuming the ratio of the geometric means of C_{trough} (SC/IV) is 1.03 and the coefficient of variation is 0.4 at Day 71, 62 patients in the ravulizumab SC group and 31 patients in the ravulizumab IV comparison group will achieve 90% power to detect noninferiority using a one-sided test at an alpha level of 0.05 and a PK noninferiority margin (NIM) of 0.8. The alpha level and NIM are based on recommendations in guidance documents "Statistical Approaches to Establishing Bioequivalence" and "Guideline on the Investigation of Bioequivalence", from the US Food and Drug Administration (FDA) and European Medicines Agency, respectively. This sample size is increased to 105 patients (70 patients in the ravulizumab SC group and 35 patients in the ravulizumab IV group) to account for the possibility that up to 10% of patients may not meet the criteria for inclusion in the PK analysis set.

Table 8: Summary of Parameters Used in Estimating Sample Size

Parameters	**Ratio of serum C_{trough}**
Power	90%
Type I error	1-sided 0.05
Noninferiority margin	0.8
Allocation ratio	2:1
Coefficient of Variation of SC/IV	0.4
Assumed treatment ratio (geometric means)	1.03
Estimated sample size (SS)	93
Adjusted SS for 10% dropouts	105

Each patient will be randomly assigned to a treatment group in a 2:1 ratio using a centralized interactive web response system. The randomization is stratified by weight (≥ 40 to < 60 kg or ≥ 60 to < 100 kg).

9.3. Technical Specifications for Derived Variables

The following derived data will be calculated prior to analysis.

9.3.1. Age

Age will be presented as the number of years between date of birth and the reference date. The following ages (in years) may be computed using the formula (reference date – date of birth+1)/365.25, with reference dates indicated as follows:

Table 9: Age and Reference Date

AGE	REFERENCE DATE
Age at enrollment	Date of signing ICF

Birthdate is collected as YYYY and no data imputation for months or days will be used to calculate age.

9.3.2. Imputation Rules for Partial and Missing Medication Dates

If medication start and/or end dates are missing, partial and concomitant medications will be determined by:

- Partial medication dates with regard to start date:
    - If year and month are present and are not equal to the year and month of the ravulizumab start date, then day will be imputed to the first of the month.
    - If year and month are present and are equal to the ravulizumab start date year and month then day will be imputed to be the same as the ravulizumab start day when the medication end date is greater than the ravulizumab start date. Otherwise, day will be imputed to use the medication end date month and day.
    - If only year is present and is not equal to ravulizumab start date year then month and date will be imputed to January 1.
    - If only year is present and the year is equal to the ravulizumab start date year then month and date will be imputed to equal the ravulizumab start date month and day (MM-DD) when the medication end date is greater than the ravulizumab start date. Otherwise, day will be imputed to use the medication end date month and day.
    - If the medication start date is completely missing, the medication end date is not missing or ongoing and the medication is not a protocol required vaccination, then the medication start date will be imputed to the lesser date of the ravulizumab start date or the medication end date.
- Partial medication dates with regard to end date:
    - If the year and month are present and are equal to ravulizumab year and month end date, then day will be imputed to the day of the ravulizumab (YYYY-MM) end date.

- If year and month are present and are not equal to the year and month of ravulizumab end date (YYYY-MM) then day will be imputed to the last day of that month.
- If only year is present and it is equal to the year of ravulizumab end date, then month and day will be imputed to equal ravulizumab end date month and day (MM-DD).
- If only year is present and it is not equal to the ravulizumab end date year, then month and day will be imputed to December 31.
- If the study medication is a protocol required vaccination, then the end date will be imputed to the medication start date.

9.3.3. Disease Duration

PNH disease duration will be presented as the number of years between the date of first study drug infusion and the date of PNH diagnosis (ie, INT [(Date of first infusion – Date of PNH diagnosis + 1)/365.25] or a similar formula using months and years or years only in the event of partial dates for PNH diagnosis).

9.3.4. Definition of Baseline Values

Baseline for all parameters summarized during the Randomized Treatment Period is defined as the last non-missing assessment value prior to the first administration of study drug (SC or IV).

Baseline for all parameters summarized at the start of the Extension Period is defined as the last non-missing value prior to the initial administration of SC treatment. For the IV group the baseline value for the start of the Extension Period is Day 71 dosing. For the SC group, the baseline value is Day 15 dosing.

9.3.5. Change from Baseline

Change in values from Baseline will be calculated as follows.

Change in Value = (subsequent value – baseline value), given that both the baseline value and subsequent value are non-missing.

9.3.6. Percent Change in Assessments from Baseline

Percent change in values from baseline will be calculated as follows.

$$\% \text{ Change in Value} = \frac{\text{Change in Value}}{\text{Baseline value}} \times 100$$

where Change in Value = (subsequent value – baseline value), given that the baseline value is non-missing and non-zero and the subsequent value is non-missing.

9.3.7. Analysis Visits

Summaries over postbaseline time points or analyses at specific postbaseline time points will be performed based on the list of visits described in the schedule of assessment of the protocol. For

all assessments in the Randomized Treatment Period, the number of days from baseline will be calculated using the following formula: (date of assessment) - (date of first study treatment) + 1. This number of days will be used to assign analysis visit.

For all assessments at the start of the Extension Period, the number of days from first dose of SC will be calculated differently for those patients initially randomized to SC since it will have been 56 days since their first dose of SC, while patients initially randomized to the IV group will be getting their first dose of ravulizumab SC. The actual time since first dose of SC will be grouped in the Extension Period analyses.

All postbaseline records including those that occurred outside the specified protocol windows will be assigned to an appropriate analysis visit by using the following scheme and will be included in the analysis of the specific assessment.

For all visits, the lower bound and the upper bound for the analysis visit windows are defined as the midpoints of the target date of scheduled visits. If the date of assessment falls in between the lower bound and the upper bound for a visit as defined in the protocol schedule of assessment, then it will be assigned to that visit.

If only 1 record is within an analysis visit window, the data from that record will be used in the analysis. If more than 1 record is within the same analysis visit window, the record closest to the target day will be selected. If more than 1 record are tied for closest to the target day, the earlier record will be used in the analysis for that visit.

9.3.8. Adverse Events

Treatment-emergent AEs (TEAEs) are events with start dates and start times on or after the date and time of the first ravulizumab dose through the end of the safety follow-up period. If the start date of an AE is partially or completely missing and the end (stop) date and time of the AE does not indicate that it occurred prior to first dose, then the determination of treatment-emergent status will be based on the following:

- If the start year is after the year of the first study drug dose, then the AE is treatment-emergent; else,
- If the start year is the same as the year of the first study drug dose and
    - The start month is missing, then the AE is treatment emergent; else if
    - The start month is present and is the same or after the month of the first study drug dose, then the AE is treatment-emergent; else,
- If the start date is completely missing, then the AE is treatment-emergent.

All other AEs are considered PTAEs.

Patient percentages are based on the total number of treated patients in the particular treatment group.

AEs are defined as related or not related to study treatment or study device.

9.3.9. Major Adverse Vascular Events

The description of the MAVE including the method of diagnosis (eg, magnetic resonance imaging, ultrasound, angiogram), date of diagnosis, and date resolved (or ongoing) will be collected on the eCRF as part of the patient's medical history (prior to Study Day 1) and throughout the study.

- A MAVE is defined as the following:
- Thrombophlebitis/deep vein thrombosis
- Pulmonary embolus
- Myocardial infarction
- Transient ischemic attack
- Unstable angina
- Renal vein thrombosis
- Acute peripheral vascular occlusion
- Mesenteric/visceral vein thrombosis or infarction
- Mesenteric/visceral arterial thrombosis or infarction
- Hepatic/portal vein thrombosis (Budd-Chiari syndrome)
- Cerebral arterial occlusion/cerebrovascular accident
- Cerebral venous occlusion
- Renal arterial thrombosis
- Gangrene (non traumatic; nondiabetic)
- Amputation (non traumatic; nondiabetic)
- Dermal thrombosis
- Other (specify)

9.4. Additional Details on Statistical Methods

9.4.1. FACIT-Fatigue Calculations

The FACIT-Fatigue questionnaire consists of 13 items scored on a 5-point Likert scale (0=not at all, 4=very much). The FACIT-Fatigue subscale scoring guideline (version 4) will be used as follows:

All negatively stated items (ie, all items except An5 and An7 from the CRF) are to be reversed by subtracting the response from 4. After reversing the proper items, all items are summed to obtain a score. The fatigue subscale score is then calculated by multiplying the sum of the item scores by 13, then dividing by the number of items answered. When there are missing data, prorating by subscale in this way is acceptable as long as more than 50% of the items were answered. The score has a range of 0-52 and a higher score indicates less fatigue.

9.4.2. EORTC QLQ-C30 Scoring Calculations

The EORTC QLQ-C30 (version 3.0) consists of a total of 30 questions related to QoL, scored on a 4-point Likert scale for the first 28 questions (1=not at all, 4=very much) and scored on a scale of 1 (very poor) to 7 (excellent) for the final two questions that probe the patient's overall health and QoL. It is composed of both multi-item scales and single-item measures. These include five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status and a number of single items assessing additional symptoms (dyspnea, loss of appetite, insomnia, constipation, and diarrhea), and financial difficulties. The following explains the scoring procedure.

Table 10: Scoring the EORTC QLQ-C30

	Scale	**Item range**[a]	**Item Numbers**	**Raw Score**[b]
Global health status/QoL	QL2	6	29,30	(Q29+Q30)/2
Functional Scales				
Physical Functioning	PF2	3	1 to 5	(Q1+Q2+Q3+Q4+Q5)/5
Role Functioning	RF2	3	6,7	(Q6+Q7)/2
Emotional Functioning	EF	3	21 to 24	(Q21+Q22+Q23+Q24)/4
Cognitive Functioning	CF	3	20,25	(Q20+Q25)/2
Social Functioning	SF	3	26,27	(Q26+Q27)/2
Symptom Scales				
Fatigue	FA	3	10,12,18	(Q10+Q12+Q18)/3
Nausea and Vomiting	NV	3	14,15	(Q14+Q15)/2
Pain	PA	3	9,19	(Q9+Q19)/2
Dyspnea	DY	3	8	Q8
Insomnia	SL	3	11	Q11
Appetite Loss	AP	3	13	Q13
Constipation	CO	3	16	Q16
Diarrhea	DI	3	17	Q17
Financial Difficulties	FI	3	28	Q28

[a] Item range is the difference between the possible maximum and the minimum response to individual items.
[b] Raw score is the mean of the component items

Once the raw scores are calculated, a linear transformation to 0-100 is applied to obtain the particular score as follows:

For functional scales: Score = {1-(Raw score-1)/Range}*100

For all other scales/items: Score = {(Raw score-1)/Range}*100

Each scale has a range of 0% - 100%. A high scale score represents a higher response level. Thus a high score for a functional scale represents a high level of functioning but a high score for a symptom scale represents a high level of symptomatology/problem.

Missing data: In the case of multi-item scales missing one of the items, raw scores can still be calculated using the completed items as long as more than 50% of the items were answered. For example, if the fatigue scale is missing Q10, the average of Q12 and Q18 would be used to calculate the raw score. For single-item measures, the score will be set to missing.

9.4.3. Treatment Administration Satisfaction Questionnaire

The TASQ is a 19-item validated questionnaire that will assess patients' perceptions and satisfaction with eculizumab IV, ravulizumab IV, or ravulizumab SC treatment (Theodore-Oklota, 2016). The TASQ scores treatment satisfaction across 5 domains: physical impact, psychological impact, impact on ADL, convenience, and satisfaction (Table 11). Each of the 16 scored items offers 5 response options with lower scores indicating a more positive response with the exception of items 8 and 15 which are reverse-scored response values. In addition, there are 4 descriptive questions that are not part of the above domains and scored separately (items 11, 16, 17 and 18).

For each complete domain (no missing responses) the domain scoring formula is:

> TASQ Domain score = [(Sum of completed item responses / Number of completed items) - 1] x 100 / (Maximum possible item response value – Minimum possible item response value)
>
> which reduces to: TASQ domain score = (mean of completed item responses – 1) * 25

For each incomplete domain (missing responses), the domain will not be scored (ie, a missing value will be assigned to the domain). Additionally, any safety data generated from this questionnaire will be documented as an AE on the AE eCRF as per the Investigator's medical judgement.

Table 11: Treatment Administration Satisfaction Questionnaire Domains

Domain Name	Item Number: Description
Physical Impact	2: Thinking about the IV/SC infusion, how do you rate the pain, swelling, or redness you experienced at the site of the drug injection? 3: Thinking about the IV/SC infusion, how do you rate the pain you experience with the IV/SC infusion process? 4: Thinking about the IV/SC infusion, are the side effects of the IV/SC infusion as you expected?
Psychological Impact	5: Before you receive the IV/SC infusion do you feel anxious about having the infusion? 6: When you receive the IV/SC infusion do you worry that your condition would get worse? 7: When you receive the IV/SC infusion do you feel anxious thinking about your disease? 8: Thinking about IV/SC infusion, how confident are you that the IV/SC infusion is treating your disease? 9: When you receive the IV/SC treatment do you feel restricted by the IV/SC infusion?
Impact on Daily Living	14a: How much does the IV/SC infusion interfere with your usual or daily activities? 14b: How much does the IV/SC infusion limit your daily activities? 15: Because of the length of time to apply the IV/SC infusion do you feel that you have lost or gained time for other things?
Convenience	10: Thinking about the IV/SC infusion, how convenient is it for you to get your IV/SC infusion? 12: Thinking about your IV/SC infusion, do you feel that the length of time to get your IV/SC infusion was as you expected? 13: Thinking about the IV/SC infusion, how bothered are you by the amount of time it takes to get the infusion?
Satisfaction	1: Thinking about your IV/SC infusion, how satisfied or dissatisfied are you with the IV/SC infusion?

	19: Thinking about the IV/SC infusion, would you recommend the way you received the treatment (IV/SC infusion) to another patient?

Items 11, 16, 17 and 18 are not scored as part of any domain.

9.4.4. SAS Code for Primary Analysis – ANOVA

The primary endpoint is the of ratio of the geometric mean C_{trough} from the ravulizumab SC group over the geometric mean C_{trough} from ravulizumab IV group in serum $C_{trough.}$ The sample SAS code for this analysis is given by:

```
proc mixed data=adam;
      class treatment weight;
      model logctrough=treatment weight;
      lsmeans treatment/pdiff cl alpha=0.1;
      estimate 'SC/IV' treatment 1 -1 / cl alpha=0.1;
run;
```

where logctrough is log-transformed Day 71 C_{trough}, treatment is the randomized treatment group, and weight is the categorical value at baseline (stratification). The ratio of geometric means will be obtained by exponentiating the difference between the least squares treatment means.

9.4.5. SAS Code for Primary (Sensitivity) Analysis – Data Imputation

The sensitivity analysis requiring data imputation for the primary endpoint of ratio in serum C_{trough} will impute missing C_{trough} values (CT) using the following SAS code:

```
proc mi data=adam seed=1111 nimpute=10;
      class treatment weight;
      fcs nbiter=200;
      var treatment weight CTDay15 CTDay22 CTDay57 CTDay64 CTDay71;
run;
```

The variables in the VAR statement will be listed according to the number of missing observations for each (from most complete to least complete). Additionally, all non-evaluable C_{trough} data that was excluded from the PK analysis set will be excluded from the imputation model. The resulting datasets from the above imputation will be analyzed using the same method as the primary analysis in Section 9.4.4 and will be combined using Rubin's rules (Rubin, 1987) with the following SAS code:

```
proc mianalyze data=effects;
      modeleffects estimate;
      stderr stderr;
run;
```

9.5. Interim Statistical Analysis Plan

Details regarding the interim analysis for futility and sample size re-estimation are specified in a separate ISAP.