

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

**Unique Protocol ID:** ALXN1210-PNH-301

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Alexion Pharmaceuticals, Inc.



**STATISTICAL ANALYSIS PLAN**

PROTOCOL NUMBER: ALXN1210-PNH-301

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

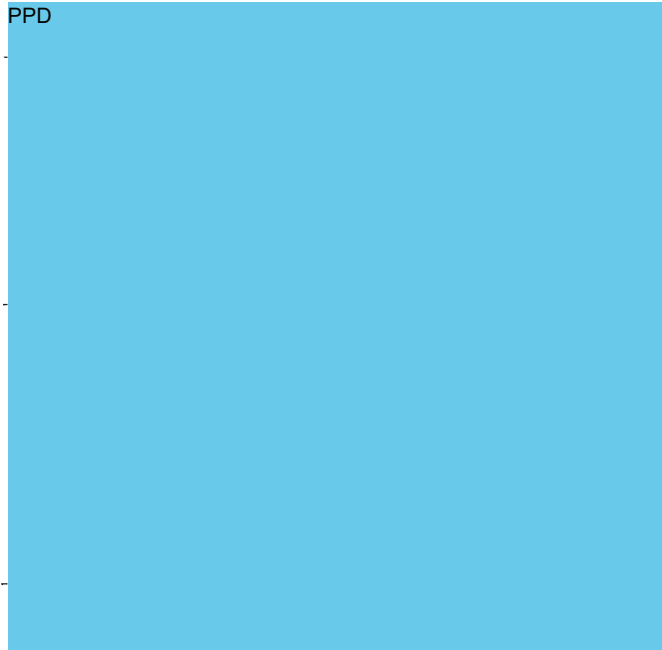
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**1. APPROVAL SIGNATURES**

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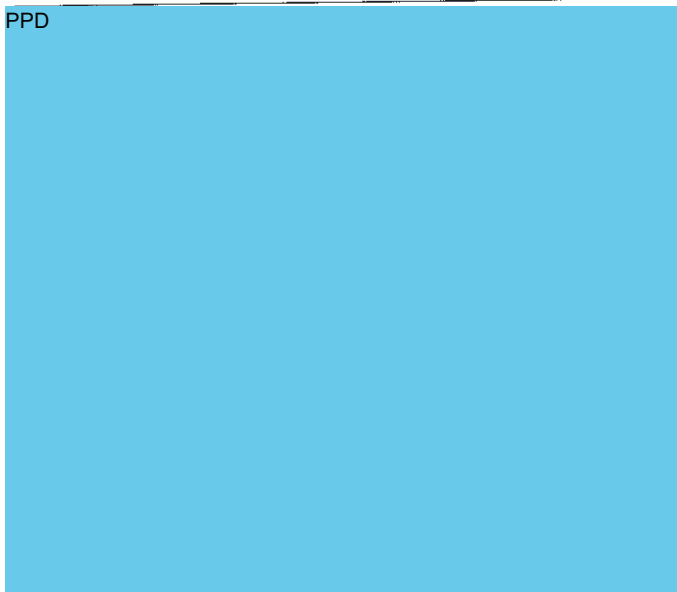
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**1. APPROVAL SIGNATURES**

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

### TABLE OF CONTENTS

1.	APPROVAL SIGNATURES .....	2
2.	TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES .....	3
3.	LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS.....	6
4.	DESCRIPTION OF THE PROTOCOL .....	8
4.1.	Changes from Analyses Specified in the Protocol .....	9
4.2.	Changes from Analyses Specified in the Previous Versions of the SAP .....	9
4.2.1.	SAP version 2 (dated 28 April 2017) .....	9
4.2.2.	SAP version 3 (dated 26October 2017).....	10
5.	DEFINITIONS .....	12
5.1.	Efficacy.....	12
5.1.1.	Coprimary Efficacy Endpoints .....	12
5.1.2.	Key Secondary Efficacy Endpoints .....	12
5.1.3.	Other Secondary Efficacy Endpoints.....	13
5.2.	Pharmacokinetic/Pharmacodynamic.....	13
5.3.	Safety .....	14
5.3.1.	Adverse Events (AEs).....	14
5.3.2.	Vital Signs .....	14
5.3.3.	Laboratory Assessments .....	15
5.3.4.	Electrocardiograms (ECGs).....	15
5.3.5.	Physical Examination .....	15
5.3.6.	Immunogenicity.....	15
6.	DATA SETS ANALYZED (STUDY POPULATIONS).....	16
6.1.	Full Analysis Set.....	16
6.2.	Per Protocol (PP) Set .....	16
6.3.	Safety Set.....	16
6.4.	Other Sets.....	17
7.	STATISTICAL ANALYSIS .....	18
7.1.	Study Patients .....	18
7.1.1.	Disposition of Patients.....	18
7.1.2.	Protocol Deviations .....	18

7.1.3.	Demographics, Disease Characteristics, and History .....	19
7.1.3.1.	Demographics .....	19
7.1.3.2.	Disease Characteristics and PNH Medical History .....	20
7.1.3.3.	Medical / Surgical History and Baseline Physical Examination .....	20
7.1.4.	Prior and Concomitant Medications / Therapies .....	20
7.2.	Efficacy Analyses .....	21
7.2.1.	Coprietary Analysis .....	21
7.2.1.1.	Transfusion Avoidance Primary Analysis .....	21
7.2.1.2.	LDH normalization (LDH-N) Primary Analysis .....	22
7.2.1.3.	Handling of Dropouts or Missing Data .....	22
7.2.1.4.	Subgroup Analysis .....	22
7.2.1.5.	Multicenter Studies .....	23
7.2.1.6.	Hypothesis Testing and Significance Level .....	23
7.2.1.7.	Sensitivity Analyses .....	23
7.2.2.	Secondary Analyses .....	24
7.2.2.1.	Key Secondary Efficacy Analyses .....	24
7.2.2.2.	Other Secondary Efficacy Analyses .....	26
7.2.3.	Other Analyses .....	26
7.2.4.	Pharmacokinetic and Pharmacodynamic Analyses .....	26
7.3.	Safety Analyses .....	27
7.3.1.	Study Duration, Treatment Compliance, and Exposure .....	27
7.3.2.	Adverse Events (AEs) .....	28
7.3.2.1.	Overall Summary of Adverse Events .....	28
7.3.2.2.	AEs and SAEs by System Organ Class (SOC) and Preferred Term (PT) .....	29
7.3.2.3.	AEs and SAEs by SOC, PT, and Relationship .....	29
7.3.2.4.	AEs and SAEs by SOC, PT, and Severity .....	29
7.3.2.5.	Deaths, Other SAEs, and Other Significant Adverse Events .....	29
7.3.3.	Other Safety .....	29
7.3.3.1.	Analyses for Laboratory Tests .....	29
7.3.3.2.	Vital Signs and Physical Examination .....	30
7.3.3.3.	Electrocardiograms (ECG) .....	30
7.3.3.4.	Immunogenicity .....	30

7.3.3.5.	Non-Drug Therapies and Procedures.....	30
8.	REFERENCES .....	31
9.	APPENDICES .....	32
9.1.	Protocol Schedule of events.....	32
9.2.	Changes from Analyses Specified in the Previous Version of the SAP.....	32
9.3.	Sample Size, Power, and Randomization .....	32
9.4.	Determination of Noninferiority Margin for Key Secondary Endpoints.....	34
9.5.	Technical Specifications for Derived Variables .....	35
9.5.1.	Adverse Events .....	36
9.6.	Additional details on Statistical Methods .....	37
9.6.1.	FACIT-Fatigue (FACIT-FATIGUE) Calculations.....	37
9.6.2.	EORTC QLQ-C30 Scoring Calculations.....	37
9.6.3.	SAS Code for Efficacy Analyses.....	39
9.6.3.1.	SAS Code for Newcombe.....	39
9.6.3.2.	SAS Code for Repeated Measures Mixed Model Analysis.....	39

#### LIST OF TABLES

Table 1:	Abbreviations and acronyms .....	6
Table 2:	Summary of Parameters Used in Estimating Sample Size with Coprimary Endpoints .....	33
Table 3:	Age and reference date .....	35
Table 4:	Scoring the EORTC QLQ-C30.....	37

### 3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and acronyms are used in this SAP.

**Table 1: Abbreviations and acronyms**

<b>Abbreviation or acronym</b>	<b>Explanation</b>
ADA	antidrug antibody
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
AST	Aspartate aminotransferase (SGOT)
AUC <sub>t</sub>	area under the serum concentration-versus-time-curve from time 0 (dosing) to the last quantifiable concentration
AUC <sub>0-τ</sub>	area under the concentration-versus-time-curve from time 0 (dosing) to the end of the dosing interval
BMI	Body mass index
BNP	brain natriuretic peptide
BP	Blood pressure
C5	complement component 5
CAP	complement alternative pathway
CKD	Chronic kidney disease
CI	Confidence Interval
CL	Total clearance
cm	Centimeters
C <sub>max</sub>	maximum observed serum concentration
C <sub>min</sub>	minimum observed serum concentration
cRBC	chicken red blood cell
CS	Clinically significant
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variance
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EAS	Extension Analysis Set
EOI	End of infusion
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 Scale
FAS	Full Analysis Set
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FDA	Food and Drug Administration
GEE	Generalized estimating equations



<b>Abbreviation or acronym</b>	<b>Explanation</b>
GOF	Goodness-of-fit
HR	Heart rate
IV	intravenous(ly)
LDH	lactate dehydrogenase
LDH-N	lactate dehydrogenase normalization
LOCF	Last Observation Carried Forward
MAVE	major adverse vascular event
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
NIM	noninferiority margin
PD	Pharmacodynamic
PK	Pharmacokinetic
PNH	paroxysmal nocturnal hemoglobinuria
pRBC	Peripheral red blood cell
PT	Preferred Term (MedDRA)
PTAEs	Pre-Treatment Adverse Events
q2w	once every 2 weeks
Q8w	once every 8 weeks
QLQ-C30	Quality of Life Questionnaire-Core 30 Scale
QoL	quality of life
QTcF	QT interval corrected using Fridericia's formula
RBC	Red blood cell
RR	Respiration rate
SAE	Serious adverse event
SAS <sup>®</sup>	Statistical Analysis Software <sup>®</sup>
SAP	Statistical Analysis Plan
SD	Standard deviation
SMQ (N)	standard MedDRA query (narrow)
SOC	System Organ Class (MedDRA)
TA	transfusion avoidance
TEAEs	Treatment-Emergent Adverse Events
t <sub>max</sub>	time to maximum observed serum concentration
TTH	table top hemolysis
ULN	upper limit of normal
WHO-DRUG	World Health Organization Drug Dictionary
λ <sub>z</sub>	apparent terminal-phase elimination rate constant

#### 4. DESCRIPTION OF THE PROTOCOL

ALXN1210-PNH-301 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 are naïve to complement inhibitor treatment.

Approximately 214 eligible patients will be randomized in a 1:1 ratio to one of two treatment arms, (1) ALXN1210 or (2) eculizumab. Patients 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 first dose of study drug) and screening lactate dehydrogenase (LDH) levels ( $1.5$  to  $< 3 \times$  upper limit of normal [ULN] or  $\geq 3 \times$  ULN). Enrollment of patients without a history of transfusion in the past year will be capped at 20%.

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. Dosages are based on the patient's body weight, as shown in table below:

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

Patients 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, patients will enter an extension period and receive ALXN1210. Beginning on Day 183, patients who had been randomized to the ALXN1210 treatment group will receive a maintenance dose (as described above) of ALXN1210 q8w, and patients who had been randomized to the eculizumab group will receive a loading dose (as described above) of ALXN1210 followed 2 weeks later and q8w thereafter by a weight-based maintenance dose of ALXN1210.

The primary objective of this study is to assess the noninferiority of ALXN1210 compared to eculizumab in adult patients 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 (ALXN1210-eculizumab) in transfusion avoidance (TA) rate is greater than -20%, and 2) the lower bound of the 95% CI for the odds ratio of ALXN1210 compared to eculizumab for lactate dehydrogenase 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 ALXN1210 in this patient population
- 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
- To evaluate the safety and efficacy in patients who switch from eculizumab to ALXN1210 in the Extension Period

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, pharmacokinetics (PK) and pharmacodynamics (PD) analyses. This statistical analysis plan (SAP) outlines only the analyses that are to be included in that report.

A final CSR will be produced at study completion and will include data on all patients in the study at the end of the extension period.

#### **4.1. Changes from Analyses Specified in the Protocol**

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 December 2016) EU draft guidance ‘Guideline on multiplicity issues in clinical trials’.

Protocol amendment 3 states that both coprimary endpoints individually need to demonstrate noninferiority. Once noninferiority is met superiority will be assessed using a Hochberg multiple comparison approach. 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 ALXN1210 is observed, then superiority will be assessed using a 2-sided 0.05 test for each parameter.

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.

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

The original SAP (dated 03February 2017) was amended twice. A summary of the changes are described below.

##### **4.2.1. SAP version 2 (dated 28 April 2017)**

See Section 4.1 for changes from analyses specified in version 1 of the SAP.

Additionally, Section 7.2.1.7 was modified to exclude summaries of transfusion avoidance and LDH normalization by Process A and Process B as Process B material was available

sooner than expected and only the following 4 patients will receive ALXN1210 Process A: 0555-301A, 0421-301A, 0552-302A, 0607-302A.

Furthermore, as the focus of the clinical study report (CSR) will be on the randomized treatment period, the analyses specified in the previous version of the SAP Section 7.4 on patients who switch from eculizumab to ALXN1210 in the extension period will be excluded. These analyses will be generated at study completion and included in the final CSR.

#### **4.2.2. SAP version 3 (dated 26 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  $>6\text{mmol/L}$ ) seen in TTH, but not PNH hemolysis, differentiates TTH (in vitro) from PNH hemolysis (in vivo), and is not clinically significant (Hollander-Rodriguez 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  $\geq 6\text{mmol/L}$  and LDH  $\geq 2\times\text{ULN}$ , 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 4, dated 23 October 2017, to reduce patient data collection burden. Therefore, Section 7.2.3 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.

Section 9.5.1 has been updated to remove the detailed derivation of adverse event of special interest as the specific terms are dependent on the Medical Dictionary for Regulatory Activities (MedDRA) version in use at the time of analysis. The details will be documented in the appropriate analysis data model (ADaM) specifications.

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

#### **4.2.3. SAP version 3.1 (dated 27 November 2017)**

The analysis of breakthrough hemolysis in Section 7.2.2.1 has been updated to be consistent with the ALXN1210-PNH-302 study. The change includes utilizing exact methods if the stratified Newcombe method fails to provide estimates of confidence intervals due to small cell sizes.

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. Coprimary Efficacy Endpoints

The coprimary efficacy endpoints of the study are:

##### 1. Transfusion Avoidance

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

A pRBC transfusion will be administered when a patient has a

- 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 presence of clinical signs or symptoms
2. Hemolysis as directly measured by LDH-N levels from Day 29 (first scheduled evaluation status post initiation of maintenance dosing) through Day 183 (Week 26)

#### 5.1.2. Key Secondary Efficacy Endpoints

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

1. Percentage change in LDH from Baseline to Day 183 (Week 26)
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 (Week 26)

The FACIT-Fatigue scale (Version 4.0) is a collection of QoL questionnaires pertaining to the management of fatigue symptoms due to a 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. Patients 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 patients with breakthrough hemolysis

Proportion of patients with breakthrough hemolysis 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  $\geq 2 \times$  upper limit of normal [ULN], after prior LDH reduction to  $< 1.5 \times$  ULN on therapy

#### 4. Proportion of patients with stabilized hemoglobin

Proportion of patients with stabilized hemoglobin is defined as avoidance of a  $\geq 2$  g/dL decrease in hemoglobin level from baseline in the absence of transfusion through Day 183 (Week 26)

### 5.1.3. Other Secondary Efficacy Endpoints

Other secondary efficacy endpoints of the study are:

- 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 (Week 26)

The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 Scale (QLQ-C30), Version 3.0, is a questionnaire developed to assess the QoL of cancer patients. 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 first occurrence of LDH-N
- Total number of units of packed red blood cells (pRBCs) transfused through Day 183 (Week 26)

Due to the low volume of pRBC in Japan, 1 unit of pRBC in Japan is to be interpreted as half pRBC units globally.

- Change in clinical manifestations of PNH (fatigue, chest pain, hemoglobinuria, abdominal pain, dyspnea, dysphagia, and erectile dysfunction) from Baseline to Day 183 (Week 26)
- Proportion of patients experiencing MAVEs through Day 183 (Week 26)

## 5.2. Pharmacokinetic/Pharmacodynamic

Assessments for PK/PD are as follows:

- Serum ALXN1210 and eculizumab concentration over time
- Chicken red blood cell (cRBC) hemolytic activity over time (exploratory)
- Free complement component 5 (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 (AEs)**

An AE is defined as any unfavorable and 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, 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.

- 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. Temperature will be obtained in degrees Celsius or Fahrenheit. 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 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 breakthrough hemolysis occurs, an unscheduled visit must take place at which 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. HR, PR, QRS, and QT will be measured and corrected intervals (Fridericia formula) 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. 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 antidrug antibodies (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 exulizumab.

## **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 and have at least 1 efficacy assessment post first infusion

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 (PP) 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 randomized treatment period
- Met following inclusion criteria:
  - #2: documented diagnosis of PNH
  - #3: presence of 1 or more PNH-related signs or symptoms
  - #4: LDH level  $\geq 1.5 \times$  ULN
- Did not meet exclusion criteria:
  - #1: current or previous treatment with a complement inhibitor
  - #2: Platelet count  $< 30,000/\text{mm}^3$
  - #3: Absolute neutrophil count  $< 500/\mu\text{L}$
  - #4: History of bone marrow transplantation
- Never received the wrong randomized treatment i.e all patients who received assigned treatment
- Followed the protocol-specified transfusion guidelines

The coprimary efficacy endpoint analyses, 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. 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 ALXN1210 and who have evaluable PK data.

## 7. STATISTICAL ANALYSIS

All data collected in this study will be presented using summary tables, figures, and data listings. For categorical variables, frequencies and percentages will be presented by treatment group and overall. For continuous variables, descriptive statistics (n, mean, median, SD, minimum, maximum) will be presented by treatment group and overall. Randomization was stratified using: transfusion history (0, 1 to 14, or > 14 units of packed red blood cells [pRBCs] in the 1 year prior to first dose of study drug) and screening LDH levels (1.5 to < 3 × upper limit of normal [ULN] or ≥ 3 × ULN)]. If, at the end of enrollment, there are less than 5% of patients in any of the 5 strata within a treatment arm, that strata will be pooled with the adjacent strata. If the middle category of 1-14 units transfused had less than 5% of the patients within a treatment arm, that category would be grouped with the >14 units. Additionally, if there are small number of patients in any of the 6 combined strata, collapsing will be undertaken, as appropriate. For all analyses and summaries, the randomization stratification variables refer to the observed transfusion history and LDH levels and pooled stratification variables.

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 and treated patients. The number and percentage of patients who 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 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: United States of 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 meet the inclusion/met the exclusion criteria.

#### 7.1.2. Protocol Deviations

All major protocol deviations will be listed for all patients in the FAS. The number of patients meeting the following protocol deviations will be summarized:

- Informed consent date is not prior to screening start date

- Patients not meeting all of the inclusion/exclusion criteria
- Patients whose granulocyte or monocyte clone size is not  $\geq 5\%$
- Patients whose screening LDH is  $<1.5 \times \text{ULN}$  or missing
- Patients whose platelet count is  $<30,000/\text{mm}^3$  ( $30 \times 10^9/\text{L}$ ) or absolute neutrophil count is  $<500/\mu\text{L}$  ( $0.5 \times 10^9/\text{L}$ ) at Screening
- Patients who had a history of bone marrow transplantation
- Patients with no PNH signs or symptoms prior to Screening
- Patients whose body weight  $< 40\text{kg}$  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 information 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 Infusion: descriptive statistics (n, mean, median, SD, minimum, maximum) and frequency of patients in the following categories:  $\leq 65$ ,  $>65$  years
- Baseline Weight: descriptive statistics (n, mean, median, SD, minimum, maximum) and frequency of patients in the following categories:  $\geq 40$  to  $< 60$  kg,  $\geq 60$  to  $< 100$  kg, and  $\geq 100$  kg
- Baseline Height
- Baseline Body Mass Index (BMI)

- LDH randomization stratification
- Packed red blood cell (pRBC) randomization stratification

### **7.1.3.2. Disease Characteristics and PNH Medical History**

The following PNH disease characteristics will be summarized:

- Age (years) at PNH diagnosis.
- Method of PNH diagnosis.
- Years from PNH diagnosis to informed consent.
- PNH clone size at screening.
- pRBC transfusion requirements in the year prior to receiving study drug including number of transfusion episodes and units transfused
- All PNH symptoms experienced at any time prior to informed consent.
- All PNH associated conditions that were diagnosed at any time prior to informed consent
- Prior Emergency Room (ER) 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 major adverse vascular event (MAVE). The number of patients (n, %) with any history of MAVE and within a particular MAVE category (e.g. thrombophlebitis/deep vein thrombosis, pulmonary embolus, myocardial infraction, etc.) will be displayed.

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 infusion and include all medications taken within 28 days prior to informed consent as well as all Neisseria meningitides vaccinations

administered within 3 years of dosing with ALXN1210. Concomitant medications are defined as medications received by the patients on/after first study 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 i.e. 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 Neisseria meningitides will be produced showing the date of vaccinations for each patient.

## **7.2. Efficacy Analyses**

Efficacy analysis will be performed using FAS. The coprimary efficacy endpoint analyses, 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 LDH is defined as the average of all available 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. Coprimary Analysis**

The coprimary efficacy endpoints are 1) the difference between treatment groups in the proportion of patients who achieve transfusion avoidance through Day 183, and 2) the relative effect between treatments in LDH-N from Day 29 through Day 183 expressed as an odds ratio.

#### **7.2.1.1. Transfusion Avoidance Primary Analysis**

Transfusion avoidance will be achieved only by those patients 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 patients achieving TA will be calculated between ALXN1210 and eculizumab treatment groups, along with a 95% CI for the difference using the stratified Newcombe confidence interval 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 groups of transfusion history (0, 1 to 14, or > 14 units of packed red blood cells [pRBCs] in the 1 year prior to first dose of study drug) and screening LDH levels (1.5 to < 3 × upper limit of normal [ULN] or ≥ 3 × ULN)] using Mantel-Haenszel weights (Agresti 2013). The confidence intervals will be computed using the common risk difference. The lower bound of this 95% CI will be used for the determination of noninferiority as previously described. 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 requiring transfusions. 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 transfusion avoidance.

#### **7.2.1.2. LDH normalization (LDH-N) Primary Analysis**

The number (%) of patients achieving LDH-N will be summarized at all study visits. 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 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-patient correlation will assume to follow a first-order autoregressive structure in which the highest correlation assumed between visits that are closest in time. Day 29 is the first scheduled assessment after initiation of maintenance dosing, and experience with eculizumab and Phase 1b/2 ALXN1210 data demonstrate 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 as previously described. Missing assessments of LDH for a particular patient at a particular visit will not be imputed.

#### **7.2.1.3. Handling of Dropouts or Missing Data**

For the coprimary endpoint of proportion of patients who achieve TA through Day 183, 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 requiring transfusions. 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 transfusion avoidance.

For the coprimary endpoint of LDH-N, 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 7.2.2 .

#### **7.2.1.4. Subgroup Analysis**

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 packed red blood cells [pRBCs] in the 1 year prior to first dose of study drug) and screening LDH levels ( $1.5 < \text{LDH} < 3 \times \text{ULN}$  or  $\text{LDH} \geq 3 \times \text{ULN}$ ). Analysis of LDH-N using GEE will include history of transfusion (as a categorical variable based on the stratification factor levels).

The percentage of patients who achieve TA with 95% exact CIs will be computed for both the ALXN1210 and eculizumab treatment groups and the randomization strata.



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

#### **7.2.1.5. Multicenter Studies**

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

#### **7.2.1.6. Hypothesis Testing and Significance Level**

For the coprimary efficacy endpoints, the two-sided 95% CI will be calculated. If noninferiority 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 breakthrough hemolysis through Day 183 (Week 26)
4. Proportion of patients with stabilized hemoglobin through Day 183 (Week 26)

If noninferiority is established for all key secondary endpoints, then superiority 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 patients with breakthrough hemolysis 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 Day 183 (Week 26)
8. Change from Baseline to Day 183 (Week 26) in FACIT-Fatigue
9. Proportion of patients with stabilized hemoglobin through Day 183 (Week 26)
10. Transfusion avoidance

Under this prespecified closed testing procedure, no adjustment of the type I error is required.

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

#### **7.2.1.7. Sensitivity Analyses**

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 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 first dose of study drug: 0, 1-4, >4-14 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 patients who did not receive a transfusion i.e. ignoring protocol-specified guidelines for transfusion.
- 95% CIs for the difference between ALXN1210 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 odds ratios with 95% confidence intervals.
- 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 upper limit of normal as being below the upper limit of normal or not and the proportion of patients whose median LDH from Day 29 through Day 183 normalize (LDH-N) will be summarized by treatment group. A difference in the percentage of patients achieving LDH-N will be calculated between ALXN1210 and eculizumab treatment groups, along with a 95% CI for the difference using the stratified Newcombe confidence interval method. 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 groups using Mantel-Haenszel weights (Agresti 2013). The confidence intervals will be computed using the common risk difference approach of Newcombe.

## **7.2.2. Secondary Analyses**

### **7.2.2.1. Key Secondary Efficacy Analyses**

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 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 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 a mixed model for repeated measures (MMRM; Mallinckrodt 2001, 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 first dose of study drug) and screening LDH levels ( $1.5$  to  $< 3 \times \text{ULN}$  or  $\geq 3 \times \text{ULN}$ ), study visit and study visit by treatment group interaction as well as 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; 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 along with a 2-sided 95% CI will be calculated. 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 ALXN1210 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 ALXN1210 will be declared noninferior for this parameter. 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 -5, then ALXN1210 will be declared noninferior for this parameter.

The same approach using the stratified Newcombe confidence interval method as described for the primary analysis of TA will be employed for the key secondary endpoints of breakthrough hemolysis 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 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. Similarly, if the rate of 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 with breakthrough hemolysis 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 the key secondary endpoints of breakthrough hemolysis and stabilized hemoglobin. 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 through Day 183 (Week 26) is less than the NIM of 20%, then ALXN1210 will be declared noninferior for this parameter. 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.

At each study visit, the proportion of patients 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**

Absolute 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 patients 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.

Pre-treatment 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 followup prior to initiating treatment with study drug are defined as:

$$(\text{first study drug dose date}-\text{initial PNH diagnosis date}+1)/365.25$$

Patient-years of followup after initiating treatment with study drug are defined as:

$$(\text{Day183}/\text{Discontinuation}/\text{death date}-\text{first study drug dose date}+1)/365.25$$

MAVE rates based on 100 patient-years of follow-up will be calculated as the number of patients with MAVE in the particular treatment group x 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 treatment group. Kaplan-Meier curves for both treatment groups and the randomization strata and estimates of time from first study drug to first occurrence of LDH-N since first study drug will be produced. Patients who do not achieve LDH-N by the end of the randomized treatment period or who were lost to follow up will be censored at the date of Day 183 or date of last contact.

No statistical testing of these parameters is planned.

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

#### **7.2.3. Other Analyses**

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

#### **7.2.4. 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 semilogarithmic 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.

Other PK/PD analyses will be described in a separate PK/PD analysis plan.

### **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 patient listings. Baseline is defined as the last available assessment prior to first study drug.

#### **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 using the FAS, and SS:

- Number of 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 (i.e 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 (i.e treatment duration=Last study drug infusion date from the randomized treatment period-first study drug infusion date + 1). Note that dosing on Day 183 is 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% (i.e.  $\geq 90\%$  to  $\leq 100\%$ ;  $\geq 80\%$  to  $< 90\%$ ; etc) will also be included. This will be calculated as follows:

Percent compliance=Total number of infusions taken from Day 1 to end of randomized treatment period (excluding Day 183 infusion) / Total number of expected infusions to end of randomized treatment period (excluding Day 183 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 PT using the latest available version of MedDRA and will be reported by treatment group and overall. The adverse events 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 Adverse Events (PTAEs) and Treatment-Emergent Adverse Events (TEAEs) through Day 183 (week 26) will be tabulated and presented separately. Patients having multiple AEs within a category (e.g., overall, SOC, PT) will be counted once in that category. For severity/relationship tables, the patient's highest grade/most related event within a category will be counted. Percentages will be based on the number of treated patients in the Safety Set within a cohort and overall. Tables will be sorted by descending frequency of SOC and by descending frequency of PT within SOC.

Listings will be provided for all TEAEs and PTAEs for the SS.

AEs will include the displays described in the following sub-sections.

#### **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. Related AEs (Japanese definition) are defined as AEs that are unlikely, possibly, probably or definitely related to study treatment. Not related AEs (Japanese definition) are 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 (SOC) and Preferred Term (PT)**

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

### **7.3.2.3. AEs and SAEs by SOC, PT, 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. SAEs will be summarized similarly.

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

The number of TEAEs and the number and percentage of patients with events will be presented by SOC and PT as described above by severity (grade 1, grade 2, grade 3, grade 4, 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 SAEs, 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 events of interest include serious cutaneous adverse reactions, cardiac disorders (including ventricular fibrillation), and angioedema. These important identified risks and adverse events of interest 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, AST, ALT, GGT, 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 (blood pressure, heart rate, respiratory rate, 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.

Absolute values and changes from baseline in weight will be summarized by visit and treatment group. A 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 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

- Agresti, A. *Categorical Data Analysis* (2013). 3rd ed. Hoboken, NJ: John Wiley & Sons
- Hillmen P, Young NS, Schubert J, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med*. 2006; 355:1233-1243
- Goyal T, Schmotzer CL. Validation of Hemolysis Index Thresholds Optimizes Detection of Clinically Significant Hemolysis . *Am J Clin Pathol* 2015; 143:579-583.
- Hochberg, Y. (1988), "A Sharper Bonferroni Procedure for Multiple Significance Testing," *Biometrika*, 75, 800–803
- Hollander-Rodriguez J, Calvert J. Hyperkalemia. *American Family Physician*; January 15, 2006; 73 (2)
- Kovesdy C. Management of hyperkalaemia in chronic kidney disease. *Nature Reviews Nephrology*, November 2014; 10
- Liang K-Y, Zeger SL. Longitudinal data analysis using generalized linear methods. *Biometrika*. 1986; 73(1):13-22.
- Mallinckrodt CH, Lane PW, Schnell D et al. Recommendations for the primary analysis of continuous endpoints in longitudinal clinical trials. *Drug Information Journal* 2008; 42: 303-319.
- Mallinckrodt CH, Clark WS, David SR. Accounting for dropout bias using mixed-effects models. *Journal of Biopharmaceutical Statistics* 2001; 11(1&2): 9-21.
- Mallinckrodt CH, Kaiser CJ, Watkin JG, et al. The effect of correlation structure on treatment contrasts estimated from incomplete clinical trial data with likelihood-based repeated measures compared with last observation carried forward ANOVA. *Clinical Trials* 2004; 1(6):477-89
- Ng Tie-Hua. Noninferiority hypotheses and choice of noninferiority margin. *Statistics in Medicine* 2008; 27:5392-5406.
- Oostendrop M, van Solinge WW, Kemperman H. Potassium but Not Lactate Dehydrogenase Elevation Due To In Vitro Hemolysis Is Higher in Capillary Than in Venous Blood Samples *Arch Pathol Lab Med*. 2012; 136:1262–1265.
- Smith, 1985. Abnormal Erythrocyte Fragmentation and Membrane Deformability in Paroxysmal Nocturnal Hemoglobinuria *Am J Hematol*.1985; 20:337-343.
- Yan, X., and Su, X. G. "Stratified Wilson and Newcombe Confidence Intervals for Multiple Binomial Proportions." *Statistics in Biopharmaceutical Research* 2010; 2:329–335.

## **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 214 patients will be randomly assigned in a 1:1 ratio to receive ALXN1210 (N = 107) or eculizumab (N = 107) to ensure at least 193 evaluable patients (assumes no more than a 10% drop-out rate). The sample size estimation is based on a noninferiority design comparing patients treated with ALXN1210 to those treated with eculizumab. Coprimary endpoints of hemolysis as directly measured by the normalization of LDH (LDH-N) from Day 29 through Day 183 and the proportion of patients who achieve transfusion avoidance (TA) through Day 183 will be used to assess noninferiority. The sample size is based on the endpoint that requires the larger number of patients.

For the coprimary endpoint of LDH-N, using a noninferiority margin (NIM) based on the relative benefit of eculizumab with respect to placebo of 0.39 and a type I error of 1-sided 2.5%, a minimum of 142 patients will provide 80% power to demonstrate noninferiority of ALXN1210 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, in order to preserve the constancy assumption, the rate of LDH-N was calculated adjusted to the observed baseline LDH of the current ALXN1210 Phase 1b and 2 data. This was done by including patients 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 Day 29 to Day 183 to be consistent with the proposed analysis plan for this study. As the proportion of LDH-N for placebo treated patients was 0% at all visits, the upper bound of the 95% CI was used in order to be able to calculate an odds ratio. The final estimate of benefit was based on a LDH-N proportion of 42% for eculizumab-treated patients and 10% for placebo for an odds ratio of 6.5. A traditional choice of NIM is one with  $\leq 50\%$  loss of benefit resulting in a NIM of an odds ratio of 0.39. The calculation of NIM follows 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 Food and Drug Administration (FDA) Guidance for Industry: Non-Inferiority Clinical Trials. While 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 patients.

For the other coprimary endpoint of proportion of patients not receiving any transfusions through Day 183, using a NIM of -20% and a type I error of 1-sided 2.5%, a minimum of 193 patients will provide 80% power to demonstrate noninferiority between the treatment arms. The NIM was determined based on the global PNH Registry for eculizumab-treated patients 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 so to preserve the constancy assumption, the NIM was assessed based on available data from treated and untreated patients in proportion to enrollment expectations in the current study. Patients treated with eculizumab (TA rate of 57.1%) showed a benefit over untreated patients (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 patients without a history of transfusions to be no more than 20%. Enrolled patients for this study will be capped at 20% for patients without a history of transfusions to ensure constancy is satisfied.

A traditional choice of NIM is one with  $\leq 50\%$  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 patients with and without a history of transfusions. Further, given the proportion of patients 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 2), the final sample size estimate selected for this study is based on the TA endpoint. Adjusting for a possible 10% dropout rate, approximately 214 patients will be enrolled in this study.

**Table 2: Summary of Parameters Used in Estimating Sample Size with Coprimary Endpoints**

Parameters	LDH Normalization (LDH-N)	Transfusion Avoidance (TA)
Power	80%	80%
Type I error	1-sided 0.025	1-sided 0.025
Noninferiority margin	0.39 <sup>a</sup>	-0.20 <sup>b</sup>
Allocation ratio	1:1	1:1
Mean eculizumab response	0.42 <sup>c</sup>	0.57 <sup>d</sup>
Standard deviation of eculizumab response	NA	NA
Assumed treatment difference	1	0
Estimated sample size (SS)	142	193
Adjusted SS for 10% dropouts	158	214

<sup>a</sup> based on odds ratio

<sup>b</sup> based on difference in rates

<sup>c</sup> Response rate from TRIUMPH study adjusted for baseline LDH

<sup>d</sup> Response rate from Global PNH Registry adjusted for history of transfusion

Note: Software package: Hintze, J. (2011). PASS 11. NCSS, LLC. Kaysville, Utah, US.  
[www.ncss.com](http://www.ncss.com).

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

### Percentage change in LDH

The margin was selected based on data from a randomized placebo-controlled study (Triumph, 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% confidence interval of -114% to -88%. Using the upper bound of -88% as a conservative estimate of benefit, a traditional choice of NIM is one with  $\leq 50\%$  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  $\leq 25\%$  loss of benefit, which results in an 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, 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 one with  $\leq 50\%$  loss of benefit. This would result in a NIM of -5. While 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 patients.

### Percent of patients with breakthrough hemolysis

The margin was selected based on data from a randomized placebo-controlled study (Triumph, Hillmen 2006). The 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. That study showed a benefit of eculizumab over placebo with a difference of -81.4% with a 95% confidence interval of -69.8% to -92.96% in breakthrough hemolysis. Using the lower bound of -69.8% as a conservative estimate of benefit, a traditional choice of NIM is one with  $\leq 50\%$  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 patients with stabilized hemoglobin

The margin was selected based on data from a randomized placebo-controlled study (Triumph, Hillmen 2006) which showed a benefit of eculizumab over placebo with a difference of 39.5% in proportion of patients with stabilized hemoglobin as defined in this protocol after 26 weeks of treatment. A traditional choice of NIM is one with  $\leq 50\%$  loss of benefit. This would result in a NIM of approximately -20%. While 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 patients.

## 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 3: Age and reference date**

<b>AGE</b>	<b>REFERENCE DATE</b>
• Age at Enrollment	• Date of Signing ICF
• Age at PNH Diagnosis	• Date of PNH diagnosis
• Age at First Infusion	• Date of First Infusion

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 infusion and the date of PNH diagnosis (i.e.  $\text{INT}[(\text{Date of first infusion} - \text{Date of PNH diagnosis} + 1)/365.25]$  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 average of all available 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.

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

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

### 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 Day 127, and a prior scheduled visit Day of 113 and subsequent scheduled visit Day of 141, the window will start at 120 days from baseline and will go to 133 days from baseline.

If only one record is within an analysis visit window, the data from that record will be used in the analysis. If more than one record is within the same analysis visit window, the record closest to the 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 Pre-Treatment Adverse Events (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 (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 (i.e. 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 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, 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 4: Scoring the EORTC QLQ-C30**

	<b>Scale</b>	<b>Item range<sup>a</sup></b>	<b>Item Numbers</b>	<b>Raw Score<sup>b</sup></b>
Global health status/QoL	QL2	6	29,30	$(Q29+Q30)/2$

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

<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:

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

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

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

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

The main analysis method for the coprimary endpoint of TA and the secondary endpoint of breakthrough hemolysis 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 strata*trt*TA/riskdiff (common CL=newcombe);
run;
```

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

#### SAS Code for GEE

The main analysis method for the coprimary endpoint 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;
  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.

#### 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 involve mixed model repeated measures analysis. The basic SAS code for percent change in LDH is given by:

```
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:

```
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 patient identifier variable, trt is the randomized 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.