TITLE PAGE

STATISTICAL ANALYSIS PLAN

Version Number: 5.0

Protocol Title: 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

Protocol Number: ALXN1210-PNH-303

Protocol Amendment Number: 5

Compound: ALXN1210

Brief Title: PK Noninferiority Study of Ravulizumab SC Versus Ravulizumab IV

Sponsor Name: Alexion Pharmaceuticals, Inc.

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Regulatory Agency Identifier Number(s):

Registry	Identification
EudraCT Number:	2017-002370-39
IND Number:	128367

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Version Date: 31 Oct 2023

1. APPROVAL SIGNATURES

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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
Sections 4, 5.3, 7.4, 7.5.1, and 9.5.4	Removed the single exploratory endpoint (PPQ).	2.0
Sections 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
Sections 4.2, 6, 6.6, and 6.8	Added modified safety and full analysis sets to include patients from Site [redacted] who have clinical study data that have 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 SC 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 and missing 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 prespecified CHW weights and removed the formula for calculating the weights.	3.0
Section 4	Added references to the administrative change letters indicating changes to the 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

Sections 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
Sections 4.2, 6.7, 6.8, 6.11, and 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 are 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 the 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
Sections 7.4.1, 7.4.2, 7.4.3, 7.4.4, and 7.4.5	Added 6-month and 1-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
Sections 7.4.6.2 and 7.5	Added the SC related populations for analysis along with listings being produced for titer values.	4.0
Sections 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 cut-off 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

Section 3	Added abbreviation for PPQ-SC.	5.0
Section 4.1.3	Added that a final CSR will be produced.	5.0
Section 4.3.4	The PPQ was added to PA5 as an endpoint.	5.0
Section 4.3.4	Described the change in efficacy and safety time intervals.	5.0
Section 5.2.1	Added Day 1093 endpoint for the Patient Preference Questionnaire.	5.0
Section 7.1.5	Added subgroup analyses by stratified weight group and geographical region.	5.0
Section 7.4	Described yearly time intervals and corresponding SC study days.	5.0
Section 7.4	Described the analysis methods for the PPQ-SC.	5.0
Section 7.4.6.1	Added weight-stratified subgroup analysis.	5.0
Section 7.4.6.2	Modified the populations for which the ADA analyses will be summarized.	5.0
Section 7.4.6.2	Added additional overall summaries and further categorized ADA-response variables.	5.0
Section 7.4.7	Added weight-stratified subgroup analyses.	5.0
Section 7.4.7.4	Added PPQ-SC analysis.	5.0
Section 7.5.2	Changed 6-month intervals to yearly intervals.	5.0
Section 7.6	Added device administration by visit type analysis.	5.0
Section 7.6	Added sequence of device administration analysis.	5.0
Section 9.44	Described the scoring methods for the PPQ-SC.	5.0

2. TABLE OF CONTENTS AND LIST OF TABLES AND FIGURES

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and acronyms are used in this Statistical Analysis Plan (SAP).

Table 1: Abbreviations and Acronyms

Abbreviation or Acronym	Definition
ADA	antidrug antibody
ADE	adverse device effect
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BP	blood pressure
CI	confidence interval
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough concentration
CV	coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full Analysis Set
FCS	fully conditional specification
HR	heart rate
HRQoL	health-related quality of life
IV	intravenous(ly)
ISAP	Interim Statistical Analysis Plan
LDH	lactate dehydrogenase
MAVE	major adverse vascular event
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified Full Analysis Set
mSCF	modified SC Treated Full Analysis Set
mSCS	modified SC Treated Safety Analysis Set
mSS	modified Safety Analysis Set
NAb	antidrug neutralizing antibody
NIM	noninferiority margin
OBDS	on-body delivery system
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PNH	paroxysmal nocturnal hemoglobinuria
PPQ	Patient Preference Questionnaire
PPS	Per Protocol Set
PT	preferred term
PTAE	pretreatment adverse event
PY	patient years
QLQ-C30	Quality of Life Questionnaire-Core 30 Scale
QoL	quality of life
QTcF	QT interval corrected using Fridericia's formula

Abbreviation or Acronym	Definition
qw	once every week
RBC	red blood cell
RR	respiration rate
SADE	serious adverse device effect
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System (software)
SC	subcutaneous(ly)
SCF	SC Treated Full Analysis Set
SCS	SC Treated Safety Analysis Set
SoA	schedule of activities
SOC	system organ class
SS	Safety Analysis Set
TA	transfusion avoidance
TASQ	Treatment Administration Satisfaction Questionnaire
TEAE	treatment-emergent adverse event
TTH	tabletop hemolysis
ULN	upper limit of normal
WHO-DRUG	World Health Organization Drug Dictionary

4. DESCRIPTION OF THE PROTOCOL

This SAP is based on ALXN1210-PNH-303 Protocol Amendment 5, 08 Jul 2021. 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 May 2019 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 ($\geq$ 40 to < 60 kg and $\geq$ 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 nondosing 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 and 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 copackaged 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 once every week (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 were 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 the patient is queried about study drug dose administration and device condition.

Table 2: Ravulizumab Study Drug Dosing

<table>
<tr><th>Treatment Group</th><th colspan="2">Randomized Treatment Period (10 Weeks)</th><th>Extension Period (Up to 172 Weeks)</th></tr>
<tr><td>Ravulizumab SC</td><td rowspan="2">Loading dose on Day 1:
Ravulizumab IV
2400 mg[a]
or
Ravulizumab IV
2700 mg[b]</td><td>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)</td><td rowspan="2">Maintenance doses on Day 71 and qw through Day 1275:
Ravulizumab SC 490 mg[d]
(2 ravulizumab OBDS kits per weekly dose)</td></tr>
<tr><td>Ravulizumab IV</td><td>Maintenance dose on Day 15:
Ravulizumab IV 3000 mg[a]
or
Ravulizumab IV 3300 mg[b]</td></tr>
</table>

[a] Weight group ≥ 40 to < 60 kg.
[b] Weight group ≥ 60 to < 100 kg.
[c] On Day 15, patients who were 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 = once 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:

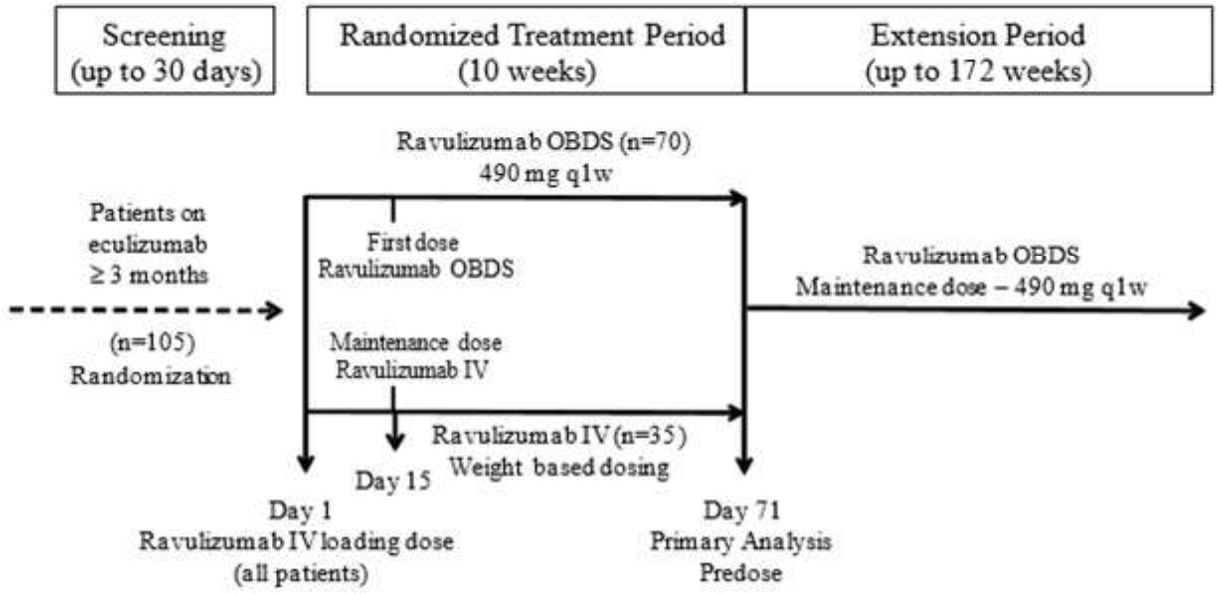
- Patients who had been randomized to the ravulizumab SC group will continue to receive 490 mg of ravulizumab SC using 2 OBDS kits on Day 71 and qw thereafter through the end of the Extension Period (up to Day 1275).
- Patients who had been randomized to the ravulizumab IV group will switch to 490 mg 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 adverse event (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 AEs and concomitant medications. If a patient discontinues treatment, but not from the study, the end of the study for such a patient will be their last visit if 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 trough concentration (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 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), treatment satisfaction, and patient preference on ravulizumab SC
- To evaluate the safety of ravulizumab SC and ravulizumab OBDS
- To evaluate the efficacy of ravulizumab SC
- To assess the 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

Two separate SAP Addendums contain the planned analyses for all coronavirus disease 2019 and expired kit-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 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 re-assess the required size of the study based on the 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 group).

The interim analysis will be performed by an independent statistical center that is not involved with the study conduct or the final analysis of study data. The interim analysis will be conducted following the approach explained in Mehta and Pocock (Mehta and Pocock, 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 SC 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 (TA), and stabilized hemoglobin) were changed to include the verbiage "from Baseline to Day 183" in the SAP Version 1.0.

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 Full Analysis Set (FAS) and Safety Analysis Set (SS) have been added and are defined in Section 6. Additional "SC-Treated" populations have been added 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 C_{trough} from the ravulizumab SC group over the geometric mean C_{trough} from ravulizumab IV group with a 2-sided 90% confidence interval (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 noninferiority boundary 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 CI.

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 FAS and SS were changed to exclude patients from Site [redacted] due to critical audit findings. Additionally, modified FAS and modified Safety Analysis Set (mSS) to include patients from Site [redacted] who have clinical study 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 patient 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 FAS and SS to exclude that patient. 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 electrocardiogram (ECG) and physical examination data at Day 365 and these assessments were not required under Protocol 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 groups (≥ 40 to < 60 kg and ≥ 60 to < 100 kg) were added to the secondary efficacy endpoints and are described in Section 7.1.5.

AEs will be analyzed using 6-month time intervals in addition to the analyses described in Version 3.0 and are described in Section 7.5.2. Additional analyses of non-serious adverse events (SAEs) occurring at a rate of at least 5% were added.

Summaries for adverse device effects (ADEs) were added for patients who 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 that are collected by the investigations group.

Scatter plots of the worst laboratory value post-first study drug versus baseline were removed during the predatabase 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, shifts 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 antidrug antibody (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 predatabase 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 tabletop 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 draw. In addition, PIGA-deficient erythrocytes from patients with PNH are more susceptible to mechanical lysis than non-PNH erythrocytes (Smith, 1985). Hemolysis results in the release of red blood cell (RBC) contents including lactate dehydrogenase (LDH), potassium, and aspartate aminotransferase (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). Marked hyperkalemia (defined as > 6 mmol/L) seen in TTH, but not PNH hemolysis, differentiates TTH (in vitro) from PNH hemolysis (in vivo), and is not clinically significant (Hollander-Rodriguez and Calvert, 2006). Due to the artifactual increase in LDH in samples affected by TTH, the potassium, alanine aminotransferase (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 laboratory LDH, in addition to new or worsening symptoms as specified in the protocol, is used by the Principal Investigator or designee to qualify patients with breakthrough hemolysis. TTH samples from the central laboratory will be defined as having serum potassium ≥ 6 mmol/L and LDH ≥ 2× upper limit of normal (ULN) and will be excluded from analyses as described above.

4.3.4. Changes From Analyses Specified in Version 4.0 of the SAP

Additional patient demographic summaries will be produced by geographical region.

OBDS dose administrations will be summarized by sequential versus simultaneous administration.

For the 52-week CSR, the following secondary endpoints were summarized at 6-month and 1-year time points:

- Disease-related laboratory parameters
  - LDH
  - Reticulocyte count
  - Estimated glomerular filtration rate
- Breakthrough hemolysis
- Transfusion avoidance
- Stabilized hemoglobin

The time points 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). These intervals are modified to yearly intervals for the final CSR as described in each corresponding section. PNH clone size and clinical manifestations of PNH will continue to be summarized at 6-month intervals as they are only assessed through Study Day 365.

In addition to the secondary endpoints, the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue), Treatment Administration Satisfaction Questionnaire (TASQ)-IV/SC,

and European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 (EORTC QLQ-30) subscales were summarized at 6-month and 1-year time points but will now be summarized for each visit.

For the 52-week CSR, AEs were summarized by 6-month intervals but will now be summarized by yearly time intervals (0 to 12 months, > 12 to 24 months, > 24 to 36 months, and > 36 months).

The PPQ-SC secondary endpoint has been added. The PPQ-SC will be collected only once for each patient; at Day 1093 or at early termination for patients who discontinue the study prior to Day 1093. PPQ-SC will not be collected at Day 1275.

5. DEFINITIONS

5.1. Primary Endpoint

The primary endpoint of the study is serum ravulizumab 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 FACIT-Fatigue Scale, Version 4.0, from Baseline to Day 183.
2. Change in the EORTC QLQ-C30 (Aaronson, 1993) Scale, Version 3.0, from Baseline to Day 183.
3. Reported treatment satisfaction and patient preference as reported by the TASQ at Baseline and Day 183.
4. Reported patient preference as measured by the PPQ-SC score at Day 1093 (or early termination).

5.2.2. Efficacy Endpoints

1. Change in LDH and the following other disease-related laboratory parameters over time:
   - Reticulocyte count
   - PNH 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 one new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin < 10 g/dL], and major adverse vascular event [MAVE] including thrombosis, dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2× ULN as assessed by the central laboratory.
3. 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, and MAVE including thrombosis, dysphagia, and erectile dysfunction) over time.

5.2.3. Device Performance Endpoint

The OBDS device performance endpoint for this study is as follows:

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

5.3. PK and PD 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 as follows:

1. Change in physical examinations, vital signs, ECGs, and laboratory assessments over time
2. Incidence and severity of AEs and SAEs over time
3. Incidence of 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 and 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) Version 4.03 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

AEs are further defined in Protocol Section 8.3.

5.4.2. Adverse Device Effects

An AE deemed associated with 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. ADEs are further described in Protocol Section 8.3.

5.4.3. Infusion Evaluation

SC 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, shaking chills, flushing, itching, alterations in heart rate (HR) and blood pressure (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 nonimmune 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 (eg, 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 PTs 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 BP, temperature, respiration rate (RR), and HR. Systolic and diastolic BPs will be documented in millimeters of mercury (ie, mmHg). Temperature will be obtained in degrees Celsius or Fahrenheit. HR will be documented in beats per minute. RR 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 ADAs by the central laboratory or bioanalytical laboratory. A central laboratory will be used to evaluate all laboratory assessments.

5.4.6. Electrocardiograms

A single 12-lead ECG will be conducted according to the SoA in the protocol. HR, RR, QRS, and QT will be measured. The QT interval corrected using Fridericia's formula (QTcF) for HR and interbeat (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's judgment and patient symptoms.

5.4.8. Immunogenicity

Blood samples will be collected to test for the 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 the definitions below, patients from Site [redacted] will be excluded from the primary PK, FAS, and SS. This decision was made based on a for-cause clinical Investigator site audit conducted on 14 and 15 Nov 2019. This audit of Site [redacted] resulted in two 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 the date and time of doses and PK sample collection; two 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. PK Analysis Set

The 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
The 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 are defined as nonmissing 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. PD Analysis Set

The PD Analysis Set consists of all patients who receive at least one 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: LDH 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 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 one 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 < 30000/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 FAS will consist of all patients (except those from Site [redacted] as mentioned in Section 6) in the enrolled analysis set who received at least one 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 [redacted] with at least one 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 [redacted]) who received at least one 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.

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 [redacted] who received at least one 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 SS will consist of all patients who receive at least one dose of ravulizumab (except those from Site [redacted] 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 Analysis Set

The mSS consists of all patients in the SS but will also include patients from Site [redacted] who received at least one 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 [redacted]) who received at least one 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.

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 [redacted] who received at least one 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 Statistical Analysis System (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 the 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 laboratory will be defined as having serum potassium ≥ 6 mmol/L and LDH ≥ 2× 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 Day 169/(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

Study Day	Day 15	Day 29	Day 43	Day 57	Day 71	Day 78	Day 85	Day 99
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 AEs 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 examination data at Day 365 and these assessments were not required under Protocol 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 (except for PNH RBC clone size and clinical manifestations of PNH and PPQ-SC), PK serum concentration, and select PD endpoints will be analyzed by stratified weight group ($\geq$ 40 to < 60 kg and $\geq$ 60 to < 100 kg).

Patient demographics will be summarized by geographical region (North America, Europe, Asia Pacific, and Latin America).

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, the 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 toward 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 prespecified CHW (Cui, Hung and Wang) weights, as described in Section 7.3, will be repeated using the PPS. Analysis of the PPS will use the same windowing schema as the PK Analysis Set (Table 4).
2. The primary noninferiority analysis, including the prespecified CHW weights, as described in Section 7.3, will be conducted using the mFAS/FAS. Nonmissing 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 prespecified CHW weights, as described in Section 7.3, will be repeated again using the mFAS/FAS. For this analysis, nonmissing 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 Version 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 predose ravulizumab serum concentration values will be continuous covariates. Nonmissing 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 9.4.6.

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 nonmissing but excluded from the primary analysis (PK Analysis Set).
3	mFAS/FAS	Repeat primary noninferiority analysis including C_{trough} data that were nonmissing but excluded from the primary analysis, by imputing missing C_{trough} values. Only valid C_{trough} data (PK Analysis 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

Patient and site protocol deviations will be coded and classified according to Alexion standard operating procedure and work instruction "Identification, Handling & Documentation of protocol deviations" (ALXN-SOP-0004743 and ALXN-WI0004204). The number and percentage 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 < 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 Sets. 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, SD, minimum, and 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 and ≥ 60 kg to < 100 kg
- Baseline height (cm)
- Observed weight stratification (≥ 40 kg to < 60 kg and ≥ 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 (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 (ie, thrombophlebitis/deep vein thrombosis, pulmonary embolus, and myocardial infarction)

By-patient listings of hemoglobin values within 60 days of informed consent and the 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 Medical Dictionary for Regulatory Activities (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 the 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 PT within a 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 (WHO-DRUG) 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 SOC and PT. 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:

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

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 (NIM), 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% CI will be calculated for Stage 1 and Stage 2. Noninferiority will be claimed based on the 90% CI that is calculated from the 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 9.4.5) 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, the use of the conventional Z-statistic at the final analysis may lead to an 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 prespecified 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 prespecified NIM on the mean difference scale (ln(0.8) or -0.223). Then the Z-statistics based on Stage 1 and Stage 2 data are as follows:

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

The final CHW test statistic is as follows:

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

where w_1 and w_2 are prespecified 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):

$$w_1 = .5 \text{ for stage 1 and } w_2 = .5 \text{ for stage 2.}$$

Statistical significance is reached (p-value for noninferiority ≤ 0.05) at the final analysis if $Z_{CHW} > c$, where c is the efficacy boundary at the 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 NIM (δ) of 0.8 (ie, equivalent to -0.223 NIM 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 the 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 the 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. For summaries by yearly interval (approximately 12 months), the corresponding time points are SC Day 351 (Study Day 365 for the SC group and Study Day 421 for the IV group), SC Day 743 (Study Day 757 for the SC group and Study Day 813 for the IV group) and SC Day 1079 (Study Day 1093 for the SC group and Study Day 1149 for the IV group). The final time points will be SC Day 1205 for the IV group and SC Day 1261 for the SC group to account for the difference in SC exposure.

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 percentage change from Baseline. Additionally, these parameters will be summarized by yearly intervals for only the SCF. Weight-stratified summaries only for the SCF will also be produced.

7.4.2. Incidence of Breakthrough Hemolysis

Breakthrough hemolysis (BTH) is defined as at least one 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.

The number and proportion of patients with BTH 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 351, SC Day 743, SC Day 1079, SC Day 1205 (IV group only), and SC Day 1261 (SC group only) for each treatment group and by period of SC treatment (0 to 12 months, > 12 to 24 months, > 24 to 36 months, and > 36 months). Total columns and 95% CIs will be produced along with weight-stratified summaries for the SCF.

For 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 and the yearly intervals, patients having at least one data for a visit will be included in the denominator. Additionally, only visits with data will be used to assess BTH.

7.4.3. Achievement of Transfusion Avoidance

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

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 351, SC Day 743, SC Day 1079, SC Day 1205 (IV group only), and SC Day 1261 (SC group only) for each treatment group and by period of SC treatment (0 to 12 months, > 12 to 24 months, > 24 to

36 months, and > 36 months). Total columns and 95% CIs will be produced along with weight-stratified summaries for the SCF.

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

7.4.4. Achievement of Stabilized Hemoglobin

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

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 351, SC Day 743, SC Day 1079, SC Day 1205 (IV group only), and SC Day 1261 (SC group only) for each treatment group and by period of SC treatment (0 to 12 months, > 12 to 24 months, > 24 to 36 months, and > 36 months). Total columns and 95% CIs will be produced along with weight-stratified summaries for the SCF.

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

7.4.5. Clinical Manifestations of PNH

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 postbaseline visit 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. PK, PD, and Immunogenicity Analyses

PK analyses will be performed for all patients who have evaluable PK data, as described in 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.

PD 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 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 semilogarithmic 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 first SC treatment summaries. Serum concentration will be summarized by stratified weight group during the RTP and since the first SC treatment using the FAS and SCF, respectively.

7.4.6.2. Incidence of Treatment-Emergent ADAs

All immunogenicity analyses will be conducted on the SS and mSS for the RTP and overall study summaries and the SCS and mSCS for the summaries since the first SC treatment. Baseline is defined as the last nonmissing ADA signal obtained before first study drug administration.

The number and percentage of patients developing ADAs and antidrug neutralizing antibodies (NAbs) will be summarized by treatment group.

The summaries of ADA incidence over the duration of the study will include the following categories:

- ADA negative: All postdose samples ADA-negative signal in the ADA assay, with baseline sample negative or missing.
- ADA positive: An ADA-positive signal in the ADA assay at any time point collected for ADA analysis.

Patients will be further categorized into ADA-response categories as follows:

- Pre-existing immunoreactivity: An ADA-positive response with either of the following two conditions met:
    - ADA-positive response at baseline with all post-first-dose ADA results negative

      OR
    - ADA-positive response at baseline with all post-first-dose ADA responses < 4-fold over the baseline titer level.

- Treatment-emergent ADA responses: An ADA-positive response post-first-dose when baseline results are negative or missing.
- Treatment-boosted ADA responses: An ADA-positive response post-first-dose that is ≥ 4-fold over the baseline titer level when the baseline result is positive.

Patients with a treatment-emergent or treatment-boosted ADA response may be further categorized as follows:

- Persistent: ADA responses with two or more consecutive ADA-positive samples separated by at least a 16-week period, with no ADA-negative samples in between, irrespective of missing samples.
- Indeterminate: ADA-positive sample only at the last collected sample.
- Transient: ADA response that is neither a persistent nor an indeterminate response.A by-patient listing will be produced and will list ADA responses and actual titer values for confirmed ADA-positive results.

ADA-positive samples will be further characterized for neutralizing activity in the NAb assay. Neutralizing antibody status categories are as follows:

- NAb positive: NAb-positive response at any time
- NAb negative: NAb-negative response at all time points

Further, the association of immunogenicity with impact on exposure, safety and efficacy may be explored including:

- Association of immunogenicity with impact on exposure
  - Associations between ADA-response categories or NAb and systemic exposure to the ravulizumab may be explored to assess the potential impact of immunogenicity on drug concentration-time (PK) profiles.
- Association of immunogenicity with impact on safety
  - Associations between ADA-response categories or NAb and serious and severe AEs may be explored, including SAEs like systemic hypersensitivity, anaphylaxis, injection/infusion-site reactions lasting more than 24 hours, and other immune-related SAEs.
- Association of immunogenicity with impact on efficacy
  - Associations between ADA-response categories or NAb and key efficacy endpoints or variables may be explored to assess the potential impact of immunogenicity on drug efficacy.

7.4.7. QoL and Treatment Satisfaction Analyses

7.4.7.1. Change in FACIT-Fatigue Subscale Score

Absolute levels, change, and percentage change in FACIT-Fatigue subscale scores (Theodore-Oklota et al, 2016 will be summarized by treatment group at baseline and each applicable postbaseline time point using descriptive statistics (including 95% CIs) for the observed values. Additionally, weight-stratified summaries will be produced for the SCF. Refer to Section 9.4.1 for a more detailed description of the FACIT-Fatigue calculations and the scoring methods.

At each postbaseline 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 et al, 2001) will be summarized by domain and by treatment group at baseline and each applicable postbaseline time point using descriptive statistics (including 95% CIs) for the observed values. Additionally, weight-stratified summaries will be produced for the SCF. 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 each applicable postbaseline time point using descriptive statistics (including 95% CIs) for the observed values. Additionally, weight-stratified summaries will be produced for the SCF. Refer to Section 9.4.3 for scoring methods and a more detailed description of the TASQ.

7.4.7.4. Patient Preference Questionnaire - Subcutaneous

Patient preference for SC or IV treatment will be evaluated using the PPQ-SC. These data will be summarized by frequency (%) for each of the 13 statements/questions at Day 1093 (SC Day 1023 for the IV group and SC Day 1079 for the SC group) or early termination. Refer to Section 9.4.4 for additional details.

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 the 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 versus 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 (TEAE). It is the time from the 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 the first SC treatment. Summary statistics (mean, SD, 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 (minutes) 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 the first SC treatment
- Primary reasons for missed doses during the RTP and since the first SC treatment (for dose administrations that take place at the site)
- Total SC infusion time during the RTP and since the first SC Treatment (for dose administrations that take place at the site)
- Infusion location for SC administrations during the RTP and since the 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 TEAE 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 Period), 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% or ≥ 80% to ≤ 90%) 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 the end of Randomized Treatment Period (excluding Day 71 study drug infusion) / total number of expected infusions to the 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, percentage 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 (one on Day 1 and two 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. AEs and ADEs

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
- TEAE: Any AE that starts during or after the first infusion of study drug
- All ADEs, 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 to Grade 5), by relationship (related or not related) to treatment, and by incidence rate of nonserious TEAEs ≥ 5%. The incidence of SAEs will also be summarized. The incidence of ADEs and SADEs will be summarized similarly by SOC and PT and by severity. All AEs and ADEs will be coded using MedDRA. ADEs will be coded appropriately according to device usage.

Analyses of TEAEs through Day 71 (Week 10) will be tabulated and presented separately. Patients having multiple AEs within a category (eg, overall, SOC, or PT) 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 PT within a SOC.

AEs will be summarized by yearly time intervals (0 to 12 months, > 12 to 24 months, > 24 to 36 months, and > 36 months) after exposure to the first SC treatment where a month = 30.4375 days.

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

AEs will include the displays described in the following subsections.

7.5.2.1. Summary of Pretreatment Adverse Events

Analyses of PTAEs will be tabulated and presented separately using the mSS. Patients having multiple PTAEs within a category (eg, overall, SOC, or PT) 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 PT within a SOC.

7.5.2.2. Overall Summary of AEs and ADEs

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
- Adverse events of special interest (AESIs)
- Not associated with the device/device use TEAEs
- 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 (except for 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 PT. Patients are counted once in each SOC and PT. Percentages will be based on the total number of treated patients in the treatment group. SAEs and SADEs will be summarized similarly. SADEs will be further classified as anticipated or unanticipated events.

7.5.2.4. AEs, SAEs, ADEs, and SADEs by SOC, PT, 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. SAEs will be summarized similarly. SADEs will be further classified as anticipated or unanticipated events.

7.5.2.5. AEs and ADEs by SOC, PT, and Severity

The number of TEAEs/ADEs and the number and percentage of patients with events will be presented by SOC and PT 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 electronic case report form (eCRF) does not include a question on whether 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 AEs

A listing of patient deaths will be produced.

AESIs include infusion reactions, malignancies, hematologic abnormalities, serious infections, ADAs, 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. AE Incidence Rates

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

AE incidence rates adjusted by PY of exposure will be summarized for the time since the 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 parameters (continuous variables) will be summarized descriptively at each visit, by treatment group. Baseline is defined as the last nonmissing 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 on

standardized units will be used. Box plots will be presented for the following central laboratory parameters by visit: hemoglobin, LDH, bilirubin (total and direct), creatinine, AST, ALT, gamma-glutamyltransferase, absolute neutrophil count, 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 nonmissing assessment value prior to the first study drug infusion. A listing of vital signs will be presented.

Absolute 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

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
  - Total number and percentage of devices used in clinic versus at home to achieve full dose administration
- The number and percentage of devices which delivered its full volume
- The number and percentage of full dose administrations using exactly 2 OBDS devices and the count of sequential versus simultaneous administration
  - Sequential administration is defined as the difference between the first and second OBDS infusion starting time ≥ 10 minutes
  - Simultaneous administration is defined as the difference between the first and second OBDS infusions < 10 minutes
- The number and percentage of devices with a reported complaint (see 21 Code of Federal Regulations 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 Section 1.3 of the protocol for the 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 group will achieve 90% power to detect noninferiority using a 1-sided test at an alpha level of 0.05 and a PK 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 FDA and EMA, 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 1 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 ($\geq$ 40 to < 60 kg or $\geq$ 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 the 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 the following:

- 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 01-Jan.
    - 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 (DD-MMM) 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 (MMM-YYYY) end date.

- If year and month are present and are not equal to the year and month of ravulizumab end date (MMM-YYYY), 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 (DD-MMM).
- 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 the 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 nonmissing 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 nonmissing 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 nonmissing.

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 nonmissing and non-zero and the subsequent value is nonmissing.

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 the 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 the 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 and upper bounds 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 and upper bounds for a visit as defined in the protocol schedule of assessment, then it will be assigned to that visit.

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

9.3.8. Adverse Events

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 the 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
- If the start year is the same as the year of the first study drug dose
    - The start month is missing, then the AE is treatment emergent
    - 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
- 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, and 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 (nontraumatic and nondiabetic)
- Amputation (nontraumatic and 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 4.0) will be used as follows:

All negatively stated items (ie, all items except An5 and An7 from the eCRF) 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 to 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, nausea, and vomiting), a global health status, 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 and 30	(Q29+Q30)/2
Functional scales				
Physical functioning	PF2	3	1 to 5	(Q1+Q2+Q3+Q4+Q5)/5
Role functioning	RF2	3	6 and 7	(Q6+Q7)/2
Emotional functioning	EF	3	21 to 24	(Q21+Q22+Q23+Q24)/4
Cognitive functioning	CF	3	20 and 25	(Q20+Q25)/2
Social functioning	SF	3	26 and 27	(Q26+Q27)/2
Symptom scales				
Fatigue	FA	3	10, 12, and 18	(Q10+Q12+Q18)/3
Nausea and vomiting	NV	3	14 and 15	(Q14+Q15)/2
Pain	PA	3	9 and 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 to 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% to 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 et al, 2016). The TASQ scores treatment satisfaction across 5 domains: physical impact, psychological impact, impact on daily living, convenience, and satisfaction (**Error! Reference source not found.**). 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] × 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. Patient Preference Questionnaire - Subcutaneous

The PPQ-SC evaluates patient preference for Ultomiris (ravulizumab) administered SC versus Soliris (eculizumab) administered IV. The questionnaire contains 13 statements/questions (in order of the questionnaire):

- One overall preference question asking patients to indicate which of the medications they prefer based on their experience with the two treatments. Patients may also select "I do not have a preference".
- One question evaluating preference for eculizumab or ravulizumab according to 14 treatment characteristics including an "other" write-in option
- One question asking patients to indicate which treatment characteristic was most important for their overall medication preference
- Five questions evaluating aspects of treatment with eculizumab
- Five questions evaluating those same aspects of treatment with ravulizumab administered SC. The overall preference question as follows:

Question 1 is scored such that "Soliris (eculizumab) via infusion" = 1, "Ultomiris SC (ravulizumab) via SC injection" = 2, and "I do not have a preference" = 3.
Question 2, which assesses preference on 13 treatment characteristics, uses a 5-point scale ("Strongly Prefer Soliris (eculizumab)" = 1; "Somewhat Prefer Soliris (eculizumab)" = 2; "I do not have a Preference" = 3; "Somewhat Prefer Ultomiris SC (ravulizumab)" = 4; and "Strongly Prefer Ultomiris SC (ravulizumab)" = 5).
Question 3 is not scored as part of this questionnaire.
Statements 4 through 13 are the 10 statements that elicit patient evaluation of each drug and use a 5-point scale ("Not at all" = 0; "A little bit" = 1; "Somewhat" = 2; "Quite a bit" = 3; or "Very much" = 4). Of these 10 statements, statements 6 and 11 will be reverse scored so that high scores in the patient evaluation section of the questionnaire represent a more favorable evaluation of the drug in consideration.

9.4.5. SAS Code for Primary Analysis – ANOVA

The primary endpoint is the 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.

9.4.6. 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 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 nonevaluable C_{trough} data that were 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 9.4.5 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.

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TITLE PAGE

STATISTICAL ANALYSIS PLAN ADDENDUM

Version Number: 1.0

Protocol Title: 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

Protocol Number: ALXN1210-PNH-303

Protocol Amendment Number: 5

Compound: ALXN1210

Brief Title: PK Noninferiority Study of Ravulizumab SC Versus Ravulizumab IV

Sponsor Name: Alexion Pharmaceuticals, Inc.

Legal Registered Address: 121 Seaport Boulevard, Boston, MA 02210

Regulatory Agency Identifier Number(s):

Registry	Identification
EudraCT Number:	2017-002370-39
IND Number:	128367

Author: [redacted]

Version Date: 31 Oct 2023

1. APPROVAL SIGNATURES

[redacted]

[redacted], Alexion Pharmaceuticals, Inc. Date dd Mmm yyyy

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[redacted], Alexion Pharmaceuticals, Inc. Date dd Mmm yyyy

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[redacted], Alexion Pharmaceuticals, Inc. Date dd Mmm yyyy

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2. TABLE OF CONTENTS AND LIST OF TABLES

LIST OF TABLES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations or acronyms are used in this Statistical Analysis Plan (SAP).

Table 1: Abbreviations and Acronyms

Abbreviation or Acronym	Definition
IMP	investigational medicinal product
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)

4. SAP ADDENDUM

This SAP Addendum details the additional analyses required to address the potential impact of the administration of expired study investigational medicinal product (IMP) during the study. This issue was reported as a serious breach to regulatory authorities as defined in QE-200580. Section 4.1 details the additional analyses that are not specified in the main study SAP (Version 5.0, 06 Oct 2023).

4.1. Additional Analyses not Specified in the Previous Version of the SAP

The following definitions will be used throughout this SAP Addendum.

Table 2: Definitions

Expired IMP	Study IMP confirmed to be administered to a patient post the labeled expiry date
Potentially expired IMP	Study IMP administered post-earliest-expiry date from all kits available at the site for administration where the kit is determined to have no confirmed expiry date due to missing or invalid kit numbers[a]

[a] The list of kits available at a site is determined from kits received at the site from the interactive voice/web response shipping reports.

Additional analyses not described in the main study SAP include the following:

1. All confirmed expired and potentially expired administered IMP will be summarized by treatment group and by total, as applicable.
    a. The summaries will provide the number and percentage of patients exposed or potentially exposed to expired IMP and the total number and percentage of expired or potentially expired kits administered subcutaneously (SC) through the time periods Day 71, SC Day 351, SC Day 757, SC Day 1261, and End of Study.
    b. A table summarizing confirmed and potential IMP exposure by a yearly interval of SC treatment (0-12 months, > 12-24 months, > 24-36 months, and > 36 months) will be produced.
    c. The summaries will include potential and confirmed exposure to expired IMP within the 10-month drug stability threshold (as described in ALXN-QD-0085554).
    d. The summaries will use the Safety and Modified Safety Analysis Sets and SC-treated Safety and Modified Safety Analysis Sets for the Randomized Treatment Period and SC Treatment Periods, respectively.
2. A by-patient listing for expired and potentially expired IMP exposure will be produced for the Modified SC-treated Safety Set. The listing will include the date/time of the confirmed or potential exposure, the study visit at which the exposure occurred, if known, the kit number of the expired or potentially expired kit, and if the kit was administered before or after the 10-month IMP stability threshold.
3. A by-patient listing of adverse events starting within 90 days of exposure to expired and/or potentially expired IMP will be produced.

ALXN1210-PNH 303 Expired kit SAP addendum

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