A Phase 3, Randomized, Open-Label, Active-Controlled Study of ALXN1210 Versus Eculizumab in Adult Patients With Paroxysmal Nocturnal Hemoglobinuria (PNH) Currently Treated With Eculizumab

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A PHASE 3, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED STUDY OF ALXN1210 VERSUS ECULIZUMAB IN ADULT PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) CURRENTLY TREATED WITH ECULIZUMAB

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Date: 12 December 2017
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1. APPROVAL SIGNATURES

PPD

18 Dec 2017
Date dd Mmm yyyy

12-12-17
Date dd Mmm yyyy

Date dd Mmm yyyy
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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and acronyms are used in this SAP.

**Table 1: Abbreviations and Acronyms**

<table>
<thead>
<tr>
<th>Abbreviation or acronym</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA</td>
<td>antidrug antibody</td>
</tr>
<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>AESI</td>
<td>adverse event of special interest</td>
</tr>
<tr>
<td>ANC</td>
<td>absolute neutrophil count</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>Analysis of Covariance</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BNP</td>
<td>brain natriuretic peptide</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>CS</td>
<td>complement component 5</td>
</tr>
<tr>
<td>CAP</td>
<td>complement alternative pathway</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>cm</td>
<td>Centimeters</td>
</tr>
<tr>
<td>cRBC</td>
<td>chicken red blood cell</td>
</tr>
<tr>
<td>CS</td>
<td>Clinically significant</td>
</tr>
<tr>
<td>CSR</td>
<td>Clinical Study Report</td>
</tr>
<tr>
<td>CTCAE</td>
<td>Common Terminology Criteria for Adverse Events</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of variance</td>
</tr>
<tr>
<td>DMC</td>
<td>Data Monitoring Committee</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic Case Report Form</td>
</tr>
<tr>
<td>eGFR</td>
<td>Estimated Glomerular Filtration Rate</td>
</tr>
<tr>
<td>EOI</td>
<td>End of infusion</td>
</tr>
<tr>
<td>EORTC QLQ-C30</td>
<td>European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 Scale</td>
</tr>
<tr>
<td>FACIT-Fatigue</td>
<td>Functional Assessment of Chronic Illness Therapy-Fatigue</td>
</tr>
<tr>
<td>FAS</td>
<td>Full Analysis Set</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GEE</td>
<td>Generalized estimating equations</td>
</tr>
<tr>
<td>GOF</td>
<td>Goodness-of-fit</td>
</tr>
<tr>
<td>HLT</td>
<td>High level term</td>
</tr>
<tr>
<td>HR</td>
<td>Heart rate</td>
</tr>
<tr>
<td>IV</td>
<td>intravenous(ly)</td>
</tr>
<tr>
<td>LDH</td>
<td>lactate dehydrogenase</td>
</tr>
<tr>
<td>LDH-N</td>
<td>lactate dehydrogenase normalization</td>
</tr>
<tr>
<td>LOCF</td>
<td>Last Observation Carried Forward</td>
</tr>
<tr>
<td>MAVE</td>
<td>major adverse vascular event</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>MMRM</td>
<td>mixed model for repeated measures</td>
</tr>
<tr>
<td>NIM</td>
<td>noninferiority margin</td>
</tr>
<tr>
<td>PCHG</td>
<td>percent change</td>
</tr>
<tr>
<td>PD</td>
<td>Pharmacodynamic</td>
</tr>
<tr>
<td>Abbreviation or acronym</td>
<td>Explanation</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetic</td>
</tr>
<tr>
<td>PNH</td>
<td>paroxysmal nocturnal hemoglobinuria</td>
</tr>
<tr>
<td>pRBC</td>
<td>Peripheral red blood cell</td>
</tr>
<tr>
<td>PT</td>
<td>Preferred Term (MedDRA)</td>
</tr>
<tr>
<td>PTAEs</td>
<td>Pre-Treatment Adverse Events</td>
</tr>
<tr>
<td>q2w</td>
<td>once every 2 weeks</td>
</tr>
<tr>
<td>q8w</td>
<td>once every 8 weeks</td>
</tr>
<tr>
<td>QLQ-C30</td>
<td>Quality of Life Questionnaire-Core 30 Scale</td>
</tr>
<tr>
<td>QoL</td>
<td>quality of life</td>
</tr>
<tr>
<td>QTcF</td>
<td>QT interval corrected using Fridericia’s formula</td>
</tr>
<tr>
<td>RBC</td>
<td>Red blood cell</td>
</tr>
<tr>
<td>RR</td>
<td>Respiration rate</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>SAP</td>
<td>Statistical Analysis Plan</td>
</tr>
<tr>
<td>SAS®</td>
<td>Statistical Analysis Software®</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SMQ (N)</td>
<td>standard MedDRA query (narrow)</td>
</tr>
<tr>
<td>SOC</td>
<td>System Organ Class (MedDRA)</td>
</tr>
<tr>
<td>SS</td>
<td>Safety Set</td>
</tr>
<tr>
<td>TA</td>
<td>transfusion avoidance</td>
</tr>
<tr>
<td>TEAEs</td>
<td>Treatment-Emergent Adverse Events</td>
</tr>
<tr>
<td>ULN</td>
<td>upper limit of normal</td>
</tr>
<tr>
<td>WHO-DRUG</td>
<td>World Health Organization Drug Dictionary</td>
</tr>
</tbody>
</table>
4. DESCRIPTION OF THE PROTOCOL

ALXN1210-PNH-302 is a Phase 3, open-label, randomized, active-controlled, multicenter study to evaluate the safety and efficacy of ALXN1210 versus eculizumab administered by intravenous (IV) infusion to adult patients with PNH who have been treated with eculizumab for at least the past 6 months.

Approximately 192 eligible patients will be stratified into 1 of 2 groups based on their transfusion history (received a transfusion of packed red blood cells [pRBCs] within 12 months prior to Day 1, yes or no). Patients within each of the 2 groups will then be randomly assigned in a 1:1 ratio to either continue on eculizumab or switch to ALXN1210.

There will be 3 periods in this study: a 4-week Screening Period, a 26-week Randomized Treatment Period, and an Extension Period.

Patients randomly assigned to the ALXN1210 group will receive a loading dose on Day 1 and maintenance doses on Day 15 and q8w thereafter. Doses are based on the patient’s body weight, as shown in Table 2.

Table 2: ALXN1210 Weight-Based Dosages

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Loading Dose (Day 1)</th>
<th>Maintenance Dose (Day 15, 71, 127 and q8w thereafter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥40 to &lt;60 kg</td>
<td>2400 mg</td>
<td>3000 mg</td>
</tr>
<tr>
<td>≥60 to &lt;100 kg</td>
<td>2700 mg</td>
<td>3300 mg</td>
</tr>
<tr>
<td>≥100 kg</td>
<td>3000 mg</td>
<td>3600 mg</td>
</tr>
</tbody>
</table>

Patients randomly assigned to the eculizumab group will continue to receive the approved dose of eculizumab for the treatment of PNH (900 mg every 2 weeks [q2w]) for a total of 26 weeks of study treatment. After completion of all assessments on Day 183, all patients will enter an Extension Period and receive ALXN1210. Beginning on Day 183, patients who had been randomized to the ALXN1210 treatment group will continue to receive their weight-based maintenance dose of ALXN1210 q8w, and patients who had been randomized to the eculizumab group will switch treatment to receive a weight-based loading dose (Table 2) of ALXN1210 followed 2 weeks later and q8w thereafter by a weight-based maintenance dose of ALXN1210. Figure 1 illustrates the study design.
**Figure 1: Study Design Schematic for Clinical Protocol ALXN1210-PNH-302**

<table>
<thead>
<tr>
<th>Screening Up to 4 weeks</th>
<th>Randomized Treatment Period 26 weeks</th>
<th>Extension Period 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALXN1210</strong></td>
<td><strong>ALXN1210</strong></td>
<td><strong>Continue</strong></td>
</tr>
<tr>
<td>loading dose* Day 1</td>
<td>maintenance dose* Day 15 and every 8 weeks</td>
<td>maintenance dose* every 8 weeks</td>
</tr>
<tr>
<td>(N = 96)</td>
<td>(N = 96)</td>
<td></td>
</tr>
<tr>
<td>Patients on eculizumab</td>
<td>Eculizumab 900 mg maintenance dose Day 1 and every 2 weeks</td>
<td></td>
</tr>
<tr>
<td>for ≥ 6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N = 192)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* ALXN1210 loading dose = 2400 mg for patients weighing ≥ 40 to < 60 kg, 2700 mg for patients weighing ≥ 60 to < 100 kg, 3000 mg for patients weighing ≥ 100 kg; maintenance dose = 3000 mg for patients weighing ≥ 40 to < 60 kg, 3300 mg for patients weighing ≥ 60 to < 100 kg, 3600 mg for patients weighing ≥ 100 kg

The primary objective is to assess the noninferiority of ALXN1210 compared to eculizumab in adult patients with PNH who are clinically stable after having been treated with eculizumab for at least the past 6 months. Noninferiority will be claimed, if after 26 weeks of treatment, the upper bound of the 95% confidence interval (CI) for the difference (ALXN1210-eculizumab) in percent change in lactate dehydrogenase level (LDH-PCHG) is less than 15%.

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

- To characterize the safety and tolerability of ALXN1210 in patients who switch from eculizumab to ALXN1210
- To evaluate the efficacy of ALXN1210 by additional efficacy measures
- To characterize the pharmacokinetics/pharmacodynamics (PK/PD) and immunogenicity of ALXN1210
- To evaluate the long-term safety and efficacy of ALXN1210

A clinical study report (CSR) will be produced after the end of the 26-week Randomized Treatment Period (Day 183) and will include efficacy, safety, PK, and PD analyses. This statistical analysis plan (SAP) outlines only the analyses that are to be included in the report developed after the 26-week Randomized Treatment Period.

A final CSR will be produced at study completion and will include data on all patients in the study through the end of the Extension Period. A separate SAP will outline the analyses to be performed for the final CSR.

**4.1. Changes From Analyses Specified in the Protocol**

The approach to control for a Type 1 error for the primary efficacy endpoint and the key secondary endpoints was updated to be consistent with the January 2017 FDA draft guidance.
‘Multiple endpoints in clinical trials guidance for industry’ and the recently updated (15 December 2016) EU draft guidance ‘Guideline on multiplicity issues in clinical trials’.

The approach in study ALXN1210-PNH-302 states that once noninferiority is met for the primary endpoint, superiority will be assessed. Additionally, the protocol states that key secondary efficacy endpoints will be tested in a hierarchical manner provided that noninferiority was declared for the primary endpoint and that if noninferiority is established for a key secondary endpoint and a larger effect for ALXN1210 is observed, then superiority will be assessed using a 2-sided 0.05 test for each parameter.

This approach has been modified in the 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.

### 4.2. Changes from Analyses Specified in the Previous Version of the SAP

The original SAP (dated 12 June 2017) has been amended twice. A summary of the changes are described below.

#### 4.2.1. SAP version 2.0 (dated 31 October 2017)

During the conduct of the study, it has been observed that up to 1% of central laboratory chemistry samples undergo in vitro erythrocyte lysis or table top hemolysis (TTH) caused by sample mishandling. This is unrelated to hemolysis due to PNH. The reasons for TTH vary and include delayed or improper centrifugation and traumatic blood draws. In addition, PIGA deficient erythrocytes from patients with PNH are more susceptible to mechanical lysis than non-PNH erythrocytes (Smith, 1985). Hemolysis results in release of RBC contents including LDH, potassium and AST. In contrast to hemolysis in patients with PNH, in which serum potassium is normal, for samples affected by TTH both potassium and LDH are markedly and proportionally increased (Goyal and Schmotzer, 2015; Ostendorp 2006). Marked hyperkalemia (defined as >6mmol/L) seen in TTH, but not PNH hemolysis, differentiates TTH (in vitro) from PNH hemolysis (in vivo), and is not clinically significant (Hollander-Rodriguez 2006; Kovesdy 2014). Due to the artefactual increase in LDH in samples affected by TTH, the potassium, ALT, AST, magnesium, phosphorous, and LDH values in samples affected by TTH will not be used in the analysis of any efficacy or safety endpoints, with the exception that the LDH value will be used for the qualification of breakthrough hemolysis events. Breakthrough hemolysis is captured on a separate form and central lab LDH, in addition to new or worsening symptoms as specified in the protocol, are used by the principal investigator or designee to qualify patients with breakthrough hemolysis. TTH samples from the central lab will be defined as having serum potassium ≥ 6 mmol/L and LDH ≥ 2x ULN, and will be excluded from analyses as described above.

The exploratory endpoints of patient reported PNH symptoms and healthcare resource utilization were removed in protocol amendment 1, dated 23 October 2017, to reduce patient data collection burden. Therefore, Section 7.2.2 has been updated so only by-patient listings will be produced rather than summary statistics.

The choice of covariance structure to be utilized in the mixed model repeated measures (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 patient errors, and if that fails to converge, to use a pre-specified list of
appropriate structures. The covariance structure converging to the best fit, as determined by Akaike’s information criterion, would then be used in the analysis.

4.2.2. SAP version 2.1 (dated 27 November 2017)

The language around using exact methods in Section 7.2.1.6 has been simplified and made consistent with the ALXN1210-PNH-301 study. The change includes utilizing exact methods only if the stratified Newcombe method fails to provide estimates of confidence intervals rather than basing it on the number of events in a given cell.

Section 7.3.2.1 was updated to remove the analysis of the number and percentage of patients who had a treatment emergent adverse event (TEAEs) during study drug administration. A separate by-patient listing will be generated.
5. **DEFINITIONS**

5.1. **Efficacy**

5.1.1. **Primary Efficacy Endpoint**

The primary efficacy endpoint of the study is hemolysis as directly measured by LDH-PCHG from baseline to Day 183.

5.1.2. **Key Secondary Efficacy Endpoints**

The key secondary efficacy endpoints of the study (to be tested in a hierarchical manner) are:

1. Proportion of patients with breakthrough hemolysis, 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 $\geq 2 \times$ upper limit of normal (ULN)

2. Change in quality of life (QoL) assessed via the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale, Version 4, from Baseline to Day 183

3. Transfusion avoidance (TA), defined as the proportion of patients who remain transfusion-free and do not require a transfusion as per protocol-specifed guidelines from Baseline to Day 183

4. Proportion of patients with stabilized hemoglobin, defined as avoidance of a $\geq 2$ g/dL decrease in hemoglobin level from Baseline in the absence of transfusion from Baseline to Day 183

5.1.3. **Other Secondary Efficacy Endpoints**

Other secondary efficacy endpoints of the study are:

- Total number of units of pRBCs transfused from Baseline to Day 183
- Proportion of patients with LDH in the normal range (LDH-N) at Day 183
- Change in the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 Scale (QLQ-C30), Version 3.0, from Baseline to Day 183
- Change in clinical manifestations of PNH (fatigue, hemoglobinuria, abdominal pain, shortness of breath, anemia, dysphagia, and erectile dysfunction) from Baseline to Day 183
- Proportion of patients experiencing MAVEs from Baseline to Day 183

5.2. **Pharmacokinetic and Pharmacodynamic Endpoints**

Assessments for PK/PD are as follows:
• Change in serum ALXN1210 and eculizumab concentration over time
• Change in chicken red blood cell (cRBC) hemolytic activity over time (exploratory)
• Change in free C5 concentrations over time

5.3. Safety

The safety and tolerability of ALXN1210 compared with eculizumab 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 patients who develop antidrug antibodies (ADAs) will also be assessed.

5.3.1. Adverse Events

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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

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

• 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

Adverse events are further defined in Protocol Section 11.7.

5.3.2. Vital Signs

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

Samples for analysis of pregnancy status, hematology, chemistry, coagulation, virus serology, and urinalysis will be collected (See Appendix F of Study ALXN1210-PNH-302 protocol for a listing of all clinical laboratory parameters). If a suspected event of breakthrough hemolysis occurs, an unscheduled visit must take place at which time a sample is collected for analysis of LDH and PK/PD by the central laboratory. A central laboratory will be used to evaluate all laboratory assessments.

5.3.4. Electrocardiograms (ECGs)

A single 12-lead electrocardiogram (ECG) will be conducted. Heart rate (HR), PR, QRS, and QT will be measured. The QT interval will be corrected for HR using Fridericia’s 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 upon Investigator judgment and patient symptoms.

5.3.6. Immunogenicity

Blood samples will be collected to test for presence and titer of ADAs to ALXN1210 or eculizumab. Further characterization of antibody responses may be conducted as appropriate, including binding and neutralizing antibodies, PK/PD, safety, and activity of ALXN1210 or eculizumab.
6. DATA SETS ANALYZED (STUDY POPULATIONS)

6.1. Full Analysis Set

The full analysis set (FAS) will consist of all patients who received at least 1 dose of ALXN1210 or eculizumab.

The primary population for assessment of efficacy is the FAS. Patients will be compared for efficacy according to the treatment they were randomized to receive, regardless of the treatment they actually received.

6.2. Per Protocol Set

The per protocol (PP) set will consist of FAS patients who meet all of the following criteria:

- Missed 0 doses of ALXN1210 or no more than 1 dose of eculizumab during the 26 weeks of the Randomized Treatment Period
- Met the following inclusion criteria:
  - #2: Treated with eculizumab according to the labelled dosing recommendation for PNH for at least 6 months prior to Day 1
  - #3: Lactate dehydrogenase \( \leq 1.5 \times \text{ULN} \) at Screening. Sample must be obtained on a scheduled eculizumab-dosing day prior to dose administration (ie, at trough eculizumab level) and analyzed by the central laboratory
  - #4: Documented diagnosis of PNH, confirmed by high-sensitivity flow cytometry evaluation of RBCs and white blood cells (WBCs), with granulocyte or monocyte clone size of \( \geq 5\% \)
- Did not meet any of the following exclusion criteria:
  - #1: Lactate dehydrogenase value \( > 2 \times \text{ULN} \) in the 6 months prior to Day 1
  - #2: Major adverse vascular event in the 6 months prior to Day 1
  - #3: Platelet count \( < 30,000/\text{mm}^3 \) \( (30 \times 10^9/\text{L}) \) at Screening
  - #4: Absolute neutrophil count \( < 500/\mu\text{L} \) \( (0.5 \times 10^9/\text{L}) \) at Screening
  - #5: History of bone marrow transplantation
- Never received the wrong randomized treatment (ie, all patients who received assigned treatment per the randomization schedule)
- Followed the protocol-specified transfusion guidelines

The primary efficacy endpoint analysis, as well as key secondary endpoint analyses, will be performed on the PP set.
6.3. Safety Set

The safety set (SS) will consist of all patients who received at least 1 dose of ALXN1210 or eculizumab. Patients will be compared for safety according to the treatment they actually received during the Randomized Treatment Period. For a patient to be analyzed according to the treatment they actually received and not according to the randomization schedule, they would have to receive that treatment for all their study drug exposure visits. Safety analysis will be performed on the SS.

6.4. Other Sets

The PK analysis set will consist of all patients who received at least 1 dose of study drug and who have evaluable PK data.
7. STATISTICAL ANALYSIS

All data collected will be presented in summary tabulations. All data, as well as any outcomes derived from the data, will be presented in data listings. Graphical displays may also be provided, when appropriate. All analyses will be performed using SAS® release, version 9.4 or higher (SAS Institute Inc., Cary, NC, USA) or other validated statistical software. Continuous variables will be summarized using descriptive statistics, including number of observations and mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized by frequency counts and percentage of patients. Randomization will be stratified using: transfusion history (received a transfusion of pRBCs within 12 months prior to Day 1, yes or no). For all analyses and summaries, the randomization stratification variable refers to the observed transfusion history.

Clinical central laboratory samples that meet the definition of TTH will be identified and all potassium, ALT, 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 breakthrough hemolysis. TTH samples from the central lab will be defined as having serum potassium ≥ 6 mmol/L and LDH ≥ 2x ULN.

7.1. Study Patients

7.1.1. Disposition of Patients

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

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

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

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

7.1.2. Protocol Deviations

All major protocol deviations will be listed for all patients in the FAS. Additionally, the following protocol deviations will be identified programmatically from the database and the number of patients meeting these deviations will be summarized:

- Informed consent date is not prior to screening start date
Patients who did not meet all of the inclusion/exclusion criteria
Patients who did not receive eculizumab for at least 6 months prior to Day 1
Patients whose granulocyte or monocyte clone size is not ≥ 5%
Patients whose screening LDH is > 1.5 × ULN or missing
Patients who had MAVE in the 6 months prior to Day 1
Patients whose platelet count is < 30,000/mm³ (30 × 10⁹/L) or absolute neutrophil count is < 500/µL (0.5 × 10⁹/L) at Screening
Patients who had a history of bone marrow transplantation
Patients whose body weight < 40 kg at screening
Patients who missed 1 or more doses of ALXN1210 or 2 or more doses of eculizumab
Patients who did not receive study drug in accordance with the randomization schedule
Patients who did not follow protocol-specified transfusion guidelines after initiating study drug
Patients with no confirmation of vaccination against meningococcal infections within 3 years prior to, or at the time of, initiating study drug

7.1.3. **Demographics, Disease Characteristics, and History**

All demographic and baseline characteristics will be summarized using the FAS and SS. Summary statistics will be presented by treatment group and overall. Demographic and baseline characteristics will also be summarized by treatment group 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.

7.1.3.1. **Demographics**

The following demographic variables will be summarized:

- Sex
- Race including number (%) of patients of Japanese descent
- Ethnicity
- Age (years) at first study drug infusion: descriptive statistics (n, mean, median, SD, minimum, maximum) and frequency of patients in the following categories: ≤65, >65 years
- Baseline weight: descriptive statistics (n, mean, median, SD, minimum, maximum) and frequency of patients in the following categories: ≥ 40 to < 60 kg, ≥ 60 kg to < 100 kg, and ≥ 100 kg
- Baseline height
• Baseline body mass index (BMI)
• Transfusion history randomization stratification (yes/no)

7.1.3.2. Disease Characteristics and PNH Medical History

The following PNH disease characteristics will be summarized:

• Age (years) at PNH diagnosis
• Age (years) at first eculizumab infusion
• Method of PNH diagnosis
• Years from PNH diagnosis to informed consent
• PNH clone size (RBC and granulocyte/monocyte) at screening
• Packed RBC transfusion requirements in the year (and 6 months) prior to receiving study drug including number of transfusion episodes and units transfused
• All PNH symptoms experienced at any time prior to informed consent
• All PNH-associated conditions that were diagnosed at any time prior to informed consent
• Prior emergency room (ER) or hospitalizations due to PNH within 1 year prior to informed consent including admittance and number of days in intensive care unit and discharge diagnoses other than PNH
• History of any MAVE, including the number of patients (n, %) with any history of MAVE and within a particular MAVE category (eg, thrombophlebitis/deep vein thrombosis, pulmonary embolus, myocardial infarction, etc)

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

7.1.3.3. Medical / Surgical History and Baseline Physical Examination

Medical history will be classified by System Organ Class (SOC) and Preferred Term (PT) using the latest available version of standardized (MedDRA) and will be reported by treatment group and overall for the SS. Likewise, baseline physical examination information will be summarized for the SS.

7.1.4. Prior and Concomitant Medications / Therapies

Prior and concomitant medications will be summarized using the SS. Prior medications are defined as medications taken prior to the first study drug infusion and include all medications taken within 28 days prior to informed consent as well as all *Neisseria meningitidis* vaccinations administered within 3 years of dosing with ALXN1210. Concomitant medications are defined as medications received by the patients on or after the first study drug infusion through Day 183.

Medications will be coded using the World Health Organization Drug Dictionary version in use by Alexion at the time of the analysis. Medication summaries by treatment group (ie, number
[%) of patients using prior and concomitant medications will be presented by WHO-DRUG Anatomical Therapeutic Chemical (ATC) Level 3 and by WHO-DRUG generic name.

Listings of prior and concomitant medications will be produced. A by-patient listing of meningococcal vaccinations will be produced showing the date of vaccinations for each patient.

7.2. Efficacy Analyses

Efficacy analysis will be performed using FAS. The primary efficacy endpoint analysis, as well as key secondary endpoint analyses, will be repeated using PP set as a sensitivity analysis. The FAS is the primary population for all efficacy analyses. Baseline for central lab LDH is defined as the average of all available on study assessments prior to the first study drug infusion. Baseline for all other parameters is defined as the last available assessment prior to treatment (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, where available, will be used as the baseline assessment.

7.2.1. Primary Analysis

The primary efficacy endpoint is the difference between treatment arms in LDH-PCHG from Baseline to Day 183. Absolute LDH levels, and the change and percent change from Baseline, will be summarized at all study visits by treatment group. Baseline is defined as the average of all assessments analyzed by the central laboratory prior to first study drug administration.

The LDH-PCHG will be analyzed using a mixed model for repeated measures (MMRM; Mallinckrodt 2001, 2004) with the fixed, categorical effects of treatment, study visit, and study visit by treatment group interaction, as well as the continuous, fixed covariate of baseline LDH and the stratification randomization indicator of pRBC transfusion history (yes/no within 12 months prior to Day 1). 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; first order autoregressive, compound symmetry and Toeplitz method. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. A difference in LDH-PCHG between the ALXN1210 and eculizumab treatment groups at Day 183 along with a two-sided 95% CI will be calculated.

If the upper bound of the 95% CI for the difference (ALXN1210-eculizumab) is less than the noninferiority margin (NIM) of 15%, then ALXN1210 treatment will be concluded to be noninferior to eculizumab.

7.2.1.1. Handling of Dropouts or Missing Data

For the primary endpoint of LDH-PCHG from Baseline to Day 183, missing assessments of LDH for a particular patient 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 7.2.1.6.
7.2.1.2. **Subgroup Analysis**

Summaries of LDH-PCHG will be produced for the subgroups of the randomization stratification variable of transfusion history (received a transfusion of pRBCs within 12 months prior to Day 1, yes or no).

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

7.2.1.3. **Multicenter Studies**

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

7.2.1.4. **Hypothesis Testing and Significance Level**

For the primary efficacy endpoint, a two-sided 95% CI will be calculated. If noninferiority is met for the primary endpoint, key secondary endpoints will be tested for noninferiority using a closed-testing procedure in the following order so that the lack of significance of a test precludes assessment of subsequent tests:

1. Proportion of patient with breakthrough hemolysis through Day 183 (Week 26)
2. Change from baseline to Day 183 (Week 26) in FACIT-Fatigue
3. Transfusion avoidance
4. Proportion of patients with stabilized hemoglobin through Day 183 (Week 26)

If noninferiority is established for all key secondary endpoints, and a larger effect for ALXN1210 is observed, then superiority will be assessed using a closed-testing procedure and using a 2-sided 0.05 test for each parameter as follows:

5. PCHG-LDH from baseline to Day 183 (Week 26)
6. Change from baseline to Day 183 (Week 26) in FACIT-Fatigue
7. Proportion of patient with breakthrough hemolysis through Day 183 (Week 26)
8. Proportion of patients with stabilized hemoglobin through Day 183 (Week 26)
9. Transfusion avoidance

For the key secondary endpoints, a 2-sided 95% CI will be calculated. Point estimates and CIs will be computed for all key secondary efficacy endpoints regardless of the hierarchical testing procedure. Under the prespecified closed testing procedure, no adjustment of the type I error is required. Refer to Section 9.4 for details around the choice of NIM.

7.2.1.5. **Sensitivity Analyses**

The following sensitivity analyses will be produced for the primary endpoint of LDH-PCHG:

- The primary efficacy endpoint analysis as described in Section 7.2.1 will be repeated using the PP set.
• The primary efficacy endpoint analysis as described in Section 7.2.1, excluding the history of transfusion stratification factor, and baseline LDH level from the model as explanatory variables.

Additional analyses may be conducted for the primary endpoint of LDH-PCHG with consideration for the “missing not at random” assumption should the patient dropout rate exceed 5%.

7.2.1.6. Key Secondary Efficacy Analyses

Key secondary endpoints will be tested in a hierarchical manner provided that noninferiority was declared for the primary endpoint. When performing the analyses for the key secondary efficacy endpoints, a closed-testing procedure for noninferiority and superiority will be used as specified in Section 7.2.1.4.

Estimates and CIs will be computed for all key secondary efficacy endpoints 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 NIM. Refer to Section 9.6.1 for a more detailed description of the FACIT-Fatigue score and the scoring methods.

A difference in the percentages of patients with breakthrough hemolysis will be calculated between ALXN1210 and eculizumab treatment groups, along with a 95% CI for the difference using the stratified Newcombe CI method (Yan and Su 2010). The difference between the ALXN1210 and eculizumab treatment groups will be computed as a weighted combination of the differences between the ALXN1210 and eculizumab treatment groups within the stratification indicator of transfusion history (received a transfusion of pRBCs within 12 months prior to Day 1, yes or no) using Mantel-Haenszel weights (Agresti A, 2013). The confidence intervals will be computed using the common risk difference. If the upper bound of the 95% CI for the difference between the ALXN1210 and eculizumab treatment groups in the proportion of patients with breakthrough hemolysis is less than the NIM of 20%, then ALXN1210 will be declared noninferior for this parameter. If the stratified Newcombe method fails to provide estimates of CIs, the exact common risk difference method will be utilized in computing the CIs. If the rate of breakthrough hemolysis is 0 in both treatment arms whereby CIs cannot be estimated, ALXN1210 will be declared noninferior for this parameter and superiority will not be tested. Patients who withdraw from the study due to lack of efficacy during the Randomized Treatment Period will be considered as non-responders and will be counted in the group with breakthrough hemolysis. For patients who withdraw from the study for any other reason during the Randomized Treatment Period, their data up to the time of withdrawal will be used to assess breakthrough hemolysis.

Change in FACIT-Fatigue from Baseline to Day 183 (Week 26) will be analyzed using the same approach used for the primary endpoint analysis with a MMRM with the fixed, categorical effects of treatment, the stratification randomization indicator of transfusion history (received a transfusion of pRBCs within 12 months prior to Day 1, yes or no), study visit, and study visit by treatment group interaction, as well as the continuous fixed covariates of baseline FACIT-Fatigue score. 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; 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 ALXN1210 and eculizumab treatment groups at Day 183 along with a 2-sided 95% CI will be calculated. Missing FACIT-Fatigue scores for a patient at a particular visit will not be imputed. If the lower bound of the 95% CI for the difference between the ALXN1210 and eculizumab treatment groups in change from Baseline in FACIT-Fatigue to Day 183 (Week 26) is greater than the NIM of -3, then ALXN1210 will be declared noninferior for this parameter.

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

At each study visit, the proportion of patients who showed an improvement of at least 3 points for the FACIT-Fatigue scores will be summarized by treatment group using the same approach used for the key secondary efficacy endpoint of breakthrough hemolysis.

The same approach using the stratified Newcombe CI method, as described for breakthrough hemolysis analysis, will be employed for TA and stabilized hemoglobin. If the stratified Newcombe method fails to provide estimates of CIs, the exact common risk difference method will be utilized in computing the CIs. If the rate of TA/stabilized hemoglobin is 100 in both treatment arms whereby CIs cannot be estimated, ALXN1210 will be declared noninferior for this parameter and superiority will not be tested. Patients who withdraw from the study due to lack of efficacy during the Randomized Treatment Period will be considered as non-responders and will be counted in the group needing transfusion or in the group who did not meet the stabilized hemoglobin definition. For patients who withdraw from the study for any other reason during the Randomized Treatment Period, their data up to the time of withdrawal will be used to assess TA and stabilized hemoglobin. If the lower bound of the 95% CI for the difference between the ALXN1210 and eculizumab treatment groups for TA is greater than the NIM of -20%, then ALXN1210 will be declared to be noninferior to eculizumab. If the lower bound of the 95% CI for the difference between the ALXN1210 and eculizumab treatment groups in the proportion of patients with stabilized hemoglobin through Day 183 (Week 26) is greater than the NIM of -20%, then ALXN1210 will be declared noninferior for this parameter.

7.2.1.7. Other Secondary Efficacy Analyses

A summary of total number of units of pRBCs transfused during the Randomized Treatment Period will be summarized by treatment group. The number (%) of patients with LDH within the normal range (ie, ≤ 1 x ULN) at each study visit will be computed for both ALXN1210 and eculizumab treatment groups. LDH-N will be analyzed using a generalized estimating equation (GEE) approach which accounts for the repeated measures of LDH-N assessment at each visit (Liang 1986). The GEE approach provides odds ratios and CIs of treatment effect while controlling for the correlation between visits for a given patient and other baseline factors. LDH-N from Day 1 through Day 183 will be used as the dependent variable and indicator variable for treatment, history of transfusion (yes/no) and baseline LDH level (as a continuous variable) will be included in the model as explanatory variables. The within-patient correlation will assume to follow a first-order autoregressive structure in which the highest correlation assumed between visits that are closest in time.

Absolute 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. 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 (fatigue, chest pain, abdominal pain, dyspnea, dysphagia, hemoglobinuria, and erectile dysfunction) will be summarized by treatment group and at the study visits where these assessments are collected.

The number of any treatment-emergent MAVEs (n) and number of patients with events (n, %) to Day 183 will be displayed by treatment group.

No hypothesis testing of these parameters is planned.

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

7.2.2. **Other Analyses**

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

7.2.3. **Pharmacokinetic and Pharmacodynamic Analyses**

Assessments for PK/PD are as follows:

- Change in serum ALXN1210 and eculizumab concentration over time
- Change in cRBC hemolytic activity over time (exploratory)
- Change in free and total C5 concentrations over time

Serum ALXN1210 and eculizumab concentrations will be summarized over time using descriptive statistics: number of subjects, mean, SD, CV, median, minimum, and maximum. Mean serum ALXN1210 and eculizumab concentrations versus nominal time will be graphically presented on both linear and semi-logarithmic scales.

Summary statistics of the absolute values and changes and percentage changes from Baseline in total and free C5 serum concentrations and cRBC hemolysis will be presented over time by treatment group using the FAS.

7.3. **Safety Analyses**

All safety analysis will be conducted on the SS. All safety data available at the time of database lock up to Day 183 will be provided in by-patient listings. Baseline is defined as the last available assessment prior to first study drug infusion.

7.3.1. **Study Duration, Treatment Compliance, and Exposure**

Summary statistics (mean, standard deviation, median, minimum, and maximum) will be produced by treatment group for the following data using the FAS and SS:

- Number of study drug infusions from Day 1 to Day 183
- Number of patients receiving 1, 2, etc loading/induction doses and maintenance doses from Day 1 to Day 183
• Total number of patients with an infusion interruption, as well as total number of infusions interrupted from Day 1 to Day 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 Randomized Treatment Period/Day 183 (ie, study duration= date of completion/discontinuation-date of informed consent + 1)

• Total time on study treatment (days) calculated as the time in days from first study drug infusion date until the last study drug infusion date from the Randomized Treatment Period (ie treatment duration= last study drug infusion date from the Randomized Treatment Period - first study drug infusion date + 1). Note that dosing on Day 183 represents the start of the Extension Period and will not be included in these calculations.

The frequency and percentage of patients who had a percentage of drug compliance range by increments of 10% (ie ≥ 90% to ≤ 100%; ≥ 80% to < 90%; etc) will also be included. This will be calculated as follows:

Percent compliance = total number of study drug infusions taken from Day 1 to end of Randomized Treatment Period (excluding Day 183 study drug infusion) / total number of expected infusions to end of Randomized Treatment Period (excluding Day 183 study drug infusion)

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

7.3.2. **Adverse Events (AEs)**

Adverse events (AEs) will be classified by SOC and Preferred Term using the latest available version of MedDRA and will be reported by treatment group and overall. The AEs will be determined as occurring prior to treatment (pre-treatment) or as on or after first treatment (treatment-emergent) as described in Section 9.5. Analyses of Pre-treatment AEs (PTAEs) and treatment-emergent AEs (TEAEs) through Day 183 (Week 26) will be tabulated and presented separately. Patients having multiple AEs within a category (eg, overall, SOC, Preferred Term) will be counted once in that category. For severity/relationship tables, the patient’s highest grade/most related event within a category will be counted. Percentages will be based on the number of treated patients in the Safety Set within a cohort and overall. Tables will be sorted by descending frequency of SOC and by descending frequency of Preferred Term within an SOC. By-patient listings will be provided for all TEAEs and PTAEs for the SS.

AEs will include the displays described in the following subsections.

7.3.2.1. **Overall Summary of Adverse Events**

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

- Total number of TEAEs and patients with TEAEs
- Related TEAEs
- Not related TEAEs
• Grade 1 TEAEs
• Grade 2 TEAEs
• Grade 3 TEAEs
• Grade 4 TEAEs
• Grade 5 TEAEs

Related AEs are defined as AEs that are possibly, probably, or definitely related to study treatment. Not related AEs are defined as AEs that are unlikely or not related to study treatment. To satisfy the reporting requirements of the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), related AEs will be defined for separate analysis as AEs that are unlikely, possibly, probably or definitely related to study treatment, with not related AEs defined as AEs that are not related to study treatment.

The number and percentage of patients who withdraw from the study due to an AE, who have any TEAE leading to study treatment discontinuation, or who died on study will be presented. These statistics will be prepared separately for SAEs, with the exception of severity grading.

7.3.2.2. AEs and SAEs by System Organ Class and Preferred Term

The number of AEs and the number and percentage of patients with events will be presented by SOC and Preferred Term (PT). Patients are counted once in each SOC and Preferred Term. Percentages will be based on the total number of treated patients in the treatment group. Serious adverse events will be summarized similarly.

7.3.2.3. AEs and SAEs by System Organ Class, Preferred Term, and Relationship

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

7.3.2.4. AEs by System Organ Class, Preferred Term, and Severity

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

7.3.2.5. Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

A listing of patient deaths will be produced.

Important identified risks in this study include meningococcal infections, sepsis, serious infections, Aspergillus infection, and infusion reactions. Additional adverse events of special interest (AESIs) include serious cutaneous adverse reactions, cardiac disorders (including ventricular fibrillation), and angioedema. These AESIs will be summarized by treatment group in
tabular form. See Section 9.5.1 for a list of AE MedDRA Preferred Terms that will be considered for these summaries.

7.3.3. **Other Safety**

7.3.3.1. **Analyses for Laboratory Tests**

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

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

7.3.3.2. **Vital Signs and Physical Examination**

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

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

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

7.3.3.3. **Electrocardiograms (ECG)**

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

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

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

All immunogenicity analyses will be conducted on the SS. The number and percentage of patients developing ADA and anti-drug neutralizing antibodies, where applicable, will be summarized by treatment group. The number and percentage of patients with anti-drug cross-reactivity to eculizumab will be summarized.

7.3.3.5. **Non-Drug Therapies and Procedures**

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


Hollander-Rodriguez J, Calvert J. Hyperkalemia. American Family Physician; January 15, 2006; 73 (2)


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

Not applicable.

9.3. Sample Size, Power, and Randomization

Approximately 192 patients will be randomly assigned in a 1:1 ratio to continue on eculizumab (N = 96) or switch to ALXN1210 (N = 96) to ensure at least 172 evaluable patients (assumes no more than a 10% dropout rate). The sample size estimation is based on a noninferiority design comparing patients treated with ALXN1210 to those treated with eculizumab. The primary endpoint of hemolysis as directly measured by LDH-PCHG from Baseline through Day 183 will be used to assess noninferiority.

For the primary endpoint of LDH-PCHG from Baseline to Day 183, using a noninferiority margin (NIM) of 15% and a type I error of 1-sided 2.5%, a SD of 30%, a minimum of 172 patients will provide 90% power to demonstrate noninferiority of ALXN1210 to eculizumab. This margin is based on data from Alexion's PNH Registry. For patients who discontinued eculizumab, the mean percent change in LDH was +134% and represents the loss of benefit relative to patients who remained on eculizumab whose change in LDH is expected to remain stable. Preserving 50% of the benefit would give a margin of 67%; however, the more conservative and clinically appropriate margin of 15% was selected to preserve a more substantial amount of treatment effect (89%).

Adjusting for a possible 10% dropout rate, approximately 192 patients will be enrolled in this study.

Table 3: Summary of Parameters Used in Estimating Sample Size

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Percent Change in LDH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Power</td>
<td>90%</td>
</tr>
<tr>
<td>Type I error</td>
<td>1-sided 0.025</td>
</tr>
<tr>
<td>Noninferiority margin</td>
<td>0.15</td>
</tr>
<tr>
<td>Allocation ratio</td>
<td>1:1</td>
</tr>
<tr>
<td>Standard deviation of eculizumab/ALXN1210 response</td>
<td>0.30/0.30</td>
</tr>
<tr>
<td>Assumed treatment difference</td>
<td>0</td>
</tr>
<tr>
<td>Estimated sample size (SS)</td>
<td>172</td>
</tr>
<tr>
<td>Adjusted SS for 10% dropouts</td>
<td>192</td>
</tr>
</tbody>
</table>

a Standard deviation from TRIUMPH study on LDH-PCHG from Week 8 to Week 26

9.4. **Determination of Noninferiority Margin for Key Secondary Endpoints**

**Proportion of Patients with Breakthrough Hemolysis**

The margin of 20% NIM was based on data from a randomized placebo-controlled study of eculizumab, TRIUMPH (Hillmen et al., 2006). The lactate dehydrogenase (LDH) portion of the definition of breakthrough hemolysis 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. At week 26, 0% of patients on eculizumab had breakthrough hemolysis (LDH ≥ 2 × ULN). Based on data from the PNH Registry, 47% of patients who discontinued eculizumab had breakthrough hemolysis. A traditional choice of NIM is one with ≤ 50% loss of benefit. This would result in a NIM of 23% and rounded to a more clinically conservative value of 20%.

**Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale**

The margin of -3 was selected based on data from the TRIUMPH study, in which patients on eculizumab had a mean (SD) FACIT-Fatigue score of 36.7 (10.5) at Baseline and a mean score of 42.9 (7.5) at Week 26. The baseline from the TRIUMPH study was used in constructing the NIM as very few patients who discontinued treatment in the PNH registry had data on FACIT-Fatigue (N = 4). A traditional choice of NIM is one with ≤ 50% loss of benefit. This would result in a NIM of -3.

**Transfusion Avoidance**

The margin of -20% was selected based on data from the PNH Registry examining loss of benefit among patients who discontinued eculizumab compared to patients who remained on eculizumab treatment. The average TA rate was 87% at Week 26 after 12, 26, 52, and 78 weeks of eculizumab treatment. The rate of TA for patients who discontinued eculizumab was 37%. Using the traditional choice of NIM, with ≤ 50% loss of benefit, gives a margin of -25%; however, the more clinically conservative margin of -20% was selected.

**Proportion of Patients with Stabilized Hemoglobin**

The margin of -20% was selected based on data from the PNH Registry examining loss of benefit among patients who discontinued eculizumab compared to patients who remained on eculizumab treatment. The hemoglobin stabilization rate was 91% while on eculizumab and 46% for patients that discontinued eculizumab. Using the traditional choice of NIM, with ≤ 50% loss of benefit, a margin of -22.5% is obtained. The selected -20% margin is more clinically conservative.

9.5. **Technical Specifications for Derived Variables**

The following derived data will be calculated prior to analysis.

**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

<table>
<thead>
<tr>
<th>Age</th>
<th>Reference Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at enrollment</td>
<td>Date of signing ICF</td>
</tr>
<tr>
<td>Age at PNH diagnosis</td>
<td>Date of PNH diagnosis</td>
</tr>
<tr>
<td>Age at first study infusion</td>
<td>Date of first study infusion</td>
</tr>
<tr>
<td>Age at first eculizumab infusion</td>
<td>Date of first eculizumab Infusion</td>
</tr>
</tbody>
</table>

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. 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.

Disease Duration

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

Definition of Baseline Values

Baseline for LDH is defined as the average of all available on study assessments prior to the first study drug infusion. Baseline for all other parameters is defined as the last non-missing assessment value prior to first study drug infusion unless otherwise specified.

Change from Baseline

Change in values from Baseline will be calculated as follows.

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

Percent Change in Assessments from Baseline

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

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

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

Analysis Visits

Summaries over postbaseline time points or analyses at specific postbaseline time points will be performed based on the list of visits described in the schedule of assessment of the protocol. For all assessments, the number of days from baseline will be calculated using the following formula: (date of assessment) - (date of first study treatment) + 1. This number of days will be used to assign analysis visit. 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 assessment, 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, and a prior scheduled visit on Day 113 and 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 more than 1 record is within the same analysis visit window, the record closest to the midpoint of the interval will be used in the analysis. If two records are “tied” before and after the middle of the interval, the earlier record will be used in the analysis.

9.5.1. Adverse Events

Treatment-emergent AEs (TEAEs) are events with start dates and start times on or after the date and time of the first ALXN1210 dose. If the start date of an AE is partially or completely missing and the end (stop) date and time of the AE does not indicate that it occurred prior to first dose, then the determination of treatment-emergent status will be based on the following:

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

All other AEs are considered PTAEs.

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

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 AESI. 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

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, 4=very much). The FACIT-Fatigue subscale scoring guideline (version 4) will be used as follows:

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

9.6.2. EORTC QLQ-C30 Scoring Calculations

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

Table 5: Scoring the EORTC QLQ-C30

<table>
<thead>
<tr>
<th>Scale</th>
<th>Item range</th>
<th>Item Numbers</th>
<th>Raw Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global health status/QoL</td>
<td>QL2</td>
<td>6</td>
<td>(Q29+Q30)/2</td>
</tr>
<tr>
<td>Functional Scales</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Functioning</td>
<td>PF2</td>
<td>3</td>
<td>(Q1+Q2+Q3+Q4+Q5)/5</td>
</tr>
<tr>
<td>Role Functioning</td>
<td>RF2</td>
<td>3</td>
<td>(Q6+Q7)/2</td>
</tr>
<tr>
<td>Emotional Functioning</td>
<td>EF</td>
<td>3</td>
<td>(Q21+Q22+Q23+Q24)/4</td>
</tr>
<tr>
<td>Cognitive Functioning</td>
<td>CF</td>
<td>3</td>
<td>(Q20+Q25)/2</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>SF</td>
<td>3</td>
<td>(Q26+Q27)/2</td>
</tr>
</tbody>
</table>

Proprietary and Confidential
<table>
<thead>
<tr>
<th>Scale</th>
<th>Item range</th>
<th>Item Numbers</th>
<th>Raw Score&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>FA 3</td>
<td>10,12,18</td>
<td>(Q10+Q12+Q18)/3</td>
</tr>
<tr>
<td>Nausea and Vomiting</td>
<td>NV 3</td>
<td>14,15</td>
<td>(Q14+Q15)/2</td>
</tr>
<tr>
<td>Pain</td>
<td>PA 3</td>
<td>9,19</td>
<td>(Q9+Q19)/2</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>DY 3</td>
<td>8</td>
<td>Q8</td>
</tr>
<tr>
<td>Insomnia</td>
<td>SL 3</td>
<td>11</td>
<td>Q11</td>
</tr>
<tr>
<td>Appetite Loss</td>
<td>AP 3</td>
<td>13</td>
<td>Q13</td>
</tr>
<tr>
<td>Constipation</td>
<td>CO 3</td>
<td>16</td>
<td>Q16</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>DI 3</td>
<td>17</td>
<td>Q17</td>
</tr>
<tr>
<td>Financial Difficulties</td>
<td>FI 3</td>
<td>28</td>
<td>Q28</td>
</tr>
</tbody>
</table>

<sup>a</sup> Item range is the difference between the possible maximum and the minimum response to individual items.

<sup>b</sup> Raw score is the mean of the component items.

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

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

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

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

Missing data: In the case of multi-item scales missing one of the items, raw scores can still be calculated using the completed items as long as more than 50% of the items were answered. So, 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 Repeated Measures Mixed Model Analysis

The main analysis method for the primary and key secondary endpoint of percentage change from baseline to Day 183 (Week 26) in LDH and change from baseline to Day 183 (Week 26) in FACIT-Fatigue involve MMRM analysis. The basic SAS code for percent change in LDH or change from baseline in FACIT-Fatigue is given by:

```sas
proc mixed data=ADEFF method=reml;
class subj id trt visit nbcstrata;
model pchg= trt visit nbcstrata nbcstrata/ddfm=kr solution;
repeated visit/type=UN subject=subj id;
lsmeans trt *visit/cl diff;
where visit>0;
run;
```

where subj id is the patient identifier variable, trt is the randomized treatment group, visit is the visit variable (0 representing the baseline visit), base is the LDH/FACIT value at baseline, pchg is the percentage change from baseline in LDH [for FACIT-Fatigue, it would be replaced with
CHG for change from baseline], and rbcstrata is the pRBC transfusion history randomization stratification variable.

9.6.3.2. SAS Code for Newcombe
The main analysis method for the secondary endpoints of breakthrough hemolysis, TA, and stabilized hemoglobin is the stratified Newcombe confidence interval method.

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

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

where trt is the randomized treatment group, rbcstrata is the pRBC transfusion history randomization stratification, TA is the categorical transfusion avoidance indicator.

9.6.3.3. SAS Code for GEE
The main analysis method for the other secondary efficacy analyses of LDH-N is the generalized estimating equation.

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

```
proc genmod descending;
class subjid trt rbcstrata;
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 patient identifier variable, trt is the randomized treatment group, ldhn is LDH-N, base is the LDH value at baseline, and rbcstrata is the rbc randomization stratification variable.