Statistical Analysis Plan for Interventional Studies

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Sponsor Name: Alexion Pharmaceuticals, Inc.

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Protocol Title: Phase 4, Single-Arm Study of Ravulizumab in Adult Participants with Paroxysmal Nocturnal Hemoglobinuria Currently Treated with High-Dose Eculizumab

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1.0	11-Jan-2022	[redacted]	Initial Release Version
2.0	09-Feb-2022		Updates to: visit windows section 6.4, sort order of outputs described in section 7.4, rule for BLQ values section 9.2

I confirm that I have reviewed this document and agree with the content.

Approvals	
Syneos Health Approval	
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Glossary of Abbreviations

Abbreviation	Description
ADA	Antidrug Antibody
AE	Adverse Event
ATC	Anatomical Theraeutic Chemical
BLQ	Below Lower Limit of Quantification
BTH	Breakthrough Hemolysis
C5	Complement Component 5
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
eCRF	Electronic Case Report Form
EOS	Early-of-study
ET	Early-termination
ECG	Electrocardiogram
FAS	Full Analysis Set
HRU	Healthcare Resource Utilization
ID	Identification
LDH	lactate dehydrogenase
IV	Intravenous
MAVE	Major Adverse Vascular Event
MedDRA	Medical Dictionary for Regulatory Activities Terminology
PD	Pharmacodynamic
PK	Pharmacokinetic
PNH	Paroxysmal Nocturnal Hemoglobinuria
PRS	Patient-Reported PNH Symptoms
PT	Preferred Term
PTAE	Pre-Treatment Adverse Event
q2w	Every 2 Weeks
q6w	Every 6 Weeks
q8w	Every 8 weeks

Abbreviation	Description
SD	Standard Deviation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TFL	table, figure, and listing
ULN	Upper Limit of Normal
WHODrug	World Health Organization Drug Dictionary

1. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables, and figures that will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

1.1. Responsibilities

Syneos Health will perform the statistical analyses and is responsible for the production and quality control of all tables, figures, and listings (TFLs), including pharmacokinetic (PK) and pharmacodynamic (PD) analyses.

1.2. Timings of Analyses

An interim analysis will be conducted on accrued data through Day 183 for publication purposes. All TFLs specified in this SAP will be included in the interim analysis.

The final analysis will be conducted after final database lock of the study.

2. Study Objectives

2.1. Primary Objective

- To evaluate the prevalence of free complement component 5 (C5)-associated breakthrough hemolysis (BTH) in participants on high-dose eculizumab who switch to ravulizumab (per approved dose regimen)

2.2. Secondary Objective

- To evaluate efficacy by other measures in participants on high-dose eculizumab who switch to ravulizumab

2.3. Exploratory Objective

- To evaluate patient-reported outcomes over time for those who switch to ravulizumab from high-dose eculizumab

2.4. Safety Objective

- To evaluate the safety and tolerability of ravulizumab in participants on high-dose eculizumab who switch to ravulizumab

2.5. PK/PD Objective

- To characterize the pharmacokinetics/pharmacodynamics of ravulizumab in participants on high-dose eculizumab who switch to ravulizumab

3. Study Details/Design

3.1. Brief Description

This is a Phase 4, multicenter, single-arm, open-label study to evaluate the safety and efficacy and of ravulizumab in adult participants with Paroxysmal Nocturnal Hemoglobinuria (PNH) who switch from eculizumab 1200 mg every 2 weeks (q2w; ie, above higher than approved dose) to ravulizumab (at the approved dose).

The study will consist of a Screening Period of approximately 3 months, a Treatment Period of 351 days, and a follow-up safety phone call 2 months after the last dose of Ravulizumab. Approximately 20 participants will be enrolled. All participants must provide informed consent prior to any procedures at the first Screening visit. All participants must have been prescribed and are receiving a stable dose of eculizumab 1200 mg q2w for at least 3 months prior to screening. During screening, eculizumab may be administered at the participant's home at the discretion of the Investigator. During screening, participants will continue to receive eculizumab 1200 mg q2w, and blood samples will be collected for PD parameters and lactate dehydrogenase (LDH) levels.

Eligible participants will receive a loading dose of ravulizumab on Day 1, followed by maintenance doses on Day 15 and every 8 weeks (q8w), administered by intravenous (IV) infusion. Ravulizumab loading and maintenance doses will be based on participants' body weight per approved dose regimen. All doses will be administered in the clinic by a trained member of the site study team or at the participant's home or at a medical facility close to the participant's home by a qualified healthcare personnel.

If a participant experiences a free C5-related BTH during maintenance treatment with ravulizumab, shortening the dosing interval to every 6 weeks (q6w) is permitted at the discretion of the Investigator after discussion with Alexion's Medical Monitor. For these participants, the assessments performed at the first q6w visit would be those indicated in the Schedule of Study Visits and Assessments. Subsequent q6w visit assessments would continue to be aligned to the example visit illustrated in Table 3 in Section 1.3 of the protocol, with the end-of-study (EOS)/early-termination (ET) visit being on/after Day 351. Between the specified visits occurring at 6-week dosing frequency and the EOS/ET visit, any additional visits are to be classified as unscheduled visits and would follow the study procedures for unscheduled visits.

The schedule of study visits and assessments is shown in Section 1.3 of the Protocol.

An interim analysis will be performed on Day 183.

3.2. Participant Selection

Inclusion and exclusion criteria will be confirmed at Screening.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

Refer to Section 5 of the Protocol for a complete list of requirements for inclusion and exclusion of participants.

3.3. Determination of Sample Size

The proposed sample size for this estimation study is approximately 20 participants. The range of possible proportions of participants experiencing free C5-associated BTH during the Treatment Period (with 95% exact confidence intervals [CI]) is as follows:

Proportion of BTH (participants with BTH/total population)	**95% CI**
95% (19/20)	75%, 100%
75% (15/20)	51%, 91%
50% (10/20)	27%, 73%
25% (5/20)	9%, 49%
10% (2/20)	1%, 32%
5% (1/20)	0%, 25%
0% (0/20)	0%, 17%

3.4. Treatment Assignment and Blinding

This is an open-label study, therefore all participants will be assigned to the same treatment and no blinding will by undertaken. Site personnel, Alexion staff, designees, and all staff directly associated with the conduct of the trial will be unblinded to participant treatment.

3.5. Administration of Study Medication

The study drug composition and doses to be administered in this study are presented in the following table.

Table 1: Details of Study Drug Administration

ARM Name	**Ravulizumab**
Drug Name	Ravulizumab
Type	Biologic
Dose Formulation	Concentrated sterile, preservative-free aqueous solution
Unit Dose Strength(s)	300 mg (10 mg/mL concentrated solution)
Dosage Level(s)	Doses based on participant weight
Route of Administration	IV infusion
Use	Experimental
IMP and NIMP	IMP
Sourcing	Provided centrally by Alexion or contracted manufacturing organization.
Packaging and Labeling	Study drug will be provided in glass vials and stoppered with a butyl rubber stopper with an aluminum overseal and a flip-off cap. Study drug will be supplied in kits and labeled as required per country requirement.

Abbreviations: IMP = investigational medicinal product; IV = intravenous; NIMP = non-investigational medicinal product

3.6. Schedule of Study Visits and Assessments

The study consists of Screening Visits, a Confirmation Visit, an Evaluation Period and a 2-month Follow-Up phone call. Visit windows will be used to associate observed visits to planned study visits, see Section 6.4. Refer to Section 1.3 of the Protocol for the schedule of visits and assessments; for the Screening Visits (see Table 1), for the Confirmation Visit and the Evaluation Period through follow-up (see Table 2), and for q6w dosing (see Table 3).

4. Endpoints

4.1. Primary Efficacy Endpoint

- Proportion of participants who experience free C5-associated BTH through Day 351. Free C5-associated BTH is defined as BTH concurrent with free C5 concentrations ≥ 0.5 µg/mL. BTH is defined as at least 1 new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin < 10 g/dL], major adverse vascular event (MAVE), including thrombosis, dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2 × upper limit of normal (ULN).

4.2. Secondary Efficacy Endpoints

- Proportion of participants who experience BTH through Day 351
- Hemolysis as directly measured by LDH-percent change from baseline to Day 351
- Proportion of participants who receive a transfusion, from baseline to Day 351
- Proportion of participants with stabilized hemoglobin, defined as avoidance of a ≥ 2 g/dL decrease in hemoglobin level from baseline in the absence of transfusion from baseline to Day 351

4.3. Exploratory Endpoints

- Patient-reported PNH Symptoms (PRS) at baseline, Day 183 and Day 351
- Healthcare Resource Utilization (HRU) at baseline, Day 183 and Day 351

4.4. Safety Endpoints

- Physical examinations, vital signs, and laboratory assessment results, and incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
- Proportion of participants who develop antidrug antibodies (ADAs) to ravulizumab

4.5. PK/PD Endpoints

- Serum ravulizumab concentration over time
- Change in serum free and total C5 concentrations over time

5. Analysis Sets

5.1. Enrolled Set

The Enrolled Set will include all participants who give informed consent and satisfy all inclusion/exclusion criteria.

5.2. Safety Set

Safety analyses will be performed on the Safety Set, defined as all participants who receive at least 1 dose of ravulizumab.

5.3. Full Analysis Set

Efficacy analyses will be performed on the Full Analysis Set (FAS). The FAS is the primary population for all analyses except Safety and PK. The FAS will include all participants who receive at least 1 dose of ravulizumab.

5.4. Pharmacokinetic Analysis Set

PK analyses will be performed on the PK analysis set, defined as all participants who receive at least 1 dose of study drug and who have evaluable PK data.

5.5. Pharmacodynamic Analysis Set

PD analysis will be performed on the PD analysis set, defined as all participants who receive at least 1 dose of study drug and who have evaluable PD data.

5.6. Protocol Deviations

Protocol deviation management at Syneos Health is detailed in Protocol Deviation and Non-compliance Management (3101.W02). For details on the process for defining analysis datasets refer to (Blind) Data Review and Definition of Analysis Sets SOP (3911)

Major protocol deviations affected by COVID-19 will be summarized by pre-specified deviation categories by the number and percentage of participants for the FAS. A by-participant listing of all protocol deviations will be produced.

6. General Aspects for Statistical Analysis

6.1. General Methods

All data collected will be presented using summary tables, figures, and data listings. All data, as well as any outcomes derived from the data, will be presented in detailed data listings. Graphical displays may also be provided, when appropriate. All analyses will be performed using SAS® release, version 9.4 or higher (SAS Institute Inc., Cary, NC, USA) or other validated statistical software. Continuous variables will be summarized using descriptive statistics, including the number of observations, and mean, standard deviation (SD), median, minimum, and maximum values. Categorical variables will be summarized by frequency counts and the percentage of participants. All statistical tests performed will be based on a 2-sided 5% level of significance unless otherwise specified. All participants entered into the database will be included in participant data listings. All relevant participant data will be included in listings.

6.2. Key Definitions

Baseline
Baseline is defined as the last non-missing value collected prior to the first administration of the study drug. This could also come from an unscheduled visit before start of study drug administration.

For LDH, baseline is defined as the average of all assessments analyzed by the central laboratory during the Screening Period prior to first study drug administration.

Baseline age
Baseline age is defined as the age (in years) of the study participant at the time of informed consent, as collected in the electronic case report form (eCRF).

Study day
The confirmation visit will occur on Study Day 1, which is defined as the day the study participant receives the first administration of the study drug. Study day of assessments will be calculated as follows:

- If date of assessment is after date of first study drug administration:
    - Date of assessment – date of first study drug administration + 1
- If date of assessment is before date of first study drug administration:
    - Date of assessment – date of first study drug administration

There is no Study Day 0.

Change from baseline
Change from baseline is calculated as (post-baseline result – baseline result).

Percent change from baseline is calculated as (change from baseline/baseline result * 100).

If either the baseline or the post-baseline result is missing, the change from baseline and/or percentage change from baseline is set to missing as well.

6.3. Missing Data

6.3.1. Missing Efficacy Endpoints

The absence of data related to BTH can only be interpreted to mean that no BTH has occurred. Thus all efficacy data will be analyzed as-is and no imputations will be performed.

6.3.2. Missing Start and Stop Dates for Prior and Concomitant Medication

Prior medication is defined as any medication with start and end dates before the date of first study drug administration. Concomitant medications are medications with start dates on or after the baseline date, or medications with end dates or ongoing after date of study drug administration. If start or end dates are unclear because of partial or missing date information, medications will be considered concomitant.

6.3.3. Missing Start and Stop Dates for Adverse Events

Treatment-emergent AEs (TEAEs) are events with start dates and start times on or after the date and time of the first administration of the study drug. 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 has 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 and
  - the start month is missing, then the AE is treatment emergent; or
  - 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 pre-treatment AEs (PTAEs).

6.4. Visit Windows

Study visits will be defined through the use of windows based on the list of visits described in Section 1.3 of the Protocol. For all assessments, 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 visits. This may not always correspond to the eCRF visit.

All post-baseline 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, where applicable.

Generally, the lower bound for each analysis visit window is defined as the midpoint of the target dates between 2 consecutive scheduled visits. The upper bound of the last visit window is set as the target date + 7 days. If the date of assessment falls between the lower and the upper bound for a visit as defined in the schedule of assessments (see Section 1.3 of the protocol), then it will be assigned to that visit. If the interval separating 2 scheduled visits is an even number of days, that middle day will be included in the lower bound of the next visit window.

If only 1 record is within an analysis visit window, the data from that record will be used in the analysis. If more than 1 record is within the same analysis visit window, the record closest to the midpoint of the

interval will be used in the analysis. If 2 records are “tied” before and after the middle of the interval, the earlier record will be used in the analysis. Participants who switch to q6w dosing will likely have more than 1 record in some visit windows. The decision rules described above will be applied to the q6w visits to determine which measurements will be used in the analysis.

See Table 2 for visit window definitions.

Table 2: Visit Windows (Days)

Visit	Nominal Day	Visit Window
Screening Period		
Day -85	-85	-85 – -79
Day -71	-71	-78 – -65
Day -57	-57	-64 – -51
Day -43	-43	-50 – -37
Day -29	-29	-36 – -23
Day -15	-15	-22 – -1
Confirmation Visit		
Day 1	1	1 - 1
Evaluation Period		
Day 15	15	8 – 42
Day 71	71	43 – 98
Day 127	127	99 – 154
Day 183	183	155 – 210
Day 239	239	211 – 266
Day 295	295	267 – 322
Day 351	351	323 – 378
Follow-up	407	379 – max

6.5. Pooling of Centers

Pooling of centers is not applicable to this study

6.6. Subgroups

No subgroup analysis is planned because of the small sample size of the study.

7. Participant Disposition, Demographic, Other Baseline Characteristics and Medication

7.1. Participant Disposition and Withdrawals

The number and percentage of participants screened, failed screening, treated, completing treatment, discontinued treatment, reasons for discontinuation of treatment, completing the study, switching to q6w dosing, discontinued from the study, reasons for discontinuation, and those included in each analysis set will be summarized. The number of participants with discontinuation status impacted by COVID-19 will be included in the summary.

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. Individuals who do not meet the criteria for participation in this study because of a reason that is expected to resolve or has resolved may be rescreened based on discussion and agreement between the Investigator and the Medical Monitor. Rescreened participants will be assigned a new participant identification (ID) number. The ID number of the previous screen failure will be linked to the new participant ID number in the eCRF.

Completion/discontinuation status, inclusion/exclusion criteria definitions, and inclusion/exclusion criteria violations will be listed by participant.

A listing of participants showing their affiliation to the different analysis sets will also be generated.

7.2. Demographic and Baseline Characteristics

Participant demographic and baseline characteristics will be summarized for the FAS. Summary statistics will be presented for the following variables:

- Age at baseline (years)
- Age group at baseline (<65 years, ≥65 years)
- Sex
- Ethnicity
- Race
- Height (cm)
- Weight (kg) at baseline
- Body mass index

All demographic data will be listed.

7.3. Medical History and Concomitant Diseases

Medical history will be classified by System Organ Class (SOC) and Preferred Term (PT) using Medical Dictionary for Regulatory Activities Terminology (MedDRA) version 23.1, and will be summarized for the FAS. Tables will be sorted alphabetically by SOC and descending frequency of PT within SOC. By-participant listings of medical history will be presented. The following medical history variables will be summarized:

- Relevant medical conditions/surgeries prior to informed consent
- Participants with any condition associated with major adverse vascular event (MAVE)
- Participants with any PNH symptoms experienced at any time prior to informed consent
- Participants with any conditions associated with PNH diagnosed at any time prior to informed consent

7.4. PNH Medical History and Disease Characteristics

PNH medical history will be listed for all participants in the FAS. The following PNH medical history and disease characteristics will be summarized:

- Age at PNH diagnosis, calculated as: year of first PNH-associated diagnosis – year of birth
- Method of PNH diagnosis
- Years from PNH diagnosis to informed consent, calculated as: year of first PNH-associated diagnosis – year of informed consent
- Total red blood cell PNH clone size at screening
- Granulocyte clone size at screening
- Monocyte clone size at screening
- Need for packed red blood cell transfusion within 6 months / 1 year prior to the first dose of study drug
- Number of packed red blood cell transfusion episodes within 6 months / 1 year prior to first dose of study drug
- Number of units transfused within 6 months / 1 year prior to the first dose of study drug

7.5. Medication and Procedures

Medications will be classified using the World Health Organization Drug Dictionary (WHODrug) version B3 Global September 2020. Medication summaries (ie, number [%] of participants using prior and concomitant medications) will be presented by therapeutic class (Anatomical Therapeutic Chemical [ATC] Level 3) and generic name.

7.5.1. Prior Medication

Prior medications are defined as medications that the participant takes within 28 days prior to the start of screening until the first dose of study drug, eculizumab taken during the 3 months prior to screening, and all meningococcal vaccinations administered within 3 years prior to the first dose of study drug.

Prior medications will be summarized for the FAS. Eculizumab taken prior to screening will be summarized separately to eculizumab taken during the Screening Period. A listing of prior medications, including eculizumab taken prior to screening, will be produced. Eculizumab taken during the screening period will be listed separately. A separate listing of meningococcal vaccinations will be produced showing the date and type of vaccination for each participant.

7.5.2. Concomitant Medication

Concomitant medications are defined as medications taken on or after the first infusion of the study drug through 30 days after the participant's last dose of the study drug.

Concomitant medications will be summarized for the FAS. A by-participant listing will also be produced.

7.5.3. Non-Pharmacologic Therapies and Procedures

Non-pharmacologic therapies and procedures will be listed for the FAS.

7.6. Extent of Exposure

Summaries of exposure will consider all infusions of ravulizumab (ie, those given under both the q8w and q6w dosing regimens). Summary statistics (mean, SD, median, minimum, and maximum) will be produced for the following using the Safety Set:

- Number of infusions from Day 1 to Day 351
- Number of participants receiving 1, 2, etc. maintenance doses prior to Day 351
- Total number of participants with an infusion interruption as well as total number of infusions interrupted from Day 1 to Day 351
- Number of participants switching to q6w dosing between Day 1 and Day 351
- Duration of study participation calculated as the time in days from the date of signing the informed consent to the date of study completion/discontinuation (ie, study duration = date of completion/discontinuation - date of informed consent + 1).
- Total time on study treatment (days) calculated as the time in days from first study drug infusion date to the last study drug infusion date (ie, treatment duration=last study drug infusion date - first study drug infusion date + 1).

By-participant listings of exposure and study duration will be presented.

7.7. Treatment Compliance

The frequency and percentage of participants who had a percentage of drug compliance range by increments of 10% (ie, ≥ 100%; ≥ 90% to < 100%; ≥ 80% to < 90%; etc.) will be calculated for the Safety Set.

This will be calculated as follows:

Percent compliance = total number of study drug infusions administered from Day 1 to study completion or discontinuation / total number of expected infusions from Day 1 to study completion or discontinuation.

Treatment compliance percentage will be summarized for participants diagnosed with or quarantined because of COVID-19 during the study.

A by-participant listing will be produced for treatment compliance.

8. Efficacy

This is an estimation study; no formal hypothesis testing will be performed.

8.1. Primary Efficacy Endpoint and Analysis

The primary efficacy endpoint is the proportion of participants who experience free C5-associated BTH through Day 351.

BTH is defined as at least 1 new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin < 10 g/dL], MAVE, including thrombosis, dysphagia, or erectile dysfunction) in the presence of elevated LDH, which is defined as LDH ≥ 2 × ULN. The determination about whether a BTH has occurred will be reflected on the BTH form of the eCRF. In the event of a BTH outside the visit schedule, an unscheduled visit will occur, at which point all information pertaining to the BTH will be collected.

Free C5-associated BTH is defined as BTH concurrent with free C5 concentrations ≥ 0.5 µg/mL. The first C5 concentration captured on or after the date of the BTH will be considered when defining a BTH event as free C5-associated.

The proportion of participants who experience free C5-associated BTH through Day 351 will be calculated along with a 2-sided exact 95% CI using the Clopper-Pearson method. All data will be listed.

Participants who withdraw from the study due to lack of efficacy during the Evaluation Period will be considered as non-responders and will be counted in the group with free C5 associated BTH if free C5 is ≥ 0.5 µg/mL at ET visit. For participants who withdraw from the study for any other reason during the Evaluation Period, their data up to the time of withdrawal will be used to assess free C5 associated BTH.

8.2. Secondary Efficacy Endpoints and Analyses

8.2.1. Proportion of participants with BTH

The proportion of participants who experience BTH through Day 351 will be summarized along with a 2-sided 95% exact CI using the Clopper-Pearson method.

The determination about whether a BTH has occurred will be reflected on the BTH form of the eCRF. In the event of a BTH outside the visit schedule, an unscheduled visit will occur, at which point all information pertaining to the BTH will be collected.

All data will be listed.

8.2.2. Hemolysis

Hemolysis is analyzed as directly measured as the percentage change in LDH from baseline.

The percentage change in LDH will be analyzed using a mixed model for repeated measures (MMRM) (Mallinckrodt, 2001; Mallinckrodt, 2004) with the fixed categorical effects of study visit, and the continuous fixed covariate of baseline LDH. Baseline is defined as the average of all assessments analyzed by the central laboratory prior to the first study drug administration. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. A p-value testing whether percent changes differ from 0 at each visit will be calculated.

Absolute LDH levels, and the change and percent change from baseline, will be summarized at all study visits up to Day 351.

The number (%) of participants achieving LDH levels at or below ULN (1.0 × ULN) and levels at or below 1.5 × ULN will be displayed.

Mean (±95% CI) of absolute LDH levels, and the change and percent change from baseline will be plotted over time.

All data will be listed.

8.2.3. Proportion of participants with transfusion

Proportion of participants receiving a transfusion from baseline to Day 351 will be summarized along with a 2-sided 95% exact CI using the Clopper-Pearson method. Number of transfusion episodes, number of units transfused will also be summarized for participants receiving transfusions.

Participants who withdraw from the study due to lack of efficacy during the Evaluation Period will be considered as non-responders and will be counted in the group receiving transfusion. For participants who withdraw from the study for any other reason during the Evaluation Period, their data up to the time of withdrawal will be used to assess the proportion of participants receiving a transfusion.

All data will be listed.

8.2.4. Proportion of participants with stabilized hemoglobin

Proportion of participants with stabilized hemoglobin in the absence of transfusion from baseline to Day 351 will be summarized along with a 2-sided 95% exact CI using the Clopper-Pearson method. Stabilized hemoglobin is defined as avoidance of a ≥ 2 g/dL decrease in hemoglobin level from baseline in the absence of transfusion from baseline to Day 351.

Participants who withdraw from the study because of lack of efficacy during the Evaluation Period will be considered as non-responders and will be counted in the group who did not meet the stabilized hemoglobin definition. For participants who withdraw from the study for any other reason during the Evaluation Period, their data up to the time of withdrawal will be used to assess stabilized hemoglobin.

All data will be listed.

8.3. Exploratory Endpoints and Analyses

8.3.1. Patient-Reported PNH symptoms

For PRS, each participant will record the presence or absence of the following signs and symptoms of PNH at baseline, Day 183, and Day 351/ET: fatigue, chest pain, abdominal pain, dyspnea, dysphagia, headache, confusion, erectile dysfunction (if applicable), discoloration of urine, and discoloration of eyes.

PRS data will be summarized descriptively by visit for the FAS. The summaries will include the proportion of participants affected by PNH symptoms, the frequency and severity of those symptoms, and the level of distress the symptoms caused.

All data will be listed.

8.3.2. Healthcare Resource Utilization

For HRU, the Investigator or designee will record for each participant the number of clinic visits, emergency services utilized, hospitalization, missed work and also record the number of times the participant had darkened urine at baseline, Day 183, and Day 351/ET.

HRU data will be summarized descriptively by visit for the FAS. The summaries will include the proportion of participants who required healthcare resource utilization within a month before the specified study visit and the frequency of HRU.

All data will be listed.

9. Pharmacokinetics

All pharmacokinetic analyses will be conducted on the PK Analysis Set.

The non-compartmental analysis will be performed using appropriate software, ie, Phoenix™ WinNonlin® (Version 8.0 or higher, Certara Corporation) to report on the basis of this SAP.

9.1. Plasma PK Endpoint

PK Sampling Schedule
Blood samples for determination of serum ravulizumab concentrations will be collected before and after administration of study drug at the timepoints as specified in the schedule of assessments (see Section 1.3 of the protocol). The predose (within 0.5 hours prior to the start of infusion) PK sample may be drawn through the venous access created for the dose infusion, prior to administration of the dose. End-of-infusion (within 0.5 hours after the end of infusion) PK samples will be drawn from the participant's opposite, non-infused arm. In the event of BTH, a serum PK sample will be collected.

9.2. Presentation of Concentration Data

9.2.1. Handling of Missing Data

Missing concentration data for all participants who are administered study treatment will be considered as non-informative missing and will not be imputed. No concentration estimates will be provided for missing sample values.

9.2.2. Handling of the Difference between the Scheduled (Nominal Time) and the Actual Sampling Times (Actual Time)

For all sampling times, the actual sampling times relative to dosing are calculated as the difference between the actual clock time of sampling and the actual clock time of dosing. The actual postdose sampling times relative to dosing expressed in hours and rounded off to 3 decimal digits are used. The predose sampling time will be reported as 0 (0.000), regardless of the time difference between the predose sampling and dosing. Scheduled sampling times are presented in concentration tables. If the actual time of sampling is missing, the nominal time is used.

9.2.3. Listing and Presentation of Individual PK Data

- The sampling time of predose samples relative to dosing is treated as 0 for all sampling periods separately;
- All concentrations are presented in original units as reported by the bioanalytical laboratory (eg, ng/mL);
- All concentrations that are below the lower limit of quantification (BLQ) will be set to half the lower limit of quantification (0.5 ug/mL).
- Listing of PK sampling times including nominal and actual time elapsed from dose with the deviation from the nominal time and measured concentrations of the drug;
- No further imputation will be applied to any missing values.

Individual serum ravulizumab concentration data will be listed by participant, timepoint, and treatment (in relevant concentration units). Data will be presented by rounding off to 2 decimal digits. Individual serum concentrations versus time profiles for individual participants will be generated on linear and log-linear scales.

9.2.4. Summary of PK Concentrations

For PK concentration summary, the following rules apply:

- PK concentrations BLQ in predose samples and in samples taken before the time of the first quantifiable value are set to half the lower limit of quantification (0.5 ug/mL).
- The PK concentrations BLQ after quantifiable concentration are set to 0;
- The sampling time of predose samples relative to dosing will be treated as 0;
- Drug concentrations will be summarized by nominal timepoint;
- Descriptive statistics will be performed;
- No further imputation is applied to any missing values.

Ravulizumab concentrations will be summarized descriptively by visit and timepoint (in relevant concentration units) using descriptive statistics (n, number and percent of participants with BLQ, arithmetic mean, geometric mean, SD, arithmetic and geometric coefficient of variation (CV) %, minimum, median and maximum) presented according to the following reporting precision.

Variable	**Summarized with:**
Minimum, Maximum	3 significant digits or as needed based on actual measured values
Arithmetic Mean, Geometric Mean, Median	4 significant digits or as needed based on actual measured values
SD	5 significant digits or as needed based on actual measured values
CV%, and Geometric CV%	1 decimal place or as needed based on actual measured values

Mean (± SD) concentration-time profiles, on linear and log-linear scales versus nominal time will be generated.

9.3. PK Parameters Derivation

Only C_{trough}, C_{max}, accumulation ratio, and attainment of steady state for ravulizumab will be reported. No other PK parameters are possible to calculate due to limited sampling schedule.

9.3.1. PK Parameters Summarization

C_{max} and C_{trough} will be summarized descriptively using n, arithmetic mean, SD, CV%, minimum, median, maximum, geometric mean, and geometric CV%.

Accumulation ratio will be calculated for both C_{max} and C_{trough} following the first and last maintenance dose of ravulizumab.

Attainment of steady state will be calculated using the slope, corresponding 95% CI, and P-value of Ctrough values at Days 15, 71, 127, 183, 239, 295, and 351.

The model will be used to assess whether steady state was achieved for ravulizumab where sufficient data are available. Aggregate assessment of trough concentrations by repeated measures ANOVA will be used to evaluate attainment of steady state. The approach is based on the comparison of log-transformed trough concentration values to the mean of the results for all the succeeding doses up to Day 351.

Repeated measures analysis will be carried out on log-transformed trough levels (predose concentrations) for Days 15, 71, 127, 183, 239, 295, and 351.

The example SAS code will be:

```
PROC MIXED DATA=xx;

  CLASS dose time patient_id;

  MODEL log(PK parameter) = treatment treatment*time / DDFM=KR;

  REPEATED / TYPE=UN SUBJECT=patient_id(dose);

  LSMEANS dose*time;

RUN;
```

The DDFM = KR (KenwardRoger) option performs the degrees-of-freedom calculations detailed by Kenward and Roger (1997). As recommended the denominator degrees of freedom for the fixed effects will be estimated as the most appropriate method in the mixed-model analysis.

Contrasts will be tested between a particular time point and the pooled mean over all remaining time points:

Day 15 / the average pre-dose Day 71 through Day 351

Day 71 / the average pre-dose Day 127 through Day 351

Day 127 / the average pre-dose Day 183 through Day 351

Day 183 / the average pre-dose Day 239 through Day 351

Day 239 / the average pre-dose Day 295 through Day 351

Day 239 / the average pre-dose Day 351

The first non-significant comparison will be concluded to be the day number (Day x) at which steady state concentrations are attained. The p-value for difference of Least Square Means (LSM), LSM Ratio, and the 95% confidence interval for the contrasts will be provided.

The precision for the descriptive statistics of PK parameters will follow the same as the aforementioned descriptive statistics of ravulizumab concentration (see Section 9.2.4).

10. Pharmacodynamics

Serum samples will be collected for free and total C5 analyses (before eculizumab dosing) during Screening on Day -57 and Day -29. During the evaluation period serum free and total C5 concentrations will be collected before and after administration of study drug at the timepoints specified in the schedule of assessments (see Section 1.3 of the Protocol). In the event of BTH, a serum sample for PD analysis will be collected. In the event of an unscheduled visit, a PD blood sample will be collected as soon as possible.

Pharmacodynamic analyses will be conducted PD set.

The PD effects of ravulizumab administered IV will be evaluated by assessing the absolute values, and changes and percentage changes from baseline in total and free C5 serum concentrations over time, as appropriate. In addition, mean free C5 concentrations, and number and percentage of participants with free C5 concentrations ≥ 0.5 µg/mL will be presented over time.

Mean (95% CI) for absolute values, change and percentage change from baseline over time will be presented graphically for free and total C5. For free C5 boxplots will also be presented over time.

A by-participant listing will also be produced.

11. Safety

The population used for safety analyses will be the Safety Set. Safety will be assessed on the basis of AE reports, clinical laboratory data, electrocardiogram (ECG) parameters, physical examinations, vital signs, and immunogenicity data, using descriptive statistics.

11.1. Adverse Events

Adverse events will be summarized by SOC and PT for the Safety Set. TEAEs are defined as AEs which commence on or after the first administration of the study drug, or those that occur before first study drug administration but worsen in frequency or severity after first study drug administration. All other AEs are considered PTAE.

TEAEs and PTAEs will be included in the summary tables; separate listings for TEAEs and PTAEs will be produced. Additional listings will be provided for deaths, SAEs, TEAEs leading to study drug withdrawal, TEAEs considered MAVE, and TEAEs of special interest.

Meningococcal infections will be collected as TEAEs of special interest. In addition, a medical review will be done to ensure that no relevant events were missed.

If the relationship to study drug is missing for TEAEs, then the relationship will be counted as related to study product for the summary tables. Missing severity for TEAEs will be counted as Grade 3.

Tables will be sorted by descending frequency of SOC and by descending frequency of PT within SOC, based on MedDRA version 23.1. Participants having multiple AEs within a category (eg, overall, SOC, PT) will be counted once in that category. For severity/relationship tables, the participant's highest grade/most related event within a category will be counted. Percentages will be based on the number of participants in the Safety Set.

An overall summary table of TEAEs will be presented using summary statistics (n, %). The number of events (n) and number of participants with events (n, %) will be displayed for the following events subcategories:

The following tables will be provided:

- *An overall summary of the number and percentage of participants reporting TEAEs, treatment-emergent SAEs (TESAEs), TEAEs leading to death, TEAEs leading to withdrawal of study drug, TEAEs by maxiumum relationship, TESAEs by maximum relationship, TEAEs by maximum Common Terminology Criteria for Adverse Events (CTCAE) grade, TEAEs considered MAVE, TEAEs of special interest, and TEAEs related to COVID-19 infection*
- PTAEs overall and by SOC and PT;
- TEAEs overall and by SOC and PT;
- TEAEs by maximum CTCAE grade, overall and by SOC and PT;
- TEAEs related to study drug, overall and by SOC and PT;
- TESAEs overall and by SOC and PT;
- TESAE related to study drug, overall and by SOC and PT;
- *TEAEs considered MAVE, overall and by SOC and PT.*

- *TEAEs of special interest, by SOC and PT.*
- *TEAEs related to COVID-19, overall and by SOC and PT.*

11.2. Laboratory Evaluations

Safety laboratory samples for hematology, chemistry, urinalysis, and coagulation will be collected by both central and local laboratory at timepoints specified in the schedule of assessments (see sections 1.3 and 10.2 of the protocol).

Descriptive statistics by visit will be presented for each central laboratory parameter and for changes from baseline (continuous variables), for the Safety set. Shift tables over time will be presented for all central laboratory values, where applicable, using normal, low, or high on the basis of normal range values. Individual participant plots as well as boxplots will be presented for the following central laboratory parameters: hemoglobin, haptoglobin, hematocrit, reticulocytes, LDH, bilirubin, direct bilirubin, creatinine, aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transferase.

Furthermore, results of PNH clone during the course of the study will be summarized.

Clinical central laboratory samples that meet the definition of table top hemolysis (TTH) will be identified and all potassium, alanine aminotransferase, aspartate aminotransferase, magnesium, phosphorous, 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 BTH. The TTH samples from the central laboratory will be defined as having serum potassium ≥ 6 mmol/L and LDH ≥ 2 × ULN, and will be listed.

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

11.3. Vital Signs

Systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), and temperature (degree Celsius) will be measured at timepoints as per the schedule of assessment (see Section 1.3 of the protocol). On dosing days vital signs will be taken before study drug administration.

Absolute values and changes from baseline in vital signs will be summarized descriptively at each visit, for the Safety set.

By-participant data listings will be provided.

11.4. ECG

ECG parameters will be measured from a single 12-lead ECG at screening and Day 351/ET visit.

Descriptive statistics by visit will be presented for ECG interpretation (normal, abnormal not clinically significant, and normal clinically significant) each ECG parameter (including PR, QRS, QT, and QTcF), and change from baseline values for the Safety set.

- 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-participant listing of ECG results will be presented.

11.5. Physical Examination

Physical examination will be performed either as complete examination (at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems) or abbreviated examination (at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen [liver and spleen]) at timepoints as per the schedule of assessments (see Section 1.3 of the protocol).

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

Physical examination data will be summarized by visit.

By-participant data listings will be provided.

11.6. Immunogenicity

Antibodies to ravulizumab will be evaluated in serum samples collected predose (within 5 to 90 minutes prior to the start of infusion of study drug) at timepoints as per the schedule of assessments (see Section 1.3 of the protocol). In the event of a BTH, serum samples for ADA analysis will be collected.

All immunogenicity analyses will be conducted on the Safety Set. The number and percentage of participants developing ADA and anti-drug neutralizing antibodies, where applicable, will be summarized for each visit where samples have been collected. A by-participant listing will also be produced.

12. COVID-19 Related Data Analysis

The following COVID-19 related data will be collected in this study:

- *Modified and missed study visits (and COVID-19 related reasons)*
- *Discontinuation (impacted by COVID-19)*
- *COVID-19 Exposure*
- *TEAEs related to COVID-19*
- *Protocol deviations related to COVID-19*

The number of participants with modified study visits and the reasons for modified study visits (COVID-19 related or other) will be summarized. Similarly, the number of participants with missed study visits and the reasons for missed study visits (COVID-19 related or other) will be summarized.

The number and percentage of participants with TEAEs related to COVID-19 will be included in the overall summary of TEAEs.

Protocol deviations related to COVID-19 will be summarized as the overall PDs specified in Section 6.5.

13. Interim Analyses

An interim analysis of the first 10 participants will be conducted on accrued data through Day 183 for publication purposes. All TFLs specified in this SAP will be included in the interim analysis.

14. Changes from Analysis Planned in Protocol

The following changes from the analysis planned in the protocol have been made:

- The formulation of the endpoint defined in section 5.5 of the SAP, section 3 of the protocol, has been changed from “Change in serum ravulizumab concentration over time” to “Serum ravulizumab concentration over time”.
- Enrolled set was added as an analysis set to allow for summaries and listings of participants who are exposed to high dose eculizumab during the screening period but do not subsequently enter the FAS.

15. Reference List

Mallinckrodt CH, Clark WS, David SR. Accounting for dropout bias using mixed-effects models. J Biopharm Stat. 2001;11(1-2):9-21.

Mallinckrodt CH, Kaiser CJ, Watkin JG, Molenberghs G, Carroll RJ. The effect of correlation structure on treatment contrasts estimated from incomplete clinical trial data with likelihood-based repeated measures compared with last observation carried forward ANOVA. Clin Trials. 2004;1(6):477-489.

16. Programming Considerations

All TFLs and statistical analyses will be generated using SAS for Windows, Release 9.4 or higher (SAS Institute Inc., Cary, NC, USA). Computer-generated TFL output will adhere to the following specifications. PK analyses will be conducted using Phoenix™ WinNonlin® (Version 8.0 or higher, Certara Corporation).

16.1. General Considerations

- A separate SAS program will be created for each output
- Each output will be stored in a separate file
- Output files will be delivered as single RTF files and combined PDF files
- Numbering of TFLs will follow ICH E3 guidance

16.2. Table, Figure, and Listing Format

16.2.1. General

- All TFLs will be produced in landscape format on A4 paper size unless otherwise specified.
- All TFLs will be produced using the Courier New font, size 8.
- Data displays for TFLs will have a minimum blank 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TFLs will be in black and white (no color) unless otherwise specified.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters and printer-specific or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (eg, μ). Certain subscripts and superscripts (eg, cm^2, C_{max}) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

16.2.2. Headers and Footers

- All output will have the following header at the top of each page:

```
Alexion INC.          Protocol ALXN1210-PNH-401   (Syneos Health Study Number 7018565)
DRY/DRAFT/FINAL RUN
```

- The date the output was generated will appear along with the program name as a footer on each page

16.2.3. Display Titles

- Each TFL will be identified by the designation and a numeral. (ie, Table 14.1.1). A decimal system (eg, x.y, x.y.z) are used to identify TFLs with related contents. The title will be centered. The analysis set will be identified on the line immediately following the title and will be enclosed in parenthesis. The title and table designation will be single spaced. A solid line spanning the margins will separate the display titles from the Column headers. There will be 1 blank line between the last title and the solid line.

```
Table x.y.z: <Title> – Full Analysis Set
```

16.2.4. Column Headers

- Column headings will be displayed immediately below the solid line described above in initial upper-case characters.
- For numeric variables, include 'unit' in column or row heading when appropriate
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of participants in the analysis set

16.2.5. Body of the Data Display

16.2.5.1. *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values will be left-justified;
- Whole numbers (eg, counts) will be right-justified; and
- Numbers containing fractional portions will be decimal aligned.

16.2.5.2. *Table Conventions*

- Units will be included where available.
- For categorical parameters,all categories will be presented in the table, even if n=0 for all treatment groups in a given category. For example, the frequency distribution for symptom severity would appear as:

Severity	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- An Unknown or Missing category will be added to each parameter for which information is not available for 1 or more participants.
- Unless otherwise specified, the estimated mean and median for a set of values will be printed out to 1 more significant digit than the original values, and SD will be printed out to 2 more significant digits than the original values. The minimum and maximum will be reported with the same significant digits as the original values.
- P-values will be output in the format: '0.xxx', where xxx is the value rounded to 3 decimal places. Every p-value less than 0.001 will be presented as <0.001. If the p-value are less than 0.0001, it will be presented as <0.0001. If the p-value is returned as >0.999, then it will be presented as >0.999.
- Percentage values will be printed to 1 decimal place, in parentheses with no spaces, 1 space after the count (eg, 7 (12.8%), 13 (5.4%)). Values that round down to 0.0 will be displayed as '<0.1'. Unless otherwise noted, for all percentages, the number of participants in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts will not be displayed and percentages equating to 100% will be presented as 100%, without decimal places.
- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of AE data will be presented by the body system, treatment class, or SOC with the highest occurrence in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by PT), drugs (by ATC1 code), and AEs (by PT) will be displayed in decreasing order. If incidence for more than 1 term is identical, they will then be sorted alphabetically.
- Missing descriptive statistics or p-values which cannot be estimated will be reported as '-'.
- For categorical summaries (number and percentage of participants) where a participant can be included in more than 1 category, a footnote or programming note will be added describing whether the participant is included in the summary statistics for all relevant categories or just 1 category as well as the selection criteria.
- Where a category with a subheading (such as SOC) has to be split over more than 1 page, output the subheading followed by '(cont)' at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

16.2.5.3. *Listing Conventions*

- Listings will be sorted for presentation in order of participant number, visit/collection day, and visit/collection time.
- Dates will be printed in SAS DATE9.format ('DD_MMM_YYYY': 01JUL2000). Missing portions of dates will be represented on participant listings as dashes (--JUL2000).
- All observed time values will be presented using a 24-hour clock HH:MM or HH:MM:SS format (eg, 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available.

16.2.5.4. *Figure Conventions*

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (eg, treatment mean change from Baseline) values will be displayed on the Y-axis.

16.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes will always begin with 'Note:' if they are informational footnotes, or 1, 2, 3, etc., if they are reference footnotes. Each new footnote will start on a new line, where possible.
- Participant specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the TFL. If more than 6 lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the ADaM source, the listing source (for tables only), the name of the program used to produce the data display, and the date/time the program was run.

```
Source: ADaM dataset: xxx, Listing: xxxx
Program name: xxxxx.sas, Run date/time: DDMMMYYYY HH:MM
```

- Sources and/or cross-references in footnotes will use the keyword prefix (in singular form) for each reference and will be separated by a comma when mutiple cross-references are displayed.
  Example: Listing 16.2.4.1.1, Listing 16.2.4.1.2, Listing 16.2.4.2.1
- All output will have Page n of N at the bottom right corner of each page. TFLs are internally paginated in relation to the total length (ie, the page number will appear sequentially as page n of N, where N is the total number of pages in the table)

17. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in Syneos Health Developing Statistical Programs SOP (3907) .

Syneos Health Developing Statistical Programs SOP (3907), Conducting the Transfer of Biostatistical Deliverables SOP (3908) and the SAS Programming and Vaidation Plan describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

For PK analysis, PK SOPs of Syneos Health (SOP 2762, and 2767) will be followed.

18. Shells

TFL shells will be provided as a separate document.