STATISTICAL ANALYSIS PLAN

Version Number: 5.0

Protocol Title: A Phase 3, Randomized, Open-label, Active-Controlled Study of ALXN1210 Versus Eculizumab in Complement Inhibitor-Naïve Adult Participants With Paroxysmal Nocturnal Hemoglobinuria (PNH)

Protocol Number: ALXN1210-PNH-301

Protocol Number: Amendment 6

Compound: ALXN1210

Short Title: ALXN1210 (Ravulizumab) Versus Eculizumab in Complement Inhibitor Treatment-Naïve Adult Participants With Paroxysmal Nocturnal Hemoglobinuria (PNH)

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2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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3. LIST OF ABBREVATIONS AND DEFINITION OF TERMS

The following abbreviations and acronyms are used in this statistical analysis plan (SAP).

Table 1: List of Abbreviations and Definitions of Terms

Abbreviation or Acronym	Explanation
ADA	antidrug antibody
AE	adverse event
AESI	adverse events of special interest
AIC	Akaike's information criterion
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BP	blood pressure
BTH	breakthrough hemolysis
C5	complement component 5
CI	confidence interval
COVID-2019	coronavirus disease 2019
cRBC	chicken red blood cell
CSR	clinical study report
ECG	electrocardiogram
eCRF	electronic case report form
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 Scale
EOS	End of Study
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full Analysis Set
FASr	Full Analysis Set for Roll-over Cohort
GEE	generalized estimating equations
HR	heart rate
IV	intravenous(ly)
LDH	lactate dehydrogenase
LDH-N	lactate dehydrogenase normalization
MAVE	major adverse vascular event
MedDRA	Medical Dictionary for Regulatory Activities
NIM	noninferiority margin
OR	odds ratio
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PNH	paroxysmal nocturnal hemoglobinuria
PP	Per Protocol (Set)
pRBC	packed red blood cell
PT	Preferred Term
PTAE	pretreatment adverse event
q8w	once every 8 weeks
QoL	quality of life
QTcF	QT interval corrected using Fridericia's formula
RR	respiration rate
RTS	Ravulizumab-Treated Set
SAE	serious adverse event
SAS®	Statistical Analysis Software®
SAP	statistical analysis plan

Abbreviation or Acronym	Explanation
SOC	System Organ Class
SS	Safety Set
SSr	Safety Set for Roll-over Cohort
TA	transfusion avoidance
TEAE	treatment-emergent adverse event
TTH	table-top hemolysis
ULN	upper limit of normal
WHO-DRUG	World Health Organization Drug Dictionary

4. DESCRIPTION OF THE PROTOCOL

ALXN1210-PNH-301 is a Phase 3, randomized, open-label, active-controlled, multicenter study to evaluate the safety and efficacy of ravulizumab versus eculizumab administered by intravenous (IV) infusion to adult participants with paroxysmal nocturnal hemoglobinuria (PNH) who are naïve to complement inhibitor treatment(hereafter referred to as the Original Study Cohort). In addition, approximately 56 participants may roll over from other ongoing studies of ravulizumab IV in participants with PNH into the Extension Period of Study ALXN1210-PNH-301 (hereafter referred to as the Roll-over Cohort per Protocol Amendment 6 dated 12 Apr 2021.

In the Original Study Cohort approximately 214 eligible participants will be randomized in a 1:1 ratio to one of 2 treatment arms, (1) ravulizumab or (2) eculizumab. Participants will be stratified into 1 of 6 groups based on their transfusion history (0, 1 to 14, or > 14 units of packed red blood cells [pRBCs] in the 1 year prior to the first dose of study drug) and screening lactate dehydrogenase (LDH) levels (1.5 to < 3 × upper limit of normal [ULN] or ≥ 3 × ULN). Enrollment of participants without a history of transfusion in the past year will be capped at 20%.

For participants enrolled directly into ALXN1210-PNH-301 there will be 3 periods in this study: a 4-week Screening Period, a 26-week Primary Evaluation Period, and an Extension Period. Participants randomly assigned to the ravulizumab group will receive a loading dose on Day 1 and maintenance doses on Day 15 and once every 8 weeks (q8w) thereafter. All Roll-over Cohort participants will enroll directly into the Extension Period.

Dosages are based on the patient's body weight, as shown in Table 2.

Table 2: Loading and Maintenance Regimes

Body Weight	Loading Dose (Day 1)	Maintenance Dose (Days 15, 71, 127 and q8w thereafter)
≥40 to <60 kg	2400 mg	3000 mg
≥60 to <100 kg	2700 mg	3300 mg
≥100 kg	3000 mg	3600 mg

Abbreviations: q8w = once every 8 weeks

Participants randomly assigned to the eculizumab group will receive induction treatment with 600 mg of eculizumab on Days 1, 8, 15, and 22, followed by maintenance treatment with eculizumab 900 mg on Day 29 and every 2 weeks (q2w) thereafter for a total of 26 weeks of treatment. After completion of all assessments on Day 183, participants will enter an Extension Period and receive ravulizumab. Beginning on Day 183, participants who had been randomized to the ravulizumab treatment group will receive a maintenance dose (as described above) of ravulizumab q8w, and participants who had been randomized to the eculizumab group will receive a loading dose (as described above) of ravulizumab followed 2 weeks later and q8w thereafter by a weight-based maintenance dose of ravulizumab. In the Roll-over Cohort,

participants will receive weight-based maintenance dosing of ravulizumab q8w from Day 1 of roll over (Table 2).

This SAP outlines the full statistical and analytical plans for participants enrolled directly into Study ALXN1210-PNH-301 as well as safety analysis performed on participants who rolled into Study ALXN1210-PNH-301.

4.1. Study Objectives

Original Study Cohort

The primary objective of this study is to assess the noninferiority of ravulizumab compared to eculizumab in adult participants with PNH who have never been treated with a complement inhibitor. Noninferiority will be claimed if, after 26 weeks of treatment: 1) the lower bound of the 95% confidence interval (CI) for the difference (ravulizumab-eculizumab) in transfusion avoidance (TA) rate is greater than -20%, and 2) the lower bound of the 95% CI for the odds ratio (OR) of ravulizumab compared to eculizumab for LDH normalization (LDH-N) is greater than 0.39.

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

- To characterize the safety and tolerability of ravulizumab in this patient population
- To evaluate the efficacy of ravulizumab by additional efficacy measures
- To characterize the pharmacokinetics (PK)/pharmacodynamics (PD) and immunogenicity of ravulizumab
- To evaluate the long-term safety and efficacy of ravulizumab
- To evaluate the safety and efficacy in participants who switch from eculizumab to ravulizumab in the Extension Period
- To quantify identified specific safety concerns during treatment with ALXN1210, including meningococcal infections, serious hemolysis after drug discontinuation in PNH, immunogenicity, serious infections, malignancies and hematologic abnormalities, and during pregnancy and breastfeeding

Roll-over Cohort

- Long-term safety of participants receiving ravulizumab after rolling over into Study ALXN1210-PNH-301

A clinical study report (CSR) will be produced after the end of the 26-week Primary Evaluation Period (Day 183) and will include efficacy, safety, PK and PD analyses. A final CSR will be produced at study completion and will include data on all participants in the study at the end of the Extension Period, including the Roll-over Cohort.

4.2. Changes From Analyses Specified in the Protocol

In the Original Study Cohort, the approach to control Type 1 error for the coprimary efficacy endpoints and the key secondary endpoints were updated to be consistent with the January 2017 FDA draft guidance "Multiple Endpoints in Clinical Trials Guidance for Industry" and the recently updated (15 Dec 2016) EU draft guidance "Guideline on Multiplicity Issues in Clinical Trials".

Protocol Amendment 3 states that coprimary endpoints individually need to demonstrate noninferiority. Once noninferiority is met superiority of ravulizumab to eculizumab will be assessed using a Hochberg multiple comparison approach for the coprimary endpoints (Hochberg, 1988). Additionally, key secondary efficacy endpoints will be tested in a hierarchical manner provided that noninferiority was declared for the coprimary endpoints. If noninferiority is established for a key secondary endpoint and a larger effect for ravulizumab is observed, then superiority of ravulizumab to eculizumab will be assessed using a 2-sided 0.05 test for each endpoint.

This has been modified in Section 7.2 so that both noninferiority and superiority are tested in a hierarchical manner whereby the lack of significance of a test precludes assessment of subsequent tests.

5. DEFINITIONS

5.1. Efficacy

Efficacy on participants in the Original Study Cohort is evaluated by the following endpoints. No efficacy analyses are planned on the Roll-over Cohort, and all data will be listed as detailed in Section 7.2.3.

5.1.1. Coprimary Efficacy Endpoints

The coprimary efficacy endpoints of the study evaluated at Primary Evaluation Period interim analysis are as follows:

1. Transfusion Avoidance (TA)

   TA is defined as the proportion of participants who remain transfusion-free and do not require a transfusion per protocol-specified guidelines through Day 183 (Week 26). Participants who meet the protocol-specified guidelines for a transfusion, as shown below, will be counted as having received a transfusion, regardless of whether a transfusion was administered. The following are the protocol specified guidelines:

   A pRBC/whole blood transfusion will be administered when a patient has any of the following:

   - Hemoglobin value of 9 g/dL or lower with signs or symptoms of sufficient severity to warrant a transfusion.
   - Hemoglobin value of 7 g/dL or lower regardless of the presence of clinical signs or symptoms.

2. Hemolysis as directly measured by LDH-N levels from Day 29 (first scheduled evaluation status after the initiation of maintenance dosing) through Day 183 (Week 26).

5.1.2. Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints of the study at the Primary Evaluation Period interim analysis (tested in a hierarchical manner) and the End of Study (EOS) analysis respectively (descriptive analysis) are as follows:

1. Percentage change in LDH from Baseline to Day 183 (Week 26), and Baseline to EOS
2. Change in quality of life (QoL) assessed via the Functional Assessment of Chronic Illness Therapy -Fatigue Scale (FACIT-Fatigue), Version 4.0, from Baseline to Day 183 (Week 26), and Baseline to EOS

   The FACIT-Fatigue Scale (Version 4.0) is a collection of QoL questionnaires pertaining to the management of fatigue symptoms due to chronic illness. It is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function over the preceding 7 days. Participants will score each item on a 5-point Likert scale: 0 (not at all) to 4 (very much). The scoring guideline for the FACIT-Fatigue scale will be used to calculate the fatigue score which has a score range of 0-52, with higher

score indicating better QoL. Refer to Section 9.6.1 for additional description and method of calculation.

3. Proportion of participants with breakthrough hemolysis (BTH)

Proportion of participants with 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], major adverse vascular event [MAVE, including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2 × upper limit of normal [ULN], after prior LDH reduction to < 1.5 × ULN on therapy from Baseline to Day 183 (Week 26), and Baseline to EOS.

4. Proportion of participants with stabilized hemoglobin

Proportion of participants with stabilized hemoglobin is defined as avoidance of a ≥ 2 g/dL decrease in hemoglobin level from Baseline in the absence of transfusion through Day 183 (Week 26), and from Baseline to EOS

At EOS, TA, and LDH-N, as described in Section 5.1.1, will be evaluated from Baseline to EOS.

- Proportion of participants who remain transfusion free from Baseline to EOS
- Proportion of participants with LDH in normal range from Baseline to EOS

5.1.3. Other Secondary Efficacy Endpoints

Other secondary efficacy endpoints of the study over time are as follows:

- Change in the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Scale (EORTC-QLQ-C30), Version 3.0, from Baseline to EOS

The EORTC-QLQ-C30, Version 3.0, is a questionnaire developed to assess the QoL of patients with cancer. The questionnaire includes the following subscales: global health status, functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social activity), symptom scales (fatigue, nausea and vomiting, and pain), and single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Thirty questions related to QoL, with the first 28-questions scored on a 4-point scale (1 = not at all to 4 = very much) and the final 2-questions that probe the patient's overall health and QoL scored on a scale of 1 (very poor) to 7 (excellent). Each subscale has a range of 0% to 100%, with a high score representing 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. See Section 9.6.2 for a more detailed description of the EORTC QLQ-C30 and the scoring methods.

- Time to the first occurrence of LDH-N.
- Total number of units of pRBC/whole blood transfused from Baseline to EOS.

A unit of pRBC/whole blood was defined as the volume of pRBC/whole blood that was sufficient to raise the hemoglobin value by approximately 1 g/dL. For Japan and Taiwan, where a unit of pRBC/whole blood contains about half the volume of pRBC/whole blood compared with a "global" unit, each unit of pRBC/whole blood was counted as 0.5 global unit".

- Change in clinical manifestations of PNH (fatigue, chest pain, hemoglobinuria, abdominal pain, dyspnea, dysphagia, and erectile dysfunction) from Baseline to EOS
- Proportion of participants experiencing MAVEs from Baseline to EOS

5.2. Pharmacokinetic/Pharmacodynamic Endpoint

Assessments for PK/PD on the Original Study Cohort and Roll-over Cohort are as follows:

- Serum ravulizumab, and in the Original Study Cohort only eculizumab concentration over time
- Chicken red blood cell (cRBC) hemolytic activity over time (exploratory)
- Free (and total) complement component 5 (C5) concentrations over time

5.3. Safety

Original Study Cohort: The safety and tolerability of ravulizumab compared with eculizumab (up to Week 26) and long-term safety of participants on ravulizumab (until EOS) will be evaluated by physical examinations, vital signs, electrocardiograms (ECGs), laboratory assessments, and incidence of adverse events (AEs) and serious adverse events (SAEs). The proportion of participants who developed antidrug antibodies (ADAs) will also be assessed.

Roll-over Cohort: The long-term safety of participants on ravulizumab after their roll over into the Extension Period of Study Roll-overALXN1210-PNH-301 will be evaluated by the incidence of AEs and SAEs, laboratory assessments, and the proportion of participants who develop ADA. Vital signs, ECG, weight, and physical abnormality will also be evaluated.

5.3.1. Adverse Events

An AE is any untoward medical occurrence in a patient administered with a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE therefore is defined as any unfavorable or unintended sign (eg, including 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 version 4.03 or higher.

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
- 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
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE

AEs are further defined in Protocol Section 11.7. Of note, related AEs will be defined as AEs that are possibly, probably, or definitely related to study treatment. Not related AEs are AEs that are unlikely or not related to study treatment.

5.3.2. Vital Signs

Vital signs will include assessments of systolic and diastolic blood pressure (BP), temperature, respiratory rate (RR), and heart rate (HR). Systolic and diastolic BPs will be documented in millimeters of mercury. 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.

5.3.3. Laboratory Assessments

Samples for analysis of serum pregnancy, hematology, chemistry, coagulation, and urinalysis will be collected (See Appendix F of the protocol for a listing of all clinical laboratory parameters). If a suspected event of BTH does not occur at a scheduled visit, an unscheduled visit must take place at which a sample is collected for analysis of LDH, PK and PD parameters by the central laboratory. A central laboratory will be used to evaluate all laboratory assessments.

5.3.4. Electrocardiograms

A single 12-lead ECG will be conducted. HR, PR, QRS, and QT will be measured and QT interval corrected using the Fridericia formula (QTcF)) and RR will be calculated.

5.3.5. 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 on Investigator judgment and participant symptoms.

For the Roll-over Cohort only an abbreviated physical examination will be performed.

5.3.6. Immunogenicity

Blood samples will be collected to test for the presence and titer of ADAs to ravulizumab or eculizumab. Further characterization of antibody responses may be conducted as appropriate, including binding and neutralizing antibodies, PK/PD, safety, and activity of ravulizumab or eculizumab.

6. DATA SETS ANALYZED (STUDY POPULATIONS)

6.1. Full Analysis Set

Original Study Cohort: The Full Analysis Set (FAS) will consist of all participants who received at least 1 dose of ravulizumab or eculizumab and have at least 1 efficacy assessment after the first infusion.

Roll-over Cohort: The Full Analysis Set for Roll-over Cohort (FASr) will consist of all rolled over participants who received at least 1 dose of ravulizumab and have at least 1 efficacy assessment after the first infusion in Study ALXN1210-PNH-301.

The population for assessment of efficacy and PD is the FAS/FASr. In the Original Study Cohort, participants will be analyzed for efficacy according to the treatment they were randomized to receive, regardless of the treatment they actually received.

6.2. Per Protocol (PP) Set

Original Study Cohort: The Per Protocol (PP) Set will consist of FAS participants who meet all of the following criteria based on data from the Primary Evaluation Period:

- Missed 0 doses of ravulizumab ≤ 1dose of eculizumab during the 26 weeks of Primary Evaluation Period
- Met following inclusion criteria:
  - No. 2: documented diagnosis of PNH
  - No. 3: presence of 1 or more PNH-related signs or symptoms within 3 months of Screening
  - No. 4: LDH level ≥1.5× ULN at Screening
- Did not meet exclusion criteria:
  - No. 1: current or previous treatment with a complement inhibitor
  - No. 2: Platelet count<30000/mm^3 at Screening
  - No. 3: Absolute neutrophil count <500/μL at Screening
  - No. 4: History of bone marrow transplantation
- Never received the wrong randomized treatment (ie, all participants who received assigned treatment) during the 26-week Primary Evaluation Period
- Followed the protocol-specified transfusion guidelines during the 26-week Primary Evaluation Period

The coprimary efficacy endpoint analyses, as well as key secondary endpoint analyses prepared at the 26-week Primary Evaluation Period interim analysis will be performed on the PP Set as a sensitivity analysis.

6.3. Safety Set

Original Study Cohort

The Safety Set (SS) will consist of all participants who received at least 1 dose of ravulizumab or eculizumab. Participants will be analyzed for safety according to the treatment they actually received during the Primary Evaluation 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 their study drug exposure visits in the Primary Evaluation Period. Safety analysis will be performed on the SS, except for analyses based on Entire Study Period during ravulizumab exposure, which will use the Ravulizumab Treated Set (RTS; refer to Section 6.4).

Roll-over Cohort

The Roll-over Safety Set (SSr) will consist of all participants who rolled over and received at least 1 dose of ravulizumab in Study ALXN1210-PNH-301.

6.4. Other Sets

Original Study Cohort

In the Original Study Cohort , PK Set will consist of all participants who received at least 1 dose of study drug and who have evaluable PK data. Note, during interim it will be at least 1 dose of eculizumab for participants randomized to eculizumab, and at EOS analysis it will be 1 dose of either eculizumab or ravulizumab.

Ravulizumab Treated Set (RTS) will consist of all participants who received at least 1 dose of ravulizumab and will be used for analyses performed on the Original Study Cohort.

Roll-over Cohort

The Roll-over PK Set (PKr) will consist of all rolled over participants, who received at least 1 dose of ravulizumab and who have evaluable PK data in Study ALXN1210 PNH 301.

7. STATISTICAL ANALYSIS

All data collected in this study will be presented using summary tables, figures, and data listings. All analyses will be performed using Statistical Analysis Software (SAS®) release, Version 9.4 or higher (SAS Institute Inc., Cary, NC, USA), or other validated statistical software.

Continuous variables will be summarized using descriptive statistics, including number of observations and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by frequency counts and percentage of participants.

In the Original Study cohort, formal hypothesis testing of efficacy on ravulizumab compared to eculizumab treatment with regard to the coprimary and key secondary efficacy endpoints will be performed at the Primary Evaluation Period interim analysis. The formal analysis and associated subgroup analysis will not be rerun at EOS. The long-term ravulizumab efficacy analyses at EOS will be analyzed descriptively over time and include all data until the end of the Extension Period.

The Roll-over Cohort consists of participants from 3 ravulizumab PNH studies: 2 in adult participants and 1 in pediatric participants. All adult data will be pooled for reporting and presented side-by-side with the pediatric data, along with the overall total (adult and pediatric data combined). Participants in the pediatric study who are ≥ 18 years of age at the time of informed consent into Study ALXN1210-PNH-301 will be considered as adults in Study ALXN1210-PNH-301 reporting. All data collected from the Roll-over Cohort will be listed.

Analyses on the Roll-over Cohort will be performed separately from the Original Study Cohort.

Clinical central laboratory samples that meet the definition of tabletop hemolysis (TTH) will be identified and all potassium, alanine aminotransferase (ALT), aspartate aminotransferase (AST), 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. TTH samples from the central laboratory will be defined as having serum potassium ≥ 6 mmol/L and LDH ≥ 2× ULN.

Original Study Cohort

Randomization was stratified using transfusion history (0, 1 to 14, or > 14 units pRBCs in the 1 year prior to the first dose of study drug) and screening LDH levels (1.5× to < 3 [×ULN] or ≥ 3× ULN)]. If, at the end of enrollment, < 5% of participants in any of the 5 strata within a treatment arm, that strata will be pooled with the adjacent strata. If the middle category of 1 to 14 units transfused had < 5% of the participants within a treatment arm, that category would be grouped with the > 14 units. Additionally, if there are small number of participants in any of the 6 combined strata, collapsing will be undertaken, as appropriate. For applicable analyses and summaries, the randomization stratification variables refer to the observed transfusion history and LDH levels and pooled stratification variables.

Data Presentation

Summaries will be prepared using analysis visit windowing, except for PK/PD data where nominal visit will be used. Summaries based solely on Primary Evaluation Period will be summarized by treatment groups ravulizumab or eculizumab. Data summarized through to EOS will be presented by treatment sequences; ravulizumab to ravulizumab or eculizumab to ravulizumab; the former denoting the treatment participants were randomized to, and the latter represents the treatment received in the Extension Period. All assessments on Day 183 will be performed prior to dosing, and dosing on Day 183 will be regarded as the start of the Extension Period. In the Extension Period all participants receive ravulizumab, thus pooled results from both treatment sequences will be provided as the total and hereafter referred to as the total. All data will be listed by treatment sequence.

Safety summary data, such as AEs and concomitant medications will be reported on the Primary Evaluation Period by treatment group (ravulizumab or eculizumab). AE summaries analyzing data after the first ravulizumab infusion by Period (Period 1 to 6, the Entire Extension Period, and the Entire Study Period) will be prepared on all data.

Study Periods

The following periods will be considered for study analysis:

- Primary Evaluation Period – also referred to as Period 1 (data through Day183 Visit)
- Period 2: > 6 to 18 months in study
- Period 3: > 18 to 30 months in study
- Period 4: > 30 to 42 months in study
- Period 5: > 42 to 54 months in study
- Period 6: > 54 months in study
- Entire Extension Period : Periods 2 to 6
- Entire Study Period (Day 1 through the EOS [ie, Primary Evaluation Period + Extension Period]. Of note, this period is utilized for reporting data during ravulizumab exposure (ie, data after the participant's first ravulizumab infusion in the study).

Baseline Definition

The analysis through to EOS utilizes 2 baselines:

- **Period 1 Baseline** defined as the last available assessment prior to the first study drug infusion (eculizumab or ravulizumab), except for LDH. For LDH data, it is the average of all available assessments (including unscheduled) prior to the first study drug infusion. In general, the Baseline assessment will be the Day 1 assessment. If the Day 1 assessment is missing, the Screening assessment will be used as the Baseline assessment.

- **Period 2 Baseline** defined as the last available assessment prior to Day 183 study drug infusion, except for LDH. For LDH data, it is the average of all pre-dose assessments (including unscheduled) at Day 183 visit. For the switch cohort Day 183 doing is the first dose of ravulizumab.

Of note, the stabilized hemoglobin endpoint will be assessed within each period and decreases in hemoglobin level are evaluated with respect to the last hemoglobin assessment value in the period prior to the start of the period analyzed. For example, for Period 3 analysis, the Baseline will be the last value obtainable from Period 2.

Roll-over Cohort

Nominal visits will be used for all analysis. Data summaries will be presented on ravulizumab treatment by population (ravulizumab −- adults and ravulizumab − pediatrics).Pediatrics are defined as participants < 18 years of age at the time of signing consent in Study ALXN1210-PNH-301. The total, whereby adult and pediatric data is combined will also be provided. All listings will include the parent study patients rolled over from.

Baseline is defined as the last assessment prior to the first infusion of study drug infusion after rolling over into Study ALXN1210-PNH-301, except for LDH, which is the average of all assessments (including unscheduled)prior to the first study drug infusion in Study ALXN1210-PNH-301.

The **Entire Study Period** is defined as Day 1 of rolling over into Study ALXN1210-PNH-301 through to the EOS Visit.

7.1. Participants

7.1.1. Disposition of Participants

Original Study Cohort

A summary of participant disposition will be presented on the Primary Evaluation Period, Extension Period, and the Entire Study Period.

A summary of patient disposition will include the number and percentage of screened participants, screen failures, randomized participants, treated participants and who completed the study.

Primary Evaluation Period disposition: All treated participants will be presented by treatment group and will include a summary of the number and percentage of screened participants, screen failures, randomized and treated participants. The number and percentage of participants who completed the Primary Evaluation Period or discontinued/withdrew (treatment and study) during this period, along with reason for discontinuation/withdrawal will be presented.

A table summarizing the above information by country and by region separately will be provided. Region will be defined based on study sites at which participants received study drug and will include North America, Europe, Japan, and the rest of Asia Pacific and Latin America.

Extension Period Disposition: The number and percentage of participants entering the Extension Period, and who completed or discontinued in this period will be presented. Study and treatment discontinuation in this period will be presented, along with the reasons and whether the discontinuation was coronavirus disease 2019 (COVID-19) related. At the start of the COVID-19 pandemic, all participants were in the Extension Period of the study.

Entire Study Period: The number and percentage of participants randomized who completed the study, discontinued the study prematurely (if COVID-19 related) and discontinued study treatment will be presented. Reasons for study and treatment discontinuation will be provided.

Roll-over Cohort

The number and percentage of participants rolling into the Extension Period, and who completed or discontinued will be presented. Reasons for study discontinuation and treatment discontinuation will be provided, along with whether the discontinuation was COVID-19 related.

A table summarizing the above information by country and by region separately will be provided. Region will be defined based on study sites at which participants received study drug and will include North America, Europe, Japan, and the rest of Asia Pacific and Latin America

The number and percentage of participants in each analysis set will be tabulated separately for the Original Study Cohort and Roll-over Cohort.

By-patient data listings of disposition data will be provided, a flag indicating whether the disposition was COVID-19 related will be added. Patient listings of those who did not meet the inclusion/exclusion criteria for the Original Study Cohort and Roll-over Cohort will be prepared.

For the Original Study Cohort and Roll-over Cohort, a summary of the number and percentage of participants with COVID-19 exposure during the study will be provided separately on the SS and SSr, respectively. By-participant listings of participants with COVID-19 exposure will be prepared.

7.1.2. Protocol Deviations

Original Study cohort: Important protocol deviations, including COVID-19 related important protocol deviations will be summarized during the Primary Evaluation Period by treatment groups and Entire Study Period during ravulizumab exposure by treatment sequence. Data will be tabulated and listed for all participants in the FAS. The number of participants with the following programmed protocol deviations during the Primary Evaluation Period will also be summarized separately on the FAS:

- Informed consent date is not prior to screening start date
- Participants not meeting all of the inclusion/exclusion criteria
- Participants whose granulocyte or monocyte clone size is not ≥ 5%

- Participants whose screening LDH is < 1.5 × ULN or missing
- Participants whose platelet count is < 30000/mm^3 (30 × 10^9/L) or absolute neutrophil count is < 500/μL (0.5 × 10^9/L) at Screening
- Participants who had a history of bone marrow transplantation
- Participants with no PNH signs or symptoms prior to Screening
- Participants whose body weight < 40 kg at Screening
- Participants who missed 1 or more doses of ravulizumab or 2 or more doses of eculizumab
- Participants who did not receive study drug in accordance with the randomization schedule.
- Participants who did not follow protocol-specified transfusion guidelines after initiating study drug.

  Participants with no confirmation of vaccination against meningococcal infections within 3 years prior to, or at the time of, initiating study drug.

Roll-over Cohort: A listing of protocol deviation in Study ALXN1210-PNH-301 will be prepared on the SSr.

7.1.3. Demographics, Disease Characteristics, and History

Original Study Cohort: All demographic and baseline characteristics information will be summarized using the FAS and SS. Summary statistics will be presented by treatment sequence and overall. Demographic and baseline characteristics will also be summarized by treatment sequence and stratification groups for the FAS and SS. By-patient listings of demographic information, disease characteristics, PNH medical history and medical/surgical history, will be produced.

Roll-over Cohort: All demographic data will be summarized on the SSr by population and overall. By-patient listings of the demographic and medical history data will be provided.

7.1.3.1. Demographics

The following demographic variables will be summarized on FAS and SS for the Original Study Cohort and on the SSr for the Roll-over Cohort. Demographics for the Roll-over Cohort are based on data collected after informed consent in Study ALXN1210-PNH-301.

- Sex
- Race, including the number (%) of participants of Japanese descent
- Ethnicity

- Age (years) at first infusion: descriptive statistics (n, mean, median, SD, minimum, maximum) and frequency of participants in the following categories:

  Original Study Cohort: 18 to ≤ 65, > 65, 18 to < 65, 65 to < 85, ≥ 65, and ≥ 85 years Roll-over Cohort (age at first infusion in Study ALXN1210-PNH-301): 2 to <1 2, 12 to < 18, 18 to < 65, ≥ 65, and ≥ 85 years.

- Baseline weight: descriptive statistics (n, mean, median, SD, minimum, maximum) and frequency of participants in the following categories:

  Original Study Cohort: ≥ 40 to < 60 kg, ≥ 60 to < 100 kg, and ≥ 100 kg

  Roll-over Cohort: ≥ 5 to < 10, ≥ 10 to < 20, ≥ 20 to < 30, ≥ 30 to < 40, ≥ 40 to < 60, ≥ 60 to < 100, and ≥ 100 kg

- Baseline height
- Baseline body mass index
- LDH randomization stratification (for the Original Study Cohort)
- pRBC randomization stratification (for the Original Study Cohort)

7.1.3.2. Disease Characteristics and PNH Medical History

The following PNH disease characteristics for the Original Study Cohort will be summarized on the FAS and SS:

- Age (years) at PNH diagnosis.
- Method of PNH diagnosis.
- Years from PNH diagnosis to informed consent.
- PNH clone size at Screening.
- pRBC/whole transfusion requirements in the year prior to receiving study drug including the number of transfusion episodes and units transfused. Summary will be repeated on the transfusions received 6 months prior to the first study drug infusion.
- 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.
- Prior emergency room or hospitalizations due to PNH prior to informed consent, including admittance and number of days in intensive care unit and discharge diagnosis in addition to PNH.
- History of any MAVE. The number of participants (n, %) with any history of MAVE and within a particular MAVE category (eg, thrombophlebitis/deep vein thrombosis, pulmonary embolus, and myocardial infraction) will be displayed. The number of pretreatment MAVE events will be summarized along with MAVE incidence rate per 100 patient-years.

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

7.1.3.3. Medical/Surgical History and Baseline Physical Examination

Original Study Cohort: 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.

Roll-over Cohort : All medical history and physical examination data will be listed on the SSr. Clinically significant AEs and SAEs (ended or ongoing in parent study) will be entered as medical history in Study ALXN1210-PNH-301.

7.1.4. Prior and Concomitant Medications / Therapies

Original Study Cohort

Prior medications will be summarized by treatment group and defined as medications taken prior to the first study infusion and include all medications taken within 28 days prior to informed consent and Neisseria meningitides vaccinations administered within 3 years of dosing with ravulizumab or eculizumab. Concomitant medications are defined as medications received by the participants on/after the first study infusion through 56 days after the participants' last dose, including those that were started prior to the first study drug infusion and continued after the first study drug infusion.

Summaries of concomitant medications on the Primary Evaluation Period based on the SS (by treatment and overall), and Entire Study Period during ravulizumab exposure based on RTS (by treatment sequence and overall) will be provided. Similarly, a summary of concomitant medications used by $\geq 5\%$ of the overall participants during the Primary Evaluation Period and Entire Study Period during ravulizumab exposure will be provided.

Medication summaries will be presented with the overall number and percentage of participants using prior and concomitant medications by WHO-DRUG Anatomical Therapeutic Chemical (ATC) Level 3 and by World Health Organization Drug Dictionary (WHO-DRUG) generic name. Nonpharmalogical therapies and procedures used during the study will be summarized similarly, but by MedDRA class and PT. Tables will be sorted based on the overall column by descending frequency of ATC level and by descending frequency of generic name within an ATC.

By-patient listings of these data will be provided separately. A by-patient listing of Neisseria meningitides will be produced showing the date of vaccinations for each patient.

Roll-over Cohort

All ongoing medications in the parent study will be entered into Study ALXN1210-PNH-301. Concomitant medications are defined as medications received on/after the first infusion in Study ALXN1210-PNH-301. A listing of all concomitant medications will be provided on the SSr.

History of meningococcal vaccination collected 3 years prior to the first dose of ravulizumab in Study ALXN1210-PNH-301 will be listed, along with the date of vaccination for each patient.

7.2. Efficacy Analyses

The efficacy section applies to the Original Study Cohort, efficacy analyses are not planned on the Roll-over Cohort, however, data collected will be listed.

Sections 7.2.1 and 7.2.2 pertain to the efficacy evaluated at the Primary Evaluation Period interim analysis, including formal analyses performed on the coprimary and key secondary efficacy endpoints. This analysis and associated subgroup analysis will not be reproduced at the EOS. Section 7.2.3 described the analyses to be performed at the EOS.

All efficacy analysis will be performed using the FAS. The formal analyses testing efficacy of ravulizumab to eculizumab with respect to the coprimary efficacy endpoint analyses, as well as key secondary endpoint analyses, will be repeated using the PP Set as a sensitivity analysis at interim analysis.

7.2.1. Coprimary Analysis

The coprimary efficacy endpoints are 1) the difference between treatment groups in the proportion of participants who achieved TA through Day 183, and 2) the relative effect between treatments in LDH-N from Day 29 through Day 183 expressed as an OR.

7.2.1.1. Transfusion Avoidance Primary Analysis (Primary Evaluation Period)

TA will be achieved only by those participants who did not receive a transfusion and did not meet the protocol-specified guidelines for transfusion up to Day 183. A difference in the percentage of participants achieving TA will be calculated between ravulizumab and eculizumab treatment groups, along with a 95% CI for the difference using the stratified Newcombe CI method (Yan, 2010). The difference between the treatment groups will be computed as a weighted combination of the differences between the ravulizumab and eculizumab treatment groups within the stratification groups of transfusion history (0, 1 to 14, or > 14 units pRBCs in the 1 year prior to the first dose of study drug) and screening LDH levels (1.5× to < 3 × ULN or ≥ 3× ULN)] using Mantel-Haenszel weights (Agresti, 2013). The CI will be computed using the common risk difference. The lower bound of this 95% CI will be used for the determination of noninferiority of ravulizumab to eculizumab as described in Section 4.1. Participants who withdrew from the study due to lack of efficacy during the Primary Evaluation Period will be considered as nonresponder and will be counted in the group requiring transfusions. For participants who withdrew from the study for any other reasons during the Primary Evaluation Period, their data up to the time of withdrawal will be used to assess TA.

7.2.1.2. (LDH-N Primary Analysis (Primary Evaluation Period)

The number (%) of participants achieving LDH-N will be summarized at all study visits in the Primary Evaluation Period. LDH-N will be analyzed using a generalized estimating equation (GEE) approach that accounts for the repeated measures of LDH-N assessment at each visit (Liang, 1986). The GEE approach provides OR and CIs of the treatment effect while controlling for the correlation between visits for a given patient and other baseline factors. LDH-N from Day 29 through Day 183 will be used as the dependent variable and an indicator variable for treatment, history of transfusion (as a categorical variable based on the stratification factor levels), and baseline LDH level (as a continuous variable) will be included in the model as explanatory variables. The within-participant correlation will assume to follow a first-order autoregressive structure in which the highest correlation is assumed between visits that are closest in time. Day 29 is the first scheduled assessment after the initiation of maintenance dosing, and experience with eculizumab and Phase 1b/2 ravulizumab data demonstrates near maximal suppression of LDH by 4 weeks of treatment. The lower bound of the 95% CI will be used for the determination of noninferiority of ravulizumab to eculizumab as described in Section 4.1. Missing assessments of LDH for a particular participant at a particular visit will not be imputed.

7.2.1.3. Handling of Dropouts or Missing Data (Primary Evaluation Period)

For the coprimary endpoint of proportion of participants who achieved TA through Day 183, participants who withdrew from the study due to lack of efficacy during the Primary Evaluation Period will be considered as nonresponder and will be counted in the group requiring transfusions. For participants who withdrew from the study for any other reasons during the Primary Evaluation Period, their data up to the time of withdrawal will be used to assess TA.

For the coprimary endpoint of LDH-N, missing assessments of LDH for a particular participant at a particular visit will not be imputed.

Missing data for QoL instruments will be handled as specified in the instructions for each instrument (see also Section 9.6).

Missing data for secondary endpoints will be handled as specified in Section 7.2.2.

7.2.1.4. Subgroup Analysis (Primary Evaluation Period)

Summaries of TA and LDH-N will be produced for the subgroups of the randomization stratification variables of transfusion history (0, 1 to 14, or > 14 units of pRBCs transfused in the 1 year prior to first dose of study drug) and screening LDH levels (1.5 to < 3 × ULN or ≥ 3 × ULN). Analyses of LDH-N using GEE will include history of transfusion (as a categorical variable based on the stratification factor levels).

The percentage of participants who achieve TA with 95% exact CIs will be computed for both the ravulizumab and eculizumab treatment groups by randomization strata. Estimates for the

treatment difference in the response rate (with 95% exact CIs) for ravulizumab minus eculizumab will be derived for each stratum.

Summaries of the coprimary endpoints of TA and LDH-N and the key secondary endpoints will also be produced for subgroups based on sex, race, region and age at the first study drug infusion (18 to 65 years and > 65 years).

7.2.1.5. Multicenter Studies

Although this is a multicenter study, a very small number of participants are anticipated at each study site. As such, the study center will not be used as an explanatory factor in the efficacy analyses.

7.2.1.6. Hypothesis Testing and Significance Level (Primary Evaluation Period)

For the coprimary efficacy endpoints, the 2-sided 95% CI of the treatment effect will be calculated. If noninferiority of ravulizumab to eculizumab is met for both coprimary endpoints, key secondary endpoints will be tested for noninferiority using a closed-testing procedure with the following order so that the lack of significance of a test precludes assessment of subsequent tests:

1. Percentage change from Baseline to Day 183 (Week 26) in LDH
2. Change from Baseline to Day 183 (Week 26) in FACIT-Fatigue
3. Proportion of patient with BTH through Day 183 (Week 26)
4. Proportion of participants with stabilized hemoglobin through Day 183 (Week 26)

If noninferiority of ravulizumab to eculizumab is established for all key secondary endpoints, then superiority of ravulizumab compared to eculizumab will be assessed using a closed-testing procedure with the following order and using a 2 sided 0.05 test for each parameter:

5. Proportion of participants with BTH through Day 183 (Week 26)
6. Percentage change from Baseline to Day 183 (Week 26) in LDH
7. Hemolysis as directly measured by LDH-N from Day 29 through Day183 (Week 26)
8. Change from Baseline to Day 183 (Week 26) in FACIT-Fatigue
9. Proportion of participants with stabilized hemoglobin through Day 183 (Week 26)
10. TA

Under this prespecified closed testing procedure, no adjustment of the Type 1error is required.

For the key secondary endpoints, 2-sided 95% CI of the treatment difference of ravulizumab minus eculizumab will be calculated. Point estimates and 95% CIs will be computed for all these key secondary efficacy endpoints regardless of hierarchical testing procedure.

7.2.1.7. Sensitivity Analyses (Primary Evaluation Period)

The following sensitivity analyses will be produced for the coprimary endpoints of TA and LDH-N:

- The coprimary efficacy endpoint analyses as described in Section 7.2.1 will be repeated using the PP Set.
- The coprimary efficacy endpoint analyses as described in Section 7.2.1 will be repeated on the FAS set using the following categorization of pRBC transfusion in the year prior to the first dose of study drug: 0, 1 to 4, > 4 to 14, and > 14 units.

The following sensitivity analyses will be produced for the coprimary endpoint of TA:

- TA will be analyzed as described in Section 7.2.1. However, TA will be defined as achieved only by those participants who did not receive a transfusion (ie, ignoring protocol-specified guidelines for transfusion).
- 95% CIs for the difference between ravulizumab and eculizumab TA rates ignoring the randomization strata and using Newcombe CI will be calculated.

The following sensitivity analyses will be produced for the coprimary endpoint of LDH-N:

- GEE as described for the primary endpoint excluding the history of transfusion stratification factor, and baseline LDH level (as a continuous variable) from the model as explanatory variables. Results from the model will be presented as ORs with 95% CIs.
- GEE as described for the primary endpoint with history of transfusion as a continuous variable.
- Weighted GEE as described for the primary endpoint to account for dropouts under the missing at random assumption.

For each patient, the median of LDH values from Day 29 through Day 183 will be categorized using the ULN as being below the ULN or not and the proportion of participants whose median LDH from Day 29 through Day 183 normalizes (LDH-N) will be summarized by treatment group. A difference in the percentage of participants achieving LDH-N will be calculated between ravulizumab and eculizumab treatment groups, along with a 95% CI for the difference using the stratified Newcombe CI method (Yan, 2010). The difference between the ravulizumab and eculizumab treatment groups will be computed as a weighted combination of the differences between the ravulizumab and eculizumab treatment groups within the stratification groups using Mantel-Haenszel weights (Agresti, 2013). The CIs will be computed using the common risk difference approach of Newcombe.

7.2.2. Secondary Analyses

7.2.2.1. Key Secondary Efficacy Analyses (Primary Evaluation Period)

Key secondary endpoints will be tested in a hierarchical manner for noninferiority followed by superiority following the order described in Section 7.2.1.6.

Point estimates and 95% CIs will be computed for all key secondary efficacy endpoints for descriptive purposes, regardless of whether a lack of significance of a test precludes assessment

of subsequent tests. Refer to Section 9.4 for details around the choice of noninferiority margin (NIM). Refer to Section 9.6.1 for a more detailed description of the FACIT-Fatigue score and the scoring methods.

The secondary endpoints that involve percentage change from Baseline (LDH) and change from Baseline (FACIT-Fatigue) will be analyzed as follows:

Absolute levels, and the change and percent change in FACIT-Fatigue (and LDH) will be summarized by randomization strata and by treatment group at Baseline and at the study visits where these assessments are collected up to Day 183 (Week 26).

Change in FACIT-Fatigue (and percent change in LDH) from Baseline to Day 183 (Week 26) will be analyzed using an MMRM (Mallinckrodt, 2001; Mallinckrodt, 2004) with the fixed categorical effects of treatment, the stratification randomization indicators of transfusion history (0, 1 to 14, or > 14 units of pRBCs in the 1 year prior to the first dose of study drug) and screening LDH levels (1.5× to < 3× ULN or ≥ 3× ULN), study visit and study visit by treatment group interaction, and with the continuous fixed covariates of baseline FACIT-Fatigue (or LDH).

For percent change in LDH, the baseline LDH level as a continuous variable will be included. An unstructured covariance matrix will be used to model the within-patient errors. If this analysis fails to converge, the following structures will be tested and the final covariance structure will be determined by Akaike's information criterion (AIC); the lowest AIC denoting the best model; first-order autoregressive, compound symmetry, and Toeplitz method. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. A difference between the ravulizumab and eculizumab treatment groups, along with a 2-sided 95% CI will be calculated. The missing LDH or FACIT-Fatigue for a patient at a particular visit will not be imputed. If the upper bound of the 95% CI for the difference between the ravulizumab and eculizumab treatment groups in the percentage change from Baseline to Day 183 (Week 26) in LDH is less than the NIM of 20%, then ravulizumab will be declared noninferior for this parameter. If the lower bound of the 95% CI for the difference between the ravulizumab and eculizumab treatment groups in change from Baseline in FACIT-Fatigue to Day 183 (Week 26) is greater than the NIM of -5, then ravulizumab will be declared noninferior for this parameter.

The same approach using the stratified Newcombe CI method as described for the primary analysis of TA will be employed for the key secondary endpoints of BTH and stabilized hemoglobin. If this method fails to provide estimates of CIs, the exact common risk difference method will be utilized in computing the CIs. If the rate of BTH is 0 in both treatment arms whereby CIs cannot be estimated, ravulizumab will be declared noninferior for this parameter and superiority will not be tested. Similarly, if the rate of stabilized hemoglobin is 100% in both treatment arms whereby CIs cannot be estimated, ravulizumab will be declared noninferior for this parameter and superiority will not be tested. Participants who withdrew from the study due to lack of efficacy during the Primary Evaluation Period will be considered as nonresponders and will be counted in the group with BTH or in the group who did not meet the stabilized hemoglobin definition. For participants who withdraw from the study for any other reason during the Primary Evaluation Period, their data up to the time of withdrawal will be used to assess the key secondary endpoints of BTH and stabilized hemoglobin. If the upper bound of the 95% CI for the difference between the ravulizumab and eculizumab treatment groups in the proportion of participants with BTH through Day 183 (Week 26) is less than the NIM of 20%, then ravulizumab will be declared noninferior for this parameter. If the lower bound of the 95%

CI for the difference between the ravulizumab and eculizumab treatment groups in the proportion of participants with stabilized hemoglobin through Day 183 (Week 26) is greater than the NIM of -20%, then ravulizumab will be declared noninferior for this parameter.

At each study visit, the proportion of participants who showed an improvement of at least 3 points for the FACIT-Fatigue will be summarized by treatment group using the same approach used for the coprimary endpoint of TA.

7.2.2.2. Other Secondary Efficacy Analyses (Primary Evaluation Period)

Absolute values and changes from Baseline in EORTC-QLQ-C30 subscales will be summarized by treatment group at Baseline and at the study visits where these assessments are collected. At each study visit, the proportion of participants who showed an improvement of at least 10 points for the following 3 subscales from the EORTC QLQ-C30 will be presented: global health status, physical functioning, and EORTC-Fatigue). Refer to Section 9.6.2 for a more detailed description of the EORTC QLQ-C30 and the scoring methods.

Shifts from Baseline in clinical manifestations of PNH will be summarized by treatment group and at the study visits where these assessments are collected.

Pretreatment and treatment-emergent MAVE rates through Day 183 (Week 26;number per 100 patient-years) along with patient- years of follow up and number of MAVEs will be displayed by treatment group. Patient-years of follow-up prior to initiating treatment with study drug are defined as follows:

(First study drug dose date - initial PNH diagnosis date + 1) / 365.25

Patient-years of follow-up after initiating treatment with study drug are defined as follows:

(Day183 / discontinuation / death date-first study drug dose date +1) / 365.25

MAVE rates based on 100 patient-years of follow-up will be calculated as the number of participants with MAVE in the particular treatment group × 100 (years) divided by the total patient-years of follow-up for that particular treatment group.

Total number of units of pRBCs transfused through Day 183 (Week 26) will be summarized by the treatment group.

Kaplan-Meier curves for both treatment groups and the randomization strata and estimates of time from first study drug to the first occurrence of LDH-N since the first study drug will be produced. Participants who did not achieve LDH-N by the end of the Primary Evaluation Period or who were lost to follow up will be censored at the date of Day 183 Visit or the date of the last contact.

No statistical testing of these parameters is planned.

By-participant data listings containing all secondary endpoints will be produced.

7.2.3. Efficacy Analyses at the EOS

Original Study Cohort

Long-term ravulizumab efficacy analyses will be evaluated on the FAS and include all data until the end of the Extension Period. Results from the Primary Evaluation Period will be presented, but no formal statistical testing of ravulizumab versus eculizumab efficacy will be performed as part of the final EOS analyses.

Analyses will be reported descriptively at each visit or within each period by treatment sequence, and total where specified. Visits in the Extension Period will be evaluated for changes from Period 1 and 2 Baselines as defined in Section 5.1. Analyses by period will report Periods 1 to 6, and the Entire Extension Period as defined in Section 7.

All efficacy data will be listed. The following endpoints will be evaluated.

Lactate Dehydrogenase

Summary statistics will be provided for absolute LDH values and change and percentage change from Period 1 and 2 Baselines at each visit by treatment sequence and total. Absolute mean and mean changes/percentage changes from Period 1 Baseline (with 95% CI) will be illustrated at each visit by treatment sequence.

A summary of the number and percentage of participants achieving LDH-N and LDH $\leq 1.5\times$ ULN at each visit will be presented by treatment sequence and total in contingency tables. The response rates along with 95% CI, along with the number of evaluable participants (used as the denominator), will be presented at each visit in a bar chart.

LDH values in samples affected by TTH will not be used in the analysis.

FACIT Fatigue Scale

Absolute levels, and changes and percentage changes in FACIT-Fatigue scores from Period 1 and 2 Baselines will be summarized at each visit by treatment sequence and total using descriptive statistics. Mean and mean changes/percentage changes from Period 1 Baseline (with 95% CI) will be plotted by treatment sequence. Refer to Appendix 9.6.1 for a more detailed description of the FACIT-Fatigue calculations and the scoring methods.

The number and percentage of participants showing an improvement of at least 3 points in the FACIT-Fatigue score from Period 1 Baseline will be summarized at each visit by treatment sequence and total in contingency tables. The response rates (with 95% CI) and the number of evaluable participants (used as the denominator for the percentage) will be presented at each visit in a bar chart.

Breakthrough Hemolysis

The number and percentage of participants with BTH and by BTH subcategories (suboptimal PD, infection complement amplifying conditions, and undetermined) will be summarized in separate tables. The response rates (with 95% CI) and the number of evaluable participants will be presented in each period (Period 1 to 6 and Entire Extension Period) by treatment sequence and total. The denominator for the percentage is the number of participants with at least 1 data value to analyze BTH within the period reported.

Aligning to the primary analysis methodology, participants who withdraw from the study due to lack of efficacy will be considered as nonresponders in the period of withdrawal (ie, reported as having a BTH event). For participants who withdrew for any other reasons, their data up to the time of withdrawal will be used to assess BTH status.

Stabilized Hemoglobin

Stabilized hemoglobin is defined as the avoidance of a ≥ 2 g/dL decrease in hemoglobin level from each period's Baseline as defined in Section 7 through the end of the period analyzed. For example, a patient is considered to have maintained stabilized hemoglobin in the Entire Extension Period if changes from Period 2 Baseline in hemoglobin level are > 2 g/dL at all evaluable visits in the Extension Period until their last visit in the study. If an accurate Baseline cannot be established (ie, due to extended missed visits) in most participants, the sensibility of analyses in the individual period will be reevaluated.

Participants who withdrew from the study due to lack of efficacy will be considered as nonresponders in the period of withdrawal (ie, reported as not maintaining stabilized hemoglobin in that period). For participants who withdrew for any other reasons, their data up to the time of withdrawal will be used to evaluate stabilized hemoglobin status.

The number and percentage of participants with stabilized hemoglobin in each period (Period 1 to 6 and the Entire Extension Period) will be tabulated and summarized by treatment sequence and total. The response rate (with 95% Cis) and the number of participants evaluable will be presented. The denominator for the percentage is the number of participants with at least 1 hemoglobin data value within the period reported.

Transfusion Avoidance

TA is defined as participants who remained transfusion free and did not require a transfusion as per protocol-specified guidelines.

Participants who withdrew from the study due to lack of efficacy will be considered as nonresponders in the period of withdrawal (ie, reported as having a transfusion). For participants who withdrew for any other reason, their data up to the time of withdrawal will be used to evaluate TA status.

The number and percentage of participants who remained transfusion free within each period (Period 1 to Period 6 and Entire Extension Period) will be summarized by treatment sequence and total. The response rates (with 95% CI) and the number of evaluable participants (used as the denominator for the percentage) will be tabulated.

Transfusions

pRBC/whole blood transfusion data will be summarized in each period (Period 1 to 6 and Entire Extension Period) by treatment sequence and total. The number of participants receiving a transfusion, the total number of transfusions and the total number of units transfused will be

tabulated. Descriptive statistics will be provided for the number of transfusions and the number of units transfused per participant.

EORTC-QLQ-C30

EORTC-QLQ-C30 comprises 30 items arranged into 9 scales and 6 single items. There are 5 functioning scales (physical, role, emotional, cognitive, and social), 3 symptom scales (fatigue, pain, and nausea and vomiting), a number of single items assessing additional symptoms (dyspnea appetite loss, insomnia, constipation and diarrhea) and 1 two-item global health status scale.

For each of the EORTC-QLQ-C30 scales data will be tabulated, summary statistics will be provided on the absolute values and changes from Period 1 and 2 Baselines at each visit by treatment sequence and total. Refer to Appendix 9.6.2 for more details on EORTC-QLQ-C30 calculations and scoring methods.

In addition, a summary of the number and percentage of participants who showed an improvement of at least 10 points from Period 1 Baseline in the following 3 subscales; Global Health Status, Physical Functioning, and EORTC-Fatigue will be presented at each visit by treatment sequence and total. The response rate (with 95% CI) and the number of participants evaluable at each visit will be presented in contingency tables and illustrated in a bar chart.

Clinical Manifestations of PNH

The Investigator or designee will assess each participant for signs and symptoms of PNH, which may include the following: fatigue, chest pain, abdominal pain, dyspnea, dysphagia, erectile dysfunction, and hemoglobinuria.

Data will be tabulated with shifts from Period 1 and 2 Baselines in clinical manifestations of PNH summarized at each visit by treatment sequence and total.

A listing of available participant-reported PNH symptoms and healthcare resource utilization will be produced.

Roll-over Cohort

By participant listings based on the SSr will be presented for the following:

- PNH clone size
- Participants with pRBC/whole blood transfusions, including units transfused.
- Clinical manifestation of PNH (fatigue, chest pain, abdominal pain, dyspnea, dysphagia, erectile dysfunction, and hemoglobinuria)
- FACIT Fatigue Scale
- EORTC QLQ-C30
- Participants with BTH, including associated new and worsening PNH symptoms.

7.2.4. PK and PD Analyses

Original Study Cohort

Assessments for PK/PD are as follows:

- Serum ravulizumab and eculizumab concentration over time
- Change in cRBC hemolytic activity over time (exploratory)
- Change in free and total C5 concentrations over time

PK analyses will be performed on the PK Set and PD analysis will be performed on the FAS. All data until the EOS will be analyzed and listed. Nominal sampling times will be used for analyses.

Serum study drug concentrations will be summarized over time using descriptive statistics: the number of participants, mean, SD, coefficient of variation, median, minimum, and maximum by treatment sequence. Mean serum ravulizumab and eculizumab 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 Period 1 and 2 Baselines in total and free C5 serum concentrations and cRBC hemolysis will be tabulated over time by treatment sequence. Mean serum free C5 concentrations will be presented at each visit alongside the number of participants with serum−free C5 concentration ≥ 0.5 ug/mL by treatment sequence. Mean and mean change from Period 1 Baseline will be presented graphically over time by treatment sequence for free C5 and cRBC. Data over time will also be illustrated through box plots for free C5.

A sensitivity analysis may be prepared excluding data corresponding to biologically implausible samples.

Roll-over Cohort

The same assessments as the Original Study Cohort will be performed using samples collected on Day 1, Day 168, Day 336, and Day 504 or ET.

Serum ravulizumab concentrations at each visit will be tabulated as specified for the Original Study Cohort based on the PKr set by population. Absolute values, changes and percent changes from Baseline in free C5 data will be summarized on the FASr by population. Listings will be provided for serum concentration, cRBC, total and free C5 concentrations data.

If needed other PK/PD analyses will be described in a separate PK/PD analysis plan.

7.3. Safety Analyses

Safety analysis will be reported for the Original Study Cohort (on SS) and Roll-over Cohort (on the SSr) separately and evaluated through to the EOS on the following endpoints.

Treatment-emergent adverse events (TEAEs) will be summarized; however, all AEs will be included in the listings with a flag indicating the period of AE onset (ie, pretreatment, Primary Evaluation Period, or Extension Period). From here onward, TEAEs are referred to as AEs.

- Original Study Cohort
  - Change in physical examinations, vital signs, ECGs, and laboratory assessments over time
  - Incidence and severity of AEs and SAEs over time
- Roll-over Cohort
  - Incidence and severity of AEs and SAEs over time
  - Laboratory assessments (including vital signs)
  - ECG and physical abnormalities

    Total ravulizumab-treated population (Original Study Cohort + Roll-over Cohort) - incidence and severity of AEs and SAEs over time

In general, the following guidelines apply to the safety analysis:

- AEs:
  - Original Study Cohort: AEs during ravulizumab (starting after the first ravulizumab infusion) will be summarized by period (Periods 1 to 6 and Entire Study Period). AEs on the Primary Evaluation Period will be summarized by treatment group on the SS, and AEs during ravulizumab treatment will be based on RTS.
  - Roll-over Cohort data will be summarized on the Entire Study Period by population and total.
- Laboratory data: Original Study Cohort will report by analysis visits and changes from Baselines 1 and 2 will be provided. Roll-over Cohort data will be summarized by nominal visits. Data from local laboratories will not be included in the summaries.

7.3.1. Study Duration, Treatment Compliance, and Exposure

Original Study Cohort − Primary Evaluation Period

The analysis of study treatment data will be reported on the Primary Evaluation Period based on the FAS and SS.

Summary statistics (mean, SD, median, minimum, and maximum) will be produced by treatment sequence for the following:

- Number of infusions from Days 1 to 183
- Number of participants receiving 1,2, etc. loading/induction doses and maintenance doses from Days 1 to 183

- Total number of participants with an infusion interruption as well as total number of infusions interrupted from Days 1 to 183
- Duration of study participation calculated as the time in days from the signing of informed consent until the date of completion/discontinuation from the Primary Evaluation Period/Day 183 (ie, study duration = date of Day 183 Visit/discontinuation - date of informed consent + 1)
- Total time on study treatment (days) calculated as the time in days from the first study drug infusion date until the last study drug infusion date from the Primary Evaluation Period (i.e., treatment duration = date of Day 183 Visit / discontinuation - first study drug infusion date + 1)

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 %) will also be included. This will be calculated as follows:

Percent compliance = total number of infusions taken from Day 1 to the end of the Primary Evaluation Period (excluding Day 183 infusion) / total number of expected infusions to the end of the Primary Evaluation Period (excluding Day 183 infusion)

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

Original Study Cohort and Roll-over Cohort EOS Analyses

Ravulizumab treatment exposure and compliance data will be summarized over the Entire Study Period. Original Study Cohort analyses will be reported on the RTS and summarized by treatment sequence and total. Roll-over Cohort data will report on the SSr by population and overall.

Summary statistics will be produced for the following:

- Total number of ravulizumab infusions throughout the study
- Total number of ravulizumab infusion interruptions and number of infusions interrupted due to AE.
- Number of ravulizumab infusions during the Primary Evaluation Period (applicable to the Original Study Cohort only).
- Study duration (days) defined as completion/discontinuation/EOS date (as applicable) − date of informed consent + 1. Of note, for the Roll-over Cohort it is the date of informed consent to Study ALXN1210-PNH-301
- Study treatment duration (days) calculated as the time in days from completion/ discontinuation/EOS date (as applicable) − first ravulizumab study drug infusion date + 1.
- Number of Participants with Ravulizumab treatment exposure to following intervals:<1 year, ≥ 1 year, ≥ 2 years, ≥ 3 years, ≥ 4 years and ≥ 5 years for Original Study Cohort and < 1 year and ≥ 1 year for Roll-over Cohort

A summary of the following will also be provided:

- Total number of participants with a ravulizumab infusion interruption.
- The frequency and percentage of participants with ravulizumab drug compliance range by increments of 10% (ie, ≥ 90% to < 100%; ≥ 80% to < 90%) will also be included.
- Total number of participants with missed ravulizumab infusions due to COVID-19 and the frequency and percentage of participants with missed ravulizumab infusions due to COVID-19 by thresholds of 1, 2, 3 and >4

By-participant listings will be produced for study duration, treatment compliance, and exposure. All scheduled visits that were missed or modified will be listed along with the reason, indicating whether discontinuation was related to COVID-19.

7.3.2. AEs

AEs will be classified by SOC and PT using the latest available version of MedDRA. The adverse events will be determined as occurring prior to study drug treatment (pretreatment) or on or after the first treatment (treatment-emergent) as described in Section9.5.7 .

For the Original Study Cohort, analyses of pretreatment adverse events (PTAEs) will be prepared. All AE summaries will be presented on 2 reporting periods 1) on the Primary Evaluation Period based on the SS and 2) on the Entire Study Period during ravulizumab treatment reported on Period 1 to 6, Entire Extension Period and Entire Study Period based on RTS.

Roll-over Cohort data will be summarized on the Entire Study Period by population and total on the SSr.

Participants having multiple AEs within a category (eg, overall, SOC and PT) will be counted once in that category. For severity/relationship tables, the participants highest grade/most related event within a category will be counted. Tables will be sorted by descending frequency of SOC and by descending frequency of PT within a SOC.

For both cohorts by-participant listings will be provided for all AEs, SAEs, adverse events of special interest (AESIs), AEs leading to study drug discontinuation, AEs amongst participants who had an SAE during the study and AEs during study drug administration. Listings will be provided on the SS for Original Study Cohort and the SSr for the Roll-over Cohort.

AEs will include the displays described in the following subsections.

7.3.2.1. Overall Summary of Adverse Events

An overall AE summary will be provided for the Original Study Cohort and Roll-over Cohort separately. For both cohorts the overall AE summary will be repeated and presented on COVID - 19 related AEs.

The number of events (n) and the number of participants with events (n, %) will be displayed for the following event subcategories for AEs and SAEs:

- Total number of events and participants with events
- Events by relationship to study drug
- Events by toxicity: Grades 1, 2, 3, 4, and 5
- Events leading to study drug discontinuation.
- Events leading to study drug interruption.
- Events considered as MAVE.
- Events of special interest
- Death

7.3.2.2. AEs and SAEs by SOC and PT

The number of events and the number and percentage of participants with events will be presented by SOC and PT, participants are counted once in each SOC, and PT. Percentages will be based on the number of participants "at risk" in each group (ie, on the SS/RTS and SSr for Original Study Cohort and Roll-over Cohort respectively). SAEs will be summarized similarly. In addition, a separate summary will be provided for upper respiratory tract infection AEs for both cohorts.

7.3.2.3. AEs and SAEs by SOC, PT, and Relationship

The number of events and the number and percentage of participants with events will be presented by SOC and PT by relationship (related, and not related for both the usual definition of related/not related [and at interim analysis for the Japanese definition of related/not related as detailed in Appendix 1 for the Original Study Cohort]. If a patient has > 1 occurrence of an AE, the strongest relationship to study treatment will be used in the summary table within the reporting period analyzed. For example, for AEs summarized during ravulizumab exposure, the strongest relationship while on ravulizumab treatment will be reported. SAEs will be summarized similarly.

7.3.2.4. AEs and SAEs by SOC, PT, and Severity

The number of events and the number and percentage of participants with events will be presented by SOC and PT as by severity (Grade 1, 2, 3, 4, and 5). If a patient has > 1 occurrence of an AE, the highest grade within the reporting period analyzed will be used in the summary table.

7.3.2.5. Deaths, Other SAEs, and Other Significant AEs

A listing of participants' deaths will be produced.

Important identified risks in this study include meningococcal infections, sepsis, serious infections, aspergillus infection, and infusion reactions. Additional events of interest include serious cutaneous adverse reactions, cardiac disorders (including ventricular fibrillation), and angioedema. These important identified risks and AESIs will be summarized by treatment sequence in tabular form. See Section 9.5.7 for a list of AE MedDRA PT that will be considered for these summaries.

7.3.2.6. Major Adverse Vascular Events

The number of treatment-emergent MAVE (as defined in Appendix 1), and the proportion of participants with MAVE will be summarized.

7.3.2.7. COVID-19 Related AEs and SAEs by SOC and PT

At the start of the COVID-19 pandemic all participants were in the Extension Period of the study, thus receiving ravulizumab treatment. The following analyses on COVID-19 related AEs will be presented:

- Overview of COVID-19 related AEs and SAEs
- Treatment emergent COVID-19 related AEs and SAEs by SOC and PT
- COVID-19 flag will be added to the by-participant listing of AEs, SAEs and AEs leading to study drug discontinuation.
- All-cause mortality table possibly added to summarize the total number of deaths by relationship to COVID-19.

7.3.2.8. Posting to ClinicalTrials.gov and EudraCT

For the legal requirement to ClinicalTrials.gov and EudraCT, the following tables are required on the Original Study Cohort and Roll-over Cohort separately. In the Original Study Cohort, non-SAEs with an incidence of ≥ 5% in the Primary Evaluation Period (in each treatment group), and non-SAEs with an incidence of ≥ 5% in the Extension Period will be provided. Similarly, non-SAEs with an incidence of ≥ 5% overall for the Roll-over Cohort will be tabulated. SAEs suspected to be related to study treatment will be tabulated. The number of events and the number and percentage of participants with events will be provided by SOC and PT.

7.3.3. Other Safety

7.3.3.1. Analyses for Laboratory Tests

Descriptive summaries on laboratory data for the Original Study Cohort (on the SS) and Roll-over Cohort (on the SSr) will be provided. Absolute values, and changes from Period 1 and 2 Baselines in central laboratory parameters (continuous variables) will be summarized descriptively at each visit, by treatment sequence and total for the Original Study Cohort.

Absolute values and changes from Baseline will be reported at each visit by population and total for the Roll-over Cohort.

In the Original Study Cohort, the shift from Period 1 Baseline tables over time will be presented for all central laboratory values, where applicable, using normal, low, or high based on normal range values. For the 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-glutamyl transferase, absolute neutrophil count and platelets. Additionally, scatter plots of the worst value after the first study infusion versus Period 1 Baseline will be provided for the parameters mentioned above at the Primary Evaluation Period interim analysis.

Potassium, ALT, AST, magnesium, phosphorous, and LDH values affected by TTH will not be used in the analysis.

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

7.3.3.2. Vital Signs and Physical Examination

Absolute values and changes from Period 1 and 2 Baselines in vital signs (BP, HR, respiratory rate, and temperature) for the Original Study Cohort will be summarized descriptively at each visit, by treatment sequence and total . Similarly, absolute values and changes from Baseline values will be reported at each visit by population and total for the Roll-over Cohort.

Absolutes values and changes from Period 1 and 2 Baselines in weight will be summarized by visit and treatment sequence and total . Summaries on absolute values and changes from Baseline values for weight at each visit will be provided by population and total for the Roll-over Cohort. Separate listings of vital signs and weight will be produced for both cohorts.

Adverse changes from Period 1 Baseline in physical examination findings will be classified as AEs and analyzed accordingly for the Original Study Cohort. By-patient listings will be prepared separately for physical examination data for both cohorts.

7.3.3.3. Electrocardiograms

Original Study Cohort: Descriptive statistics by visit and treatment sequence will be presented for each ECG parameter (including PR, QRS, QT, and QTcF) values and for change from Period 1 Baseline values. An outlier analysis will be performed that will summarize the frequency and percentage of participants who meet any of the following outlier criteria:

- QT and QTcF interval >450 msec
- QT and QTcF interval >480 msec
- QT and QTcF interval >500 msec
- QT and QTcF interval increase from Baseline >30 msec
- QT and QTcF interval increase from Baseline > 60 msec

For both cohorts, a listing of ECG results will be presented.

7.3.3.4. Immunogenicity

All immunogenicity analyses will be conducted on the SS for the Original Study Cohort and on the SSr for the Roll-over Cohort. The number and percentage of participants developing ADA, and antidrug neutralizing antibodies, where applicable will be presented at each visit. In the Original Study Cohort, for participants randomized to ravulizumab, the number and percentage of participants with antidrug cross-reactivity to eculizumab during the Primary Evaluation Period will be summarized.

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9. APPENDICES

9.1. Protocol Schedule of Events

Refer to the protocol for a schedule of events.

9.2. Changes From Analyses Specified in the Previous Version of the SAP

The original SAP (dated 03 Feb 2017) was amended, and the summary of changes is described below.

SAP Version 2 (Dated 28 Apr 2017)

See Section 4.1 for changes from analyses specified in Version 1.0 of the SAP.

Additionally, Section 7.2.1.7 was modified to exclude summaries of TA and LDH-N by Processes A and B as Process B material was available sooner than expected and only the following 4 participants received ravulizumab under Process A: Participants 0555-301A, 0421-301A, 0552-302A and 0607-302A.

Furthermore, as the focus of the CSR will be on the Primary Evaluation Period, the analyses specified in the previous version of the SAP Section 7.4 on participants who switched from eculizumab to ravulizumab in the Extension Period were excluded. These analyses were generated at study completion and included in the final CSR.

SAP Version 3.0 (Dated 26 Oct 2017)

During the conduct of the study, it was observed that up to 1% of central laboratory chemistry samples underwent in vitro erythrocyte lysis or TTH caused by sample mishandling. This is unrelated to hemolysis due to PNH. The reasons for TTH varied and included delayed or improper centrifugation and traumatic blood draws. In addition, PIGA- deficient erythrocytes from participants with PNH are more susceptible to mechanical lysis than non-PNH erythrocytes (Smith, 1985). Hemolysis resulted in release of red blood cell contents including LDH, potassium and AST. In contrast to hemolysis in participants with PNH, in which serum potassium is normal, for samples affected by TTH both potassium and LDH are markedly and proportionally increased (Goyal, 2015; Oostendorp, 2012). Marked hyperkalemia (defined as > 6mmol/L) seen in TTH, but not PNH hemolysis, differentiates TTH (in vitro) from PNH hemolysis (in vivo), and is not clinically significant (Hollander-Rodriguez, 2006; Kovesdy, 2014). Due to the artifactual increase in LDH in samples affected by TTH, the potassium, ALT, AST, magnesium, phosphorous, and LDH values in samples affected by TTH were not used in the analysis of any efficacy or safety endpoints, with the exception that the LDH value will be used for the qualification of BTH events. BTH was captured on a separate form, and the central laboratory parameter LDH, in addition to new or worsening symptoms as specified in the protocol, was used by the principal Investigator or designee to qualify participants with BTH. TTH samples from the central laboratory was defined as having serum potassium $\geq$ 6 mmol/L and LDH $\geq$ 2 $\times$ ULN and was excluded from analyses as described above.

The exploratory endpoints of participants reported PNH symptoms and healthcare resource utilization were removed in Protocol Amendment 4, dated 23 Oct 2017, to reduce patient data collection burden. Therefore, Section 7.2.3 had been updated so only by-participant listings were produced rather than summary statistics.

The choice of covariance structure to be utilized in the MMRM analysis has been updated to follow the recommendation by Mallinckrodt et al (Mallinckrodt, 2008). The recommendation is to use an unstructured covariance structure to model the within participant errors, and if that fails to converge, to use a prespecified list of appropriate structures. The covariance structure converging to the best fit, as determined by AIC, would then be used in the analysis.

Section 9.5.1 had been updated to remove the detailed derivation of AESIs as the specific terms were dependent on the MedDRA version in use at the time of analysis. The details were documented in the appropriate analysis data model (ADaM) specifications.

Additionally, the SAS code for the MMRM analysis in Section 9.6.3.2 for FACIT-Fatigue was updated to include Baseline for internal consistency with Section 7.2.2.

SAP Version 3.1 (Dated 27 Nov 2017)

The analysis of BTH in Section 7.2.2.1 had been updated to be consistent with Study ALXN1210-PNH-302. The change included utilizing exact methods if the stratified Newcombe method would fail to provide estimates of CIs due to small cell sizes.

Section 7.3.2.1 was updated to remove the analysis of the number and percentage of participants who had a TEAEs during study drug administration. A separate by-participant listing was generated.

SAP Version 4.0 (Dated 23 Apr 2023)

This amendment details planned analyses performed at the EOS on the Original Study Cohort to support the final CSR and stipulates analyses on the Roll-over Cohort. To assess the impacts of COVID-19 pandemic on the study, additional analysis will be included, and where applicable, modifications made to existing analyses will be described.

In the Original Study Cohort AEs will be analyzed on the Primary Evaluation Period by ravulizumab and eculizumab treatment and on the Entire Study Period while exposed to ravulizumab treatment. The latter summary will be presented on the Primary Evaluation Period, and thereafter at 12-month time intervals in the Extension Period as well as the Entire Extension Period and Entire Study Period. Additional analyses of non-SAEs occurring in at least 5% of the overall populations were added. AESIs will be included in the overview AE tables and added to the respective section of the SAP.

Derivation of exposure to study treatment is updated to align with the time the participant is “at risk” of reporting a TEAE, that is defined as time from the first dose of study drug infusion to the

date of completion/discontinuation for each reporting period as opposed to time from the first study drug infusion date until the last study drug infusion date in each reporting period.

The language in Section 5.4 provisioned only for participants randomized to ravulizumab. It has been adjusted to represent all study participants with defining the pharmacokinetic set as including participants with at least 1 dose of study drug.

Section 7.1.2 updated to clarify the list stipulates programmable protocol deviations. Both programmable and important protocol deviations as collected will be summarized separately.

Updated wording throughout to align with the reporting, both packed red blood cells (pRBC) and whole blood transfusions were analyzed at Primary Evaluation Interim analysis and will be analyzed at End of Study analysis.

Clarification around superiority of ravulizumab to eculizumab added.

The 'total' column will be removed from efficacy summary tables for the Primary Evaluation Period where specified.

General typographic edits are made to improve the document.

SAP Version 5.0

The following secondary objective is added into Section 4.1, based on Protocol Amendment 6, dated 12 Apr 2021:

To quantify identified specific safety concerns during treatment with ALXN1210, including meningococcal infections, serious hemolysis after drug discontinuation in PNH, immunogenicity, serious infections, malignancies and hematologic abnormalities, and during pregnancy and breastfeeding

Cross-reference edits are made to restore the correct hyperlinks.

9.3. Sample Size, Power, and Randomization

Approximately 214 participants will be randomly assigned in a 1:1 ratio to receive ravulizumab (N = 107) or eculizumab (N = 107) to ensure at least 193 evaluable participants (assumes no more than a 10% dropout rate). The sample size estimation is based on a noninferiority design comparing participants treated with ravulizumab to those treated with eculizumab. Coprimary endpoints of hemolysis as directly measured by the LDH-N from Days 29 through 183 and the proportion of participants who achieved TA through Day 183 will be used to assess noninferiority. The sample size is based on the endpoint that requires the larger number of participants.

For the coprimary endpoint of LDH-N, using a NIM based on the relative benefit of eculizumab with respect to placebo of 0.39 and a Type 1 error of 1-sided 2.5%, a minimum of 142 participants will provide 80% power to demonstrate noninferiority of ravulizumab to eculizumab. The NIM was determined based on a randomized placebo-controlled study

(TRIUMPH study;(Hillmen, 2006)). The NIM determination was based on several factors. As baseline LDH is a predictor of the rate of normalization, to preserve the constancy assumption, the rate of LDH-N was calculated and adjusted to the observed baseline LDH of the current ALXN1210 Phase 1b and 2 data. This was done by including participants from the TRIUMPH study whose baseline LDH was < 2400. The estimate of LDH-N for eculizumab was then calculated to be a weighted average of the proportions of LDH-N from Days 29 to 183 to be consistent with the proposed analysis plan for this study. As the proportion of LDH-N for placebo-treated participants was 0% at all visits, the upper bound of the 95% CI was used to be able to calculate an OR. The final estimate of benefit was based on an LDH-N proportion of 42% for eculizumab-treated participants and 10% for placebo for an OR of 6.5. A traditional choice of NIM is the one with ≤ 50% loss of benefit resulting in a NIM of an OR of 0.39. The calculation of NIM follows Ng (Ng, 2008) in which the NIM is given by $1 / \{OR^{0.5}\}$ where OR represents the odds ratio of eculizumab compared to placebo and is given by [0.42 / (1 - 0.42)] / [0.1 / (1 - 0.1)] and 0.5 is the fraction of benefit to be preserved. This approach chooses the NIM on the log odds scale, as described in Section IV of the 2010 FDA Guidance for Industry: Non-Inferiority Clinical Trials. Although more conservative approaches for constructing NIMs could be used, such as using the lower bound of the 95% CI for eculizumab, the resulting estimated sample size would make this study operationally infeasible in light of the rarity of PNH and the paucity of eculizumab-naïve participants.

For the other coprimary endpoint of proportion of participants not receiving any transfusions through Day 183, using a NIM of -20% and a Type 1 error of 1-sided 2.5%, a minimum of 193 participants will provide 80% power to demonstrate noninferiority between the treatment arms. The NIM was determined based on the Global PNH Registry for eculizumab-treated participants enrolling into the registry in 2012 or later (Soliris Type II Variation Procedure No. EMEA/H/C/000791/II/66). History of transfusion is a predictor of on-treatment transfusion; thus, to preserve the constancy assumption, the NIM was assessed based on available data from treated and untreated participants in proportion to enrollment expectations in the current study. Participants treated with eculizumab (TA rate of 57.1%) showed a benefit over untreated participants (TA rate of 18.6%) with a difference of approximately 40% (38.5%) after adjustment for history of transfusions 12 months prior to enrollment. The adjustment comes from an expected proportion of participants without a history of transfusions to be no more than 20%. Enrolled participants for this study will be capped at 20% for participants without a history of transfusions to ensure that constancy is satisfied.

A traditional choice of NIM is the one with ≤ 50% loss of benefit, which gives a NIM of approximately -20%. A more conservative NIM could be used using the lower bound of the 95% CI for the difference in rates, but the resulting estimated sample size would make the study operationally infeasible in light of the rarity of PNH and the paucity of eculizumab-naïve participants with and without a history of transfusions. Further, given the proportion of participants with TA observed in preliminary results from the Phase 1b/2 program, it is expected that noninferiority can be demonstrated with more conservative NIMs for the given sample size with limited loss of power.

Because the sample size estimate based on LDH-N is smaller than that based on TA (Table 3), the final sample size estimate selected for this study is based on the TA endpoint. Adjusting for a possible 10% dropout rate, approximately 214 participants will be enrolled in this study.

Table 3: Summary of Parameters Used in Estimating Sample Size With Coprimary Endpoints

Parameters	LDH-N	TA
Power	80%	80%
Type 1 error	1-sided 0.025	1-sided 0.025
Noninferiority margin	0.39[a]	-0.20[b]
Allocation ratio	1:1	1:1
Mean eculizumab response	0.42[c]	0.57[d]
SD of eculizumab response	NA	NA
Assumed treatment difference	1	0
Estimated sample size	142	193
Adjusted sample size for 10% dropouts	158	214

Source: (Hintze, 2011)
[a] Based on odds ratio
[b] Based on difference in rates
[c] Response rate from the TRIUMPH study adjusted for baseline LDH
[d] Response rate from Global PNH Registry adjusted for history of transfusion
Abbreviations: LDH-N = lactate dehydrogenase normalization; PNH = paroxysmal nocturnal hemoglobinuria; TA = transfusion avoidance

9.4. Determination of NIM for Key Secondary Endpoints

Percentage Change in LDH

The margin was selected based on data from a randomized placebo-controlled study (TRIUMPH study; (Hillmen, 2006), which showed a benefit of eculizumab over placebo with a difference in LDH percent change from Baseline to Week 26 of -101% with a 95% CI of -114% to -88%. Using the upper bound of -88% as a conservative estimate of benefit, a traditional choice of NIM is the one with ≤ 50% loss of benefit resulting in a NIM of approximately 44%. However, because the benefit of eculizumab over placebo is so great, a more conservative and clinically appropriate choice is a NIM with ≤ 25% loss of benefit, which results in a NIM of 22% and rounded to 20%.

Change in FACIT-Fatigue

The margin was selected based on data from a randomized placebo-controlled study (TRIUMPH study; (Hillmen, 2006), which showed a benefit of eculizumab over placebo with a difference in FACIT-Fatigue change from Baseline to Week 26 of 10.4. A traditional choice of NIM is the one with ≤ 50% loss of benefit. This would result in a NIM of -5. Although a more conservative NIM could be constructed using the lower bound of the 95% CI for the difference, the resulting sample size would be prohibitive in light of the rarity of PNH and the paucity of eculizumab-naïve participants.

Percent of Participants With BTH

The margin was selected based on data from a randomized placebo-controlled study (TRIUMPH study; (Hillmen, 2006). The LDH portion of the definition of BTH was utilized in defining NIM for this endpoint as the TRIUMPH study did not collect the necessary data to include the other part of the definition. That study showed a benefit of eculizumab over placebo with a difference

of -81.4% with a 95% CI of -69.8% to -92.96% in BTH. Using the lower bound of -69.8% as a conservative estimate of benefit, a traditional choice of NIM is the one with ≤ 50% loss of benefit resulting in a NIM of approximately 35%. However, a more conservative and clinically appropriate choice is a NIM of 20%.

Percent of Participants With Stabilized Hemoglobin

The margin was selected based on data from a randomized placebo-controlled study (TRIUMPH study; (Hillmen, 2006), which showed a benefit of eculizumab over placebo with a difference of 39.5% in proportion of participants with stabilized hemoglobin as defined in this protocol after 26 weeks of treatment. A traditional choice of NIM is the one with ≤ 50% loss of benefit. This would result in a NIM of approximately -20%. Although a more conservative NIM could be constructed using the lower bound of the 95% CI for the difference, the resulting sample size would be prohibitive in light of the rarity of PNH and the paucity of eculizumab-naïve participants.

9.5. Technical Specifications for Derived Variables

The following derived data will be calculated prior to the analysis.

9.5.1. Age

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

Table 4: Age and Reference Date

Age	Reference Date
Age at enrollment	Date of signing ICF
Age at PNH diagnosis	Date of PNH diagnosis
Age at the first infusion	Date of the first infusion

Abbreviations: ICF = informed consent form; PNH = paroxysmal nocturnal hemoglobinuria

For all dates, in cases where only the month and year are provided for a date, the day for the date will be imputed as 15. The missing month will be imputed as June. In cases where the day is observed but the month is missing, the date will be imputed as June 15.

9.5.2. Disease Duration

PNH disease duration will be presented as the number of years between the date of the first infusion and the date of PNH diagnosis (ie, INT [(date of the 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).

9.5.3. 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.

9.5.4. 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 nonzero and the subsequent value is nonmissing.

9.5.5. Study Day and Other Study Days

The date of the first study drug infusion is defined as Study Day 1 or Day 1. All other days will be labeled relative to Day 1 in the listings. For event dates on or after Day 1, a study day for a particular event is calculated as [date of the event] - [date of the first infusion] + 1. For event dates before Day 1, a study day for an event is calculated as [date of the event] - [date of the first infusion]. Duration of an event will be calculated as [event end date] - [event start date] + 1.

9.5.6. Analysis Visits

Analysis visits are utilized for the Original Study Cohort reporting. Summaries over postbaseline timepoints or analyses at specific postbaseline timepoints will be performed based on the list of visits described in the schedule of assessments of the protocol. As visits differ with respect to participants randomized to eculizumab or ravulizumab, windows are based on study evaluation schedule and composed of a set of days around eculizumab and ravulizumab visit.

For all assessments, the number of days from baseline will be calculated using the following formula: (date of assessment) - (date of the first study treatment) + 1. This number of days will be used to assign the analysis visit. This may not always correspond to the electronic case report form (eCRF) visit.

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

For all visits, the lower bound and the upper bound for the analysis visit windows are defined as the midpoints of the target date of scheduled visits. If the date of assessment falls in between the lower bound and the upper bound for a visit as defined in the protocol schedule of assessments, 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. For example, for an assessment with a scheduled visit on Day 127, a prior scheduled visit on Day 113, and a subsequent scheduled visit on Day 141, the window will start at 120 days from Baseline and will go to 133 days from Baseline.

If only 1 record is within an analysis visit window, the data from that record will be used in the analysis. If > 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.

9.5.7. Adverse Events

TEAEs are events with start dates and start times on or after the date and time of the first study drug infusion. In the Original Study Cohort, at EOS, for AEs summarized on the Entire Study Period during ravulizumab exposure, TEAEs will be considered as all AEs with start dates and start times on or after the date and time of the first ravulizumab infusion. For the Roll-over Cohort, TEAEs are events on or after the date of the first ravulizumab infusion in Study ALXN1210-PNH-301.

If the start date of an AE is partially or completely missing and the end (stop) date and time of the AE do 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; else,
- If the start year is the same as the year of the first study drug dose and
  - The start month is missing, then the AE is treatment emergent; else if
  - The start month is present and is the same as or after the month of the first study drug dose, then the AE is treatment emergent; else.
- If the start date is completely missing, then the AE is treatment emergent.

All other AEs are considered PTAEs.

Participant percentages are based on the total number of treated participants in the particular treatment group.

Related AEs are defined as possible, probable, or definitely related. Unrelated AEs are defined as unlikely or not related. Related AEs (Japanese definition) are defined as unlikely, possible, probable, or definitely related. Unrelated AEs (Japanese definition) are defined as not related.

The following provides a list of AESIs. In addition, a medical review will be done to ensure that no relevant events were missed:

- Infections:
  - Meningococcal infections
  - Aspergillus infections
  - Other serious infections
- Sepsis
- Infusion reactions: serious cutaneous adverse reactions
- Cardiac disorders
- Angioedema

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 participant's medical history (prior to Study Day 1) and throughout the study.

A MAVE is defined as the following:

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

9.6. Additional Details on Statistical Methods

9.6.1. FACIT-Fatigue Calculations

The FACIT-Fatigue questionnaire consists of 13 items scored on a 5-point Likert scale (0 = not at all to 4 = very much). The FACIT-Fatigue Scale scoring guideline (Version 4.0) will be used as follows:

All negatively stated items (ie, all items except An5 and An7 from the case report form) 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 > 50% of the items were answered. The score has a range of 0 to 52, and the higher the score, the better the QoL.

9.6.2. EORTC-QLQ-C30 Scoring Calculations

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 to 4 = very much) and scored on a scale of 1 (very poor) to 7 (excellent) for the final 2 questions that probe the participant's overall health and QoL. It is composed of both multi-item scales and single-item measures. These include 5 functional scales (physical, role, emotional, cognitive, and social), 3 symptom scales (fatigue, pain, and nausea and vomiting), a global health status, a number of single items assessing additional symptoms (dyspnea, appetite loss, insomnia, constipation and diarrhea), and financial difficulties. The following explains the scoring procedure.

Table 5: 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	6,7	(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.
Abbreviations: EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Scale; QoL = quality of life

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 > 50% of the items were answered. Thus, 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.

9.6.3. SAS Code for Efficacy Analyses

9.6.3.1. SAS Code for Newcombe

The main analysis method for the coprimary endpoint of TA and the secondary endpoints of BTH and stabilized hemoglobin is the stratified Newcombe CI method.

The basic SAS code for such an analysis is given by the following:

```
proc freq  data=ADEFF;
tables strata*trt*TA/riskdiff (common CL=newcombe);
run;
```

where trt is the Primary Evaluation Period treatment group, strata are the combined transfusion history and LDH level randomization stratification, and TA is the categorical transfusion avoidance indicator.

SAS Code for GEE

The main analysis method for the coprimary endpoint of LDH-N is the GEE.

The basic SAS code for such an analysis is given by the following:

```
proc genmod descending;
  class subjid trt;
  model ldhn = trt base rbcstrata / dist=bin link=logit;
  repeated subject=subjid / type=ar1 ;
  estimate "1210 vs ECU" trt 1 -1 /exp;
  lsmeans trt/ilink cl;
run;
```

where subjid is the participant identifier variable, trt is the randomized treatment group, ldhn is LDH-N, base is the LDH value at Baseline, and rbc strata is the rbc randomization stratification variable.

9.6.3.2. SAS Code for Repeated Measures Mixed Model Analysis

The main analysis method for the secondary endpoints of percentage change from Baseline to Day 183 (Week 26) in LDH and change from Baseline to Day 183 (Week 26) in FACIT-Fatigue involves an MMRM analysis. The basic SAS code for percent change in LDH is given by the following:

```
proc mixed data=ADEFF method=reml;
```

```
class subjid trt avisitn rbcstrata;
model pchg= trt  avisitn trt*avisitn base rbcstrata/ddfm=kr solution;
repeated avisitn/type=AR1 subject=subjid;
lsmeans trt *avisitn/cl diff;
where avisitn>0;
run;
```

The basic SAS code for change from Baseline in FACIT-Fatigue is given by the following:

```
proc mixed data=ADEFF method=reml;
class subjid trt avisitn rbcstrata ldhstrata;
model chg= trt  avisitn trt*avisitn base ldhstrata rbcstrata/ddfm=kr solution;
repeated avisitn/type=UN subject=subjid;
lsmeans trt *avisitn/cl diff;
where avisitn>0;
```

run;

where subjid is the participant identifier variable, trt is the Primary Evaluation Period by treatment group, avisitn is the visit variable (0 representing the Baseline Visit), base is the LDH (FACIT-Fatigue) value at Baseline, pchg is the percentage change from Baseline in LDH, chg is the change from Baseline in FACIT-Fatigue, rbcstrata is the rbc randomization stratification variable, and ldhstrata is the LDH randomization stratification variable.