

**A Phase 2, Open-Label, Multiple Ascending Dose Study to Evaluate the Efficacy, Safety, Tolerability, Immunogenicity, Pharmacokinetics, and Pharmacodynamics of ALXN1210 Administered Intravenously to Patients With Paroxysmal Nocturnal Hemoglobinuria**

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Alexion Pharmaceuticals, Inc.



## STATISTICAL ANALYSIS PLAN

PROTOCOL NUMBER: ALXN1210-PNH-201

**A PHASE 2, OPEN-LABEL, MULTIPLE ASCENDING DOSE STUDY TO EVALUATE THE EFFICACY, SAFETY, TOLERABILITY, IMMUNOGENICITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF ALXN1210 ADMINISTERED INTRAVENOUSLY TO PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA**

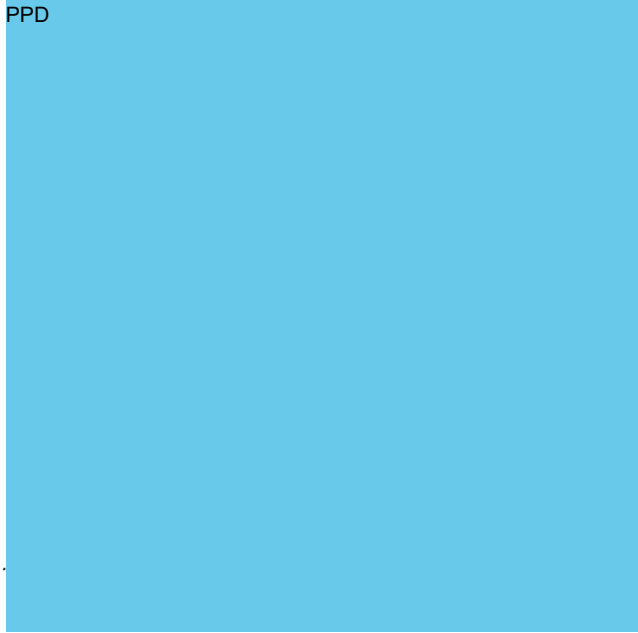
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## 1. APPROVAL SIGNATURES

PPD



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## 1. APPROVAL SIGNATURES



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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**

Abbreviation or acronym	Explanation
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
cm	centimeters
BNP	brain natriuretic peptide
BP	Blood pressure
CKD	Chronic kidney disease
CI	Confidence Interval
CL	Total clearance
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
EOI	End of infusion
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 Scale
FA	Full Analysis
FACIT-FATIGUE	Functional Assessment of Chronic Illness Therapy-Fatigue
FDA	Food and Drug Administration
GEE	Generalized estimating equations
GOF	Goodness-of-fit
HR	Heart rate
IV	intravenous(ly)
LDH	lactate dehydrogenase
LOCF	Last Observation Carried Forward
MAVE	major adverse vascular event
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
PD	Pharmacodynamic
PK	Pharmacokinetic

<b>Abbreviation or acronym</b>	<b>Explanation</b>
PNH	paroxysmal nocturnal hemoglobinuria
pRBC	Peripheral red blood cell
PT	Preferred Term (MedDRA)
PTAEs	Pre-Treatment Adverse Events
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
SOC	System Organ Class (MedDRA)
TEAEs	Treatment-Emergent Adverse Events
t <sub>max</sub>	time to maximum observed serum concentration
ULN	upper limit of normal
VAS	Visual analog scale
V <sub>ss</sub>	volume of distribution at steady state
WHO-DRUG	World Health Organization Drug Dictionary

#### 4. DESCRIPTION OF THE PROTOCOL

ALXN1210-PNH-201 is a Phase 2, open-label, multiple ascending dose study to evaluate the efficacy, safety, tolerability, immunogenicity, PK, and PD of multiple doses of ALXN1210 administered IV to patients with PNH who have not been previously treated with a C5 complement inhibitor.

Four treatment cohorts and up to 26 patients (at least 6 per cohort) are planned for enrollment, with at least 20 patients planned for evaluation. All patients are to be screened for study eligibility after providing written informed consent to participate. Patients who fail to meet any of the eligibility criteria may be rescreened once for study participation, at the discretion of the Investigator.

Patients enrolled in Cohort 1 will receive induction doses of ALXN1210 of 1400 mg on Day 1 and 1000 mg on Day 15. On Day 29, they will receive the first of 8 maintenance doses of 1000 mg of ALXN1210 (administered every 28 days or 4 weeks) (Table 1). Patients enrolled in Cohort 2 will receive induction doses of ALXN1210 of 2000 mg on Day 1 and 1600 mg on Day 22. On Day 43, they will receive the first of 5 maintenance doses of 1600 mg of ALXN1210 (administered every 42 days or 6 weeks). Patients enrolled in Cohort 3 will receive induction doses of ALXN1210 of 1600 mg on Day 1 and 1600 mg on Day 15. On Day 29, they will receive the first of 4 maintenance doses of 2400 mg of ALXN1210 (administered every 56 days or 8 weeks). Patients enrolled in Cohort 4 will receive an induction dose of ALXN1210 of 3000 mg on Day 1. On Day 29 they will receive the first of 3 maintenance doses of 5400 mg of ALXN1210 (administered every 84 days or 12 weeks). The first 2 patients in Cohort 4 will receive their induction dose (3000 mg) at least 1 day apart. The third patient will receive the induction dose at least 7 days after the second patient has received the induction dose.

If additional patients are screened and are eligible for enrollment before a dose-escalation decision has been made by the DMC for any cohort, those patients will be assigned to the active cohort with the lowest dose level.

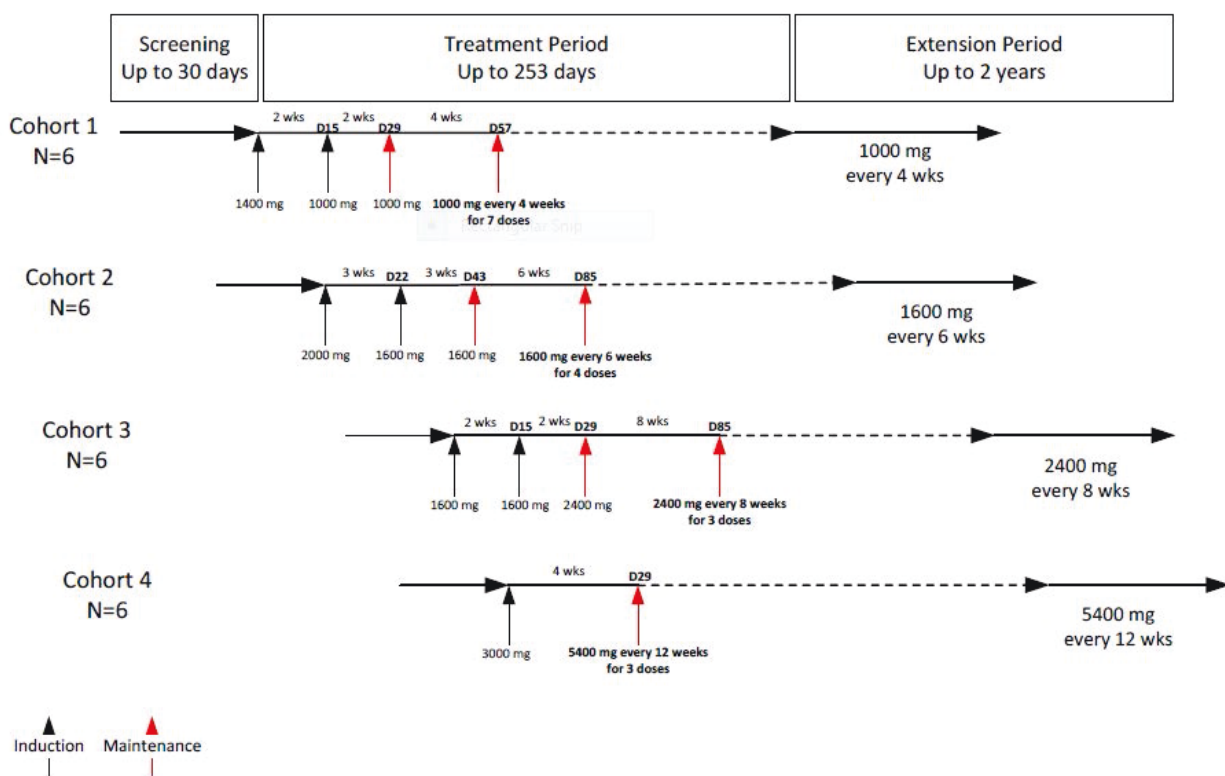
On Day 253, patients will continue treatment in a long-term Extension Period of the study, at the same maintenance dose and frequency as their final dose of ALXN1210 administered during the Treatment Period.

The dosing schedule is provided in Table 1 and the overall study design is presented in Figure 1 .

**Table 1: Dosing Schedule**

Cohort	Patients	Induction	Maintenance
1	6	1400 mg on Day 1 1000 mg on Day 15	1000 mg on Day 29 and then every 28 days or 4 weeks (Days 57, 85, 113, 141, 169, 197, 225) 8 maintenance doses
2	6	2000 mg on Day 1 1600 mg on Day 22	1600 mg on Day 43 and then every 42 days or 6 weeks (Days 85, 127, 169, 211) 5 maintenance doses
3	6	1600 mg on Day 1 1600 mg on Day 15	2400 mg on Day 29 and then every 56 days or 8 weeks (Days 85, 141, 197) 4 maintenance doses
4	6 to 8	3000 mg on Day 1	5400 mg on Day 29 and then every 84 days or 12 weeks (Days 113 and 197) 3 maintenance doses

**Figure 1: ALXN1210-PNH-201 Study Schematic**



The study objectives are as follows:

Primary Objective

The primary objective of this study is to evaluate the efficacy, safety, and tolerability of multiple doses of ALXN1210 administered IV to complement inhibitor treatment-naïve patients with PNH.

Secondary Objectives

The secondary objectives are to:

- Characterize the PK and PD effects of multiple doses of ALXN1210 administered IV to complement inhibitor treatment-naïve patients with PNH.
- Investigate the immunogenicity of ALXN1210 administered IV to complement inhibitor treatment-naïve patients with PNH.

Additional information about the study can be found in the protocol.

A clinical study report (CSR) will be produced after the end of the maintenance period plus the Day 281 visit for cohort 4, and will include safety, efficacy, Pharmacokinetics (PK) and Pharmacodynamics (PD) analyses. The Day 281 visit (the first dose in the Extension Period) will be included for Cohort 4 as patients in Cohort 4 receive their last dose during Maintenance on Day 197 and Day 281 would provide safety and efficacy at the trough concentration of ALXN1210. 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**

There are no changes from analyses specified in the protocol apart from the inclusion of data up to the Day 281 visit for Cohort 4 (the first dose in the Extension Period) in the analyses.

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

Not Applicable.

## **5. EFFICACY AND SAFETY**

### **5.1. Efficacy**

#### **5.1.1. Primary Endpoint(s)**

The primary efficacy endpoint is:

- Change in lactate dehydrogenase (LDH) from baseline to Day 253 (Week 36).

#### **5.1.2. Secondary Endpoints**

The secondary efficacy endpoints include:

- Changes in hemolysis-related hematologic parameters: free hemoglobin, haptoglobin, reticulocyte count, PNH red blood cell (RBC) clone, and D-dimer.
- Changes in clinical manifestations of PNH: fatigue, abdominal pain, dyspnea, dysphagia, chest pain, and erectile dysfunction.

#### **5.1.3. Exploratory Endpoints**

The exploratory endpoints include:

- Change from baseline in the need for blood transfusions
- Change from baseline in the following disease-associated biomarkers: estimated glomerular filtration rate (eGFR), spot urine albumin:creatinine ratio, and plasma brain natriuretic peptide (BNP)
- Change from baseline in quality of life (QoL), assessed via the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale, version 4 and European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 Scale, Version 3.0 (EORTC QLQ-C30) scales
- Change from baseline in major adverse vascular events (MAVEs). The definition of a MAVE is provided in Section 13.5 of the protocol.

##### **5.1.3.1. Functional Assessment of Chronic Illness Therapy -Fatigue (FACIT-FATIGUE)**

The FACIT-Fatigue (FACIT-FATIGUE) scale (Version 4.0) is a collection of QoL questionnaires targeted to the management of fatigue symptoms due to a chronic illness. It is a self-reported questionnaire that assesses patient health-related fatigue over the preceding 7 days. The FACIT-FATIGUE questionnaire consists of 13 items scored on a 5-point Likert scale (0=not at all, 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 and the higher the score the better the QoL. Refer to Section 9.5.1 for additional description and method of calculation.

### **5.1.3.2. European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 Scale, Version 3.0 (EORTC QLQ-C30)**

The EORTC QLQ-C30 scale (Version 3.0) is a questionnaire developed to assess the QoL of cancer patients. EORTC QLQ-C30 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 an instrument from which several scales can be constructed. 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. Refer to Section 9.5.2 for a more detailed description of the EORTC QLQ-C30 and the scoring methods.

## **5.2. Immunogenicity**

The immunogenicity endpoints include:

- Measurement of antidrug antibody (ADA) to ALXN1210

## **5.3. Pharmacokinetic/Pharmacodynamic**

The Pharmacokinetic/Pharmacodynamic endpoints include:

- Changes in serum ALXN1210 concentration over time
- Change in cRBC hemolytic activity
- Change in free and total C5 concentration

## **5.4. Safety**

Safety endpoints include:

- Changes from baseline in physical examination assessments and vital signs
- Change from baseline in electrocardiogram (ECG) parameters
- Change from baseline in laboratory assessments
- Incidence of AEs and SAEs

### **5.4.1. 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 or procedure, whether or not considered related to the medicinal product or procedure, which occurs during the course of the clinical study.

Exacerbations of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition, are all to be considered AEs.

All AEs will be graded according to criteria from CTCAE v4.03, published June 14, 2010.

- Grade 1: Mild (awareness of sign or symptom, but easily tolerated)
- Grade 2: Moderate (discomfort sufficient to cause interference with normal activities)
- Grade 3: Severe (incapacitating, with inability to perform normal activities)
- Grade 4: Life threatening
- Grade 5: Fatal

Adverse events are further defined in Protocol Section 15.1.

#### **5.4.2. 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 mmHg. Temperature will be obtained in degrees Celsius. HR will be documented in beats per minute.

#### **5.4.3. Laboratory Assessments**

Blood samples for analysis of hematology, clinical chemistry, coagulation, BNP, urinalysis/urine chemistry, and virus serology parameters will be collected as specified in the Schedule of Assessments (See Appendix 1 of the protocol for a listing of all clinical laboratory parameters). A central laboratory will be used to evaluate all laboratory assessments. If a screening laboratory sample is cancelled by the central laboratory due to hemoglobin interference in a grossly hemolyzed specimen, a local retest may be performed.

#### **5.4.4. Physical Examination**

A physical examination assessing general appearance, skin, head/eyes/ears/nose/throat, neck, lymph nodes, chest, heart, abdominal cavity, limbs, central nervous system and musculoskeletal will be performed. An abbreviated physical exam consisting of a body system relevant examination based upon Investigator judgment and subject symptoms will be performed as specified in the Schedule of Assessments.

#### **5.4.5. Electrocardiograms (ECGs)**

A triplicate 12-lead electrocardiogram (ECG) will be obtained at screening, prior to the first dose of ALXN1210 on Day 1, and at the end of study (Day 1009 for Cohorts 1 and 2, Day 981 Cohort 3, and Day 1037 for Cohort 4) or Early Termination visit. A single ECG will be obtained at pre-dose, Day 253 for all Cohorts.

Heart rate, PR, QRS, RR, and QT will be measured and corrected intervals (Fridericia formula) will be calculated.

#### **5.4.6. Infusion Site Evaluation**

Evaluation for infusion site reaction will be made at the time point described in the protocol Schedule of Assessments (Section 7). Infusion site reactions will be recorded as an AE using the appropriate coding terms.



An induration or reaction of <10 mm will not be listed as an AE unless it persists for more than 24 hours. Pain at site of infusion will be assessed using a 100 mm visual analog scale (VAS) as soon as practical after completion of the infusion.

## **6. DATA SETS ANALYZED (STUDY POPULATIONS)**

### **6.1. Safety Set**

The safety set will consist of all patients who received at least 1 dose of ALXN1210; this population will be used for the safety analyses.

### **6.2. Full Analysis (FA)**

The full analysis set (FA) will consist of all patients in the safety set with a baseline and at least 1 LDH measurement post-first ALXN1210 dose. The FAS will be used for all efficacy analyses.

### **6.3. Other Sets**

The PK analysis set will consist of all patients who have sufficient serum concentration data to enable the calculation of PK parameters. The PK analysis set will be used for PK summaries.

The PD analysis set will consist of all patients with a baseline and at least 1 PD measurement post-first ALXN1210 dose. The PD analysis set will be used for all PD summaries.

The immunogenicity analysis set will consist of all patients who have an ADA sample both pre and post first ALXN1210 dose. The immunogenicity analysis set will be used for immunogenicity summaries.

## **7. STATISTICAL ANALYSIS**

All data collected in this study will be documented using summary tables, figures, and data listings. For categorical variables, frequencies and percentages will be presented for each cohort, and for the combined cohorts. For continuous variables, descriptive statistics (n, mean, median, SD, minimum, maximum) will be presented for each cohort, and for the combined cohorts.

Descriptive statistics for PK parameters will include the number of observations, mean, SD, coefficient of variance (CV), median, minimum, maximum, geometric mean, and geometric %CV.

### **7.1. Study Patients**

#### **7.1.1. Disposition of Patients**

A summary of patient disposition for all treated patients will be presented and will include a summary of the number and percentage of screened patients, screen failures, and treated patients. The number and percentage of patients who completed the study through the end of the maintenance period or discontinued/withdrew from the study through the end of the maintenance period, along with reason for discontinuation/withdrawal will be presented.

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

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

#### **7.1.2. Protocol Deviations**

All protocol deviations will be listed for all patients in the safety set.

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

All demographic and baseline characteristics information will be summarized using the FA Set. Summary statistics will be presented by cohort and overall. 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
- Ethnicity
- Age (years) at First Infusion
- Baseline Weight
- Baseline Height

- Baseline Body Mass Index (BMI)
- Subjects of Japanese Descent

#### **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 (granulocyte, and red blood cell (RBC)) at screening.
- Peripheral red blood cell (pRBC) transfusion requirements in the year prior to receiving ALXN1210 including number of transfusion episodes and units transfused.
- First PNH symptoms.
- 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.

#### **7.1.3.3. Medical / Surgical History and Baseline Physical Examination**

Medical history information will be summarized by cohort for the safety and FA set (if different) using the number (%) of patients who have a medical or surgical history. Likewise, baseline physical examination information will be summarized by cohort.

#### **7.1.4. Prior and Concomitant Medications / Therapies**

Prior and concomitant medications will be summarized using the Safety set. 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 meningitidis vaccinations administered within 3 years of dosing with ALXN1210. Concomitant medications are defined as medications received by the patients on/after first study infusion.

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

Listings of prior and concomitant medications will be produced.

## 7.2. Efficacy Analyses

Efficacy analyses will be performed on the Full Analysis Set (FAS).

### 7.2.1. Primary Analysis

The primary efficacy endpoint is the change from baseline in lactate dehydrogenase (LDH) levels to Day 253. Absolute LDH levels, and the change and percent change from baseline will be summarized at all study visits, by cohort and overall. Baseline is defined as the average of all available assessments prior to first ALXN1210 infusion.

A mixed model for repeated measures (MMRM) (Mallinckrodt, 2001; Mallinckrodt, 2004) with the fixed, categorical effect of visit and fixed, continuous effect of baseline LDH levels as covariates will be fit to test whether changes and percent changes differ from zero at each time point for the combined cohorts. 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. Confidence intervals (CI) and p-values from the model will be presented.

As a sensitivity analysis, changes and percent changes from baseline will be analyzed using the Wilcoxon signed-rank test. Last observation carried forward (LOCF) will be used for patients with missing Day 253. If MMRM analysis fails to converge given the small sample size in this study, Wilcoxon signed-rank test will be used for the primary analysis of LDH.

The number (%) of patients achieving LDH levels at or below 1.0 times upper limit of normal (1.0 x ULN) and levels at or below 1.5 x ULN) will be displayed.

Mean ( $\pm 95\%$  CI) of absolute LDH levels, and the change and percent change from baseline will be plotted over time, by cohort and overall.

By-patient data listings of LDH data will be produced.

#### 7.2.1.1. Handling of Dropouts or Missing Data

Missing data for primary, secondary and exploratory endpoints analyses will be handled as indicated for the specific analysis.

Missing data for QOL instruments will be handled as specified in the instructions for each instrument and as specified in Section 9.5 .

#### 7.2.1.2. Subgroup Analysis

Summaries will be presented as indicated for the specific analysis by cohort. No other subgroup analyses are planned due to the small sample size.

#### 7.2.1.3. Multicenter Studies

This is a multicenter study; however, the expected sample size is not sufficient to perform any meaningful efficacy summaries by center.

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

Hypothesis testing for the change and percent change in LDH from baseline to Day 253 will be two-sided and performed at the 0.05 level of significance. For all the other parameters, p-values will be provided descriptively. Estimates of treatment effect on efficacy parameters will be accompanied by two-sided 95% confidence intervals, as indicated for the specific analysis.

#### **7.2.1.5. Sensitivity Analyses**

Sensitivity analyses for the primary efficacy endpoint, LDH, are presented in Section 7.2.1. Sensitivity analyses for the secondary efficacy endpoints are presented in Section 7.2.2.

#### **7.2.2. Secondary Analyses**

Descriptive statistics for the secondary endpoints of absolute, changes and percentage changes from baseline in hemolysis-related hematologic parameters (free hemoglobin, haptoglobin, reticulocyte count, PNH red blood cell (RBC) clone, and D-dimer ) will be produced for each visit, by cohort and overall. Baseline is defined as the last non-missing assessment value prior to the first ALXN1210 infusion. For any hemolysis-related hematologic parameter with a result value below or above the limit of quantification (i.e., a result of  $<x$  or  $>x$ ) the numeric result without the  $<$  or  $>$  symbol will be used in the analyses. The changes and percentage changes from baseline in hemolysis-related hematologic parameters will be analyzed in the same manner as described for the primary efficacy endpoint utilizing the MMRM approach.

As a sensitivity analysis, changes and percent changes from baseline will be analyzed using the Wilcoxon signed-rank test. Last observation carried forward (LOCF) will be used for patients with missing Day 253.

Individual patient plots of the hemolysis-related parameters will be produced. The following figures will also be produced by cohort and overall:

- Mean ( $\pm 95\%$  CI) endpoint values over time
- Mean change/percentage change ( $\pm 95\%$  CI) from baseline in endpoint values over time

Shift tables will be produced for all study visits by cohort and overall for the following clinical manifestations of PNH: fatigue, abdominal pain, dyspnea, dysphagia, chest pain, and erectile dysfunction.

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

#### **7.2.3. Exploratory Analyses**

The exploratory efficacy endpoints include:

1. Change from baseline in the need for blood transfusions
2. Change from baseline in disease-associated biomarkers such as estimated glomerular filtration rate (eGFR), spot urine albumin:creatinine ratio, and plasma brain natriuretic peptide (BNP)

3. Change from baseline in QoL, assessed via the Functional Assessment of Chronic Illness Therapy -Fatigue (FACIT-FATIGUE) and European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 Scale, Version 3.0 (EORTC QLC-C30) scales
4. Change from baseline in major adverse vascular events (MAVEs). The definition of a MAVE is provided in Section 13.8 of the protocol.

A summary of the number of pRBC transfusion requirements up to Day 253 (Day 281 for Cohort 4) will be presented including number of transfusion episodes and units transfused. For patients who had received transfusions in the year prior to receiving ALXN1210, the number (%) of patients achieving transfusion independence will be presented.

Descriptive statistics for the exploratory efficacy endpoints of absolute, changes and percentage changes from Baseline in disease associated biomarkers such as eGFR, spot urine albumin:creatinine ratio, and BNP will be produced for each visit, by cohort and overall. Baseline is defined as the last non-missing assessment value prior to the first ALXN1210 infusion. Additionally, patients' stages of chronic kidney disease (CKD) will be assigned based on the following classifications and the number (%) of patients in the different CKD stages will be presented over time. CKD stages are defined as: Stage 1 CKD, eGFR greater than 90 ml/min/1.73 m<sup>2</sup> and there is presence of proteinuria; Stage 2 CKD, eGFR 60-89 ml/min/1.73 m<sup>2</sup> and there is presence of proteinuria; Stage 3 CKD, eGFR 30-59 ml/min/1.73 m<sup>2</sup>; Stage 4 CKD, eGFR 15-29 ml/min/1.73 m<sup>2</sup>; Stage 5 CKD, eGFR less than 15 ml/min/1.73 m<sup>2</sup>. Patients failing to meet the criteria for Stages 1 to 5 will be classified as not having CKD.

The scoring guideline for the FACIT-FATIGUE and EORTC QLQ-C30 instruments will be used to calculate a FACIT-FATIGUE score and the different EORTC QLQ-C30 scale scores. Refer to Section 9.5 for a more detailed description of the FACIT-FATIGUE score and EORTC QLQ-C30 and the scoring methods. Descriptive statistics of FACIT-FATIGUE scores and changes from baseline in FACIT-FATIGUE scores will be produced for all study visits at which they are collected, by cohort and overall. Changes from baseline will be analyzed in the same manner as described for the primary efficacy endpoint utilizing the MMRM approach and Wilcoxon signed-rank test.

The number of any treatment emergent MAVEs (n) and number of patients with events (n, %) will be displayed by cohort and overall. Each of the MAVE categories will be similarly summarized. Patients having multiple MAVEs within a category will be counted once in that category.

#### **7.2.4. Other Efficacy Analyses**

##### **7.2.4.1. Pharmacokinetic and Pharmacodynamic Analyses**

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

Mean serum ALXN1210 concentrations versus nominal time, and individual serum ALXN1210 concentrations versus actual time will be graphically presented.

Individual serum concentration data for ALXN1210-treated patients, with actual sampling dates and times, will be used to derive the PK parameters by noncompartmental analyses, using Phoenix WinNonlin 6.3 or more current version.

The following PK parameters will be estimated following the first (loading) and last (maintenance) dose in each cohort:  $C_{max}$ ,  $C_{max}$  dose normalized,  $t_{max}$ ,  $AUC_t$  (first dose only), and  $AUC_t$  dose normalized (first dose only),  $AUC_{0-\tau}$  (last maintenance dose only) and  $AUC_{0-\tau}$  dose normalized (last maintenance dose only), and  $C_{trough}$ . Descriptive statistics (mean, SD, CV, median, minimum, maximum, geometric mean, and geometric %CV) of the serum concentration and PK parameter summaries will be provided, as appropriate.

The summaries of PK parameter results will be reported to 2 decimal places except for CV and geometric CV which will be reported to 1 decimal place.

Assessment of steady state and accumulation at steady state also will be evaluated. Additional PK analyses, such as assessment of PK linearity, may be conducted.

The PD effects of ALXN1210 administered IV will be evaluated by assessing changes and percent changes in serum total and free C5 concentrations, and cRBC hemolysis over time. Assessments of PK-PD relationships may be explored using data from this study or in combination of data from other studies.

#### **7.2.4.2. Immunogenicity Analyses**

All immunogenicity analyses will be conducted on the Immunogenicity Set. The number and percentage of subjects developing ADA will be summarized by cohort and overall.

### **7.3. Safety Analyses**

All safety analysis will be conducted on the Safety Set. All safety data available at the time of database lock up to Day 253 (Day 281 for Cohort 4) will be provided in patient listings. AEs will be encoded in the latest available version of standardized Medical Dictionary for Regulatory Activities (MedDRA) and presented by system organ class (SOC) and preferred term (PT). 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. No formal hypothesis testing will be performed.

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

Summary statistics (mean, standard deviation, median, minimum, and maximum) will be produced for the following using the Safety Set:

- Number of infusions from Day 1 to Day 253 (Day 281 for Cohort 4)
- Total number of patients with an infusion interruption as well as total number of infusions interrupted from Day 1 to Day 253 (Day 281 for Cohort 4)
- Duration of study participation from informed consent to Day 253 (Day 281 for Cohort 4)
- Total time on study treatment (days) from Day 1 to Day 253 (Day 281 for Cohort 4)

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.



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 System Organ Class (SOC) and Preferred Term (PT) using the latest available version of MedDRA and will be reported by cohort 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 9.4. Analyses of Pre-Treatment Adverse Events (PTAEs) and Treatment-Emergent Adverse Events (TEAEs) 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 Safety Set.

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

#### 7.3.2.1. Overall Summary of Adverse Events

All 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:

**Table 2: Treatment-Emergent Adverse Events (TEAEs) and Serious TEAEs**

Relationship	Severity
Related AEs (Possibly, Probably, or Definitely Related)	Grade 1 AEs
Not Related AEs (Not Related or Unlikely Related)	Grade 2 AEs
	Grade 3 AEs
	Grade 4 AEs
	Grade 5 AEs

Additionally, the number and percentage of patients who withdraw from the study due to an AE or who die will be presented. These statistics will be prepared separately for all TEAEs and SAEs.

#### 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. 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). In addition, AEs will be summarized as not related, unlikely related, possibly related, probably related, or definitely

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, if applicable.

### **7.3.3. Other Safety**

#### **7.3.3.1. Analyses for Laboratory Tests**

Descriptive statistics by visit will be presented for each central laboratory parameter and for changes from Baseline (continuous variables), by cohort and overall. Baseline is defined as the last non-missing assessment value prior to the first ALXN1210 infusion. Shift tables over time will be presented for all central laboratory values, where applicable, using grading criteria from CTCAE v4.03. For purposes of analyses, laboratory results based upon standardized units will be used. Individual patient plots as well as box plots will be presented for the following central lab parameters: hemoglobin, free hemoglobin, hematocrit, reticulocytes, LDH, bilirubin, creatinine AST, ALT and GGT.

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

#### **7.3.3.2. Vital Signs**

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 cohort and overall. Baseline is defined as the last non-missing assessment value prior to the first ALXN1210 infusion. A listing of vital signs will be presented.

#### **7.3.3.3. Electrocardiograms (ECG)**

The average of the triplicate ECG reading, where applicable, will be calculated and descriptive statistics by visit will be presented for each ECG parameter (including PR, QRS, QT, and QTcF) values and for change from baseline values. The mean of the three pre-dose readings will be considered the baseline values for each patient. If values are not available for all three readings, an average will be calculated based on the available non-missing values. For records with missing RR, HR will be used to calculate RR as defined in Section 9.4 An outlier analysis will be performed that will summarize the frequency and percentage of subjects 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. Non-Drug Therapies and Procedures**

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

#### **7.3.3.5. Infusion Site Evaluation**

By-patient listing of infusion site evaluation and pain at site of infusion as assessed by a visual assessment scale (VAS) will be produced.

## **8. REFERENCES**

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

## 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

A sample size of 20 patients from the combined cohorts provides approximately 95% power to detect a mean paired difference in LDH from baseline of -40% at Day 253, with an estimated SD of 45%. This was based on a 2-sided, paired t-test, with a 5% type 1 error rate. To account for a possible 15% dropout rate and additional patients in screening, up to 26 patients will be enrolled.

### 9.4. 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**

AGE	REFERENCE DATE
• 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 Table 3, 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 is defined as the last non-missing assessment value prior to the first ALXN1210 dose unless otherwise specified.

### **Baseline for LDH**

Baseline for LDH is defined as the average of all available assessments prior to first ALXN1210 infusion.

### **Baseline for Electrocardiograms (ECGs)**

The mean of the three pre-dose readings on Day 1 for heart rate and RR, PR, QT, and QTcF will be considered the baseline values for each patient. If values are not available for all three readings, an average will be calculated based on the available non-missing values.

### **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.

### **ECG Respiratory Rate**

For records with missing RR, HR (beats/min) will be used to calculate RR (Milliseconds) as follows:

$$RR = 60000 / HR$$

### **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 cohort.

Related AEs are defined as possible, probable or definitely related. Unrelated AEs are defined as unlikely or not related.

## 9.5. Additional details on Statistical Methods

### 9.5.1. 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.

### 9.5.2. 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 (1=not at all, 4=very much). 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 QLQ-C30**

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

	Scale	Item range <sup>a</sup>	Item Numbers	Raw Score <sup>b</sup>
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:

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

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

Each scale has a range of 0-100%. 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.