A Phase 3, Open-label Study Of ALXN1210 In Children And Adolescents With Paroxysmal Nocturnal Hemoglobinuria (PNH)

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Alexion Pharmaceuticals, Inc.

STATISTICAL ANALYSIS PLAN

PROTOCOL NUMBER: ALXN1210-PNH-304

A PHASE 3, OPEN-LABEL STUDY OF ALXN1210 IN CHILDREN AND ADOLESCENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

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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
AESI	adverse event of special interest
ALT	alanine aminotransferase (SGPT)
ATC	Anatomical Therapeutic Chemical
AST	aspartate aminotransferase (SGOT)
AUC_t	area under the serum concentration-versus-time-curve from time 0 (dosing) to the last quantifiable concentration
$AUC_{0-\tau}$	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
CAP	complement alternative pathway
CKD	chronic kidney disease
CI	confidence interval
CL	total clearance
C_{max}	maximum observed serum concentration
C_{min}	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
FAS	Full Analysis Set
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FDA	Food and Drug Administration
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
OC	observed case
PD	pharmacodynamic
PK	pharmacokinetic
PNH	paroxysmal nocturnal hemoglobinuria

Abbreviation or acronym	Explanation
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®	Statistical Analysis Software®
SAP	Statistical Analysis Plan
SD	standard deviation
SDV	source data verification
SOC	System Organ Class (MedDRA)
TEAEs	treatment-emergent adverse events
t_{max}	time to maximum observed serum concentration
ULN	upper limit of normal
WHO-DRUG	World Health Organization Drug Dictionary
λ_z	apparent terminal-phase elimination rate constant

4. DESCRIPTION OF THE PROTOCOL

ALXN1210-PNH-304 is a Phase 3, open-label, single-arm multicenter study to evaluate the PK/PD, safety, and efficacy of ALXN1210 administered by intravenous (IV) infusion to pediatric patients (< 18 years of age) with paroxysmal nocturnal hemoglobinuria (PNH). The study consists of a 4-week Screening Period, a 26-week Primary Evaluation Period, and an Extension Period.

Patients will receive a loading dose of ALXN1210 on Day 1, followed by maintenance dosing of ALXN1210 on Day 15 and q8w thereafter for patients weighing ≥ 20 kg, or q4w for patients weighing < 20 kg, as shown in Table 2. With the agreement of the Alexion Medical Monitor, the 600 mg loading dose may be given to patients weighing ≥ 5 to < 10 kg as 2 separate infusions administered no more than 24 hours apart. Dosages are based on the patient's body weight recorded on the day of dosing or the most recently recorded weight. For patients entering the study on eculizumab therapy, Day 1 of study treatment will occur 2 weeks from the patient's last dose of eculizumab.

Table 2: Loading and Maintenance Treatment Regimens

Body Weight Range (kg)[a]	Loading Dose (mg)	Maintenance Doses (mg)	Maintenance Dosing Frequency
≥ 5 to < 10	600[b]	300	q4w
≥ 10 to < 20	600	600	q4w
≥ 20 to < 30	900	2100	q8w
≥ 30 to < 40	1200	2700	q8w
≥ 40 to < 60	2400	3000	q8w
≥ 60 to < 100	2700	3300	q8w
≥ 100	3000	3600	q8w

[a] Dose regimen will be based on body weight obtained at the study visit. If the study drug needs to be prepared the night prior to the visit, the weight from the previous visit may be used.
[b] With the agreement of the Alexion Medical Monitor, the 600 mg loading may be given to patients weighing ≥ 5 to < 10 kg as 2 separate infusions administered no more than 24 hours apart.
Abbreviations: q4w = once every 4 weeks; q8w = once every 8 weeks

With the agreement of the Alexion Medical Monitor, administration of a supplemental dose of ALXN1210 is permitted.

An interim analysis of data, including ALXN1210 PK and free C5 levels, will be conducted after 4 patients weighing ≥ 5 kg to < 40 kg have completed dosing through Day 71. Enrollment of patients will proceed without interruption while the analysis is ongoing. The accrued safety and PK/PD data will be assessed to ensure that ALXN1210 treatment is well tolerated and is providing adequate complement inhibition. Based on this review, the dose regimen may be adjusted. In addition, an independent Data Monitoring Committee (DMC) will review safety data from the study on a regular basis. Prior to the initiation of the study, the committee will develop a charter to describe their activities and responsibilities.

To support regulatory filings, interim analyses may be conducted based on efficacy, safety, PK, PD, and immunogenicity data collected through the end of the 26-week Primary Evaluation Period (Day 183) after 12 patients are enrolled, and after enrollment is completed.

After completion of all pre-dose assessments on Day 183, all patients will enter an Extension Period and continue to receive ALXN1210 according to the appropriate weight-based regimen. The Extension Period will continue until the product is registered or approved (in accordance with country-specific regulations) or for up to 4 years, whichever occurs first, except in Norway where the Extension Period will be 4 years. The end of study is defined as the last patient's last visit or follow-up (whether on site or via phone call) in the Extension Period.

The study objectives are as follows:

The objectives of this study are to assess the pharmacokinetics (PK), pharmacodynamics (PD), safety, and efficacy of ALXN1210 in pediatric patients with paroxysmal nocturnal hemoglobinuria (PNH). Additional information about the study can be found in the protocol.

To support regulatory filings, interim CSRs may be prepared based on efficacy, safety, PK, PD, and immunogenicity data collected through the end of the 26-week Primary Evaluation Period (Day 183) after 12 patients are enrolled, and after enrollment is completed. This statistical analysis plan (SAP) outlines only the analyses that are to be included in the report developed after the 26-week Primary Evaluation Period after 12 patients are enrolled. A final CSR to summarize long-term efficacy, safety, PK, PD, and immunogenicity parameters will be produced at study completion.

4.1. Changes From Analyses Specified in the Protocol

Not applicable

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

During the conduct of the phase 3 studies ALXN1210-PNH-301 and ALXN1210-PNH-302, it was observed that up to 1% of central laboratory chemistry samples undergo in vitro erythrocyte lysis or table top hemolysis (TTH) caused by sample mishandling. This is unrelated to hemolysis due to PNH. The reasons for TTH vary and include delayed or improper centrifugation and traumatic blood draws. In addition, PIGA deficient erythrocytes from patients with PNH are more susceptible to mechanical lysis than non-PNH erythrocytes (Smith, 1985). Hemolysis results in release of RBC contents including LDH, potassium, and AST. In contrast to hemolysis in patients with PNH, in which serum potassium is normal, for samples affected by TTH both potassium and LDH are markedly and proportionally increased (Goyal and Schmotzer, 2015; Ostendorp, 2006). Marked hyperkalemia (defined as > 6mmol/L) seen in TTH, but not PNH hemolysis, differentiates TTH (in vitro) from PNH hemolysis (in vivo), and is not clinically significant (Hollander-Rodriguez, 2006; Kovesdy, 2014). Due to the artefactual increase in LDH in samples affected by TTH, the potassium, ALT, AST, magnesium, phosphorous, and LDH values in samples affected by TTH will not be used in the analysis of any efficacy or safety endpoints, with the exception that the LDH value will be used for the qualification of breakthrough hemolysis events. Breakthrough hemolysis is captured on a separate form and central lab LDH, in addition to new or worsening symptoms as specified in the protocol, are used by the Principal Investigator or designee to qualify patients with breakthrough hemolysis. Table top hemolysis samples from the central lab will be defined as having serum potassium $\geq$ 6 mmol/L and LDH $\geq$ 2 × ULN, and will be excluded from analyses as described above.

In order to be consistent with ALXN1210-PNH-301 and ALXN1210-PNH-302, patients who withdraw from the study due to lack of efficacy during the Primary Evaluation Period will be considered as non-responders in the analyses of breakthrough hemolysis, transfusion avoidance (TA), and stabilized hemoglobin. Shift tables over time will be presented for all central laboratory values, where applicable, using normal, low, or high based on normal range values. The visit window definition is also added in the appendix.

A small portion of the data may not go through source data verification (SDV) process due to the COVID-19 pandemic. The non-SDV' d data will be flagged in listings.

5. DEFINITIONS

5.1. Efficacy

5.1.1. Primary Endpoint(s)

Pharmacokinetic/Pharmacodynamic parameters (trough and peak) at baseline and Weeks 2, 10, 18, and 26

- PK: maximum serum concentration (C_{max}), trough serum concentration (measured at end of dosing interval at steady state; C_{trough}), accumulation ratio
- PD: change in free C5 concentrations and in chicken red blood cell (cRBC) hemolytic activity over time.

5.1.2. Secondary Endpoints

The secondary endpoints include:

- Percentage change in LDH from baseline to Day 183 (Week 26)
- Transfusion avoidance (TA), defined as the proportion of patients who remain transfusion-free and do not require a transfusion through Day 183 (Week 26)
- Change in quality of life (QoL), as measured by Pediatric Functional Assessment of Chronic Therapy (FACIT) Fatigue questionnaire (patients $\geq$ 5 years of age), from baseline to Day 183 (Week 26)
- Proportion of patients with stabilized hemoglobin, defined as avoidance of a $\geq$ 2 g/dL decrease in hemoglobin level from baseline in the absence of transfusion through Day 183 (Week 26)
- Percentage change in free hemoglobin from baseline to Day 183 (Week 26)
- Proportion of patients with breakthrough hemolysis, defined as at least one new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia, major adverse vascular event [MAVE, including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH as follows:
  - For patients who enter the study naïve to complement inhibitor treatment, elevated LDH $\geq$ 2 × ULN after prior LDH reduction to < 1.5 × ULN on therapy
  - For patients who enter the study stabilized on eculizumab treatment, elevated LDH $\geq$ 2 × ULN.

5.2. Pharmacokinetic/Pharmacodynamic

Total C5 concentrations over time will be assessed besides the PK/PD endpoints specified in Section 5.1.1.

5.3. Safety

The safety and tolerability of ALXN1210 will be evaluated from baseline to Week 26 and throughout the Extension Period by AEs and serious adverse events (SAEs), physical examinations, vital signs, physical growth (height, weight, and head circumference [the latter only in patients who are ≤ 3 years of age]), electrocardiograms (ECGs), and laboratory assessments. 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 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 14 Jun 2010 or higher.

Grade	Description
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 ADL[a]
Grade 3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

[a] Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Abbreviations: ADL = activities of daily living; AE = adverse event

Adverse events are further defined in Protocol Section 11.7.

5.3.2. Vital Signs

Vital sign measurements will be taken after the patient has been resting for at least 5 minutes, and will include systolic and diastolic blood pressure (BP; millimeters of mercury [mmHg]), heart rate (beats/minute), respiratory rate (breaths/minute), and temperature (degrees Celsius [°C] or degrees Fahrenheit [°F]).

5.3.3. Laboratory Assessments

Samples for serum pregnancy, hematology, chemistry, coagulation, and urinalysis will be collected (See Appendix D of the protocol for a listing of all clinical laboratory parameters). An alternative blood sampling schedule for infants, for whom less blood volume should be collected, must be used as detailed in the laboratory manual. 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. Physical Examination

A physical examination will include the following assessments: general appearance; skin; head, ear, eye, nose, and throat; neck; lymph nodes; chest; heart; abdominal cavity; limb; central nervous system; and musculoskeletal system. An abbreviated physical examination consists of a body system relevant examination based upon Investigator judgment and patient symptoms. Physical growth (height, weight and head circumference [the latter only in patients $\leq$ 3 years of age]) will be assessed.

5.3.5. Electrocardiograms (ECGs)

For each patient, single 12-lead digital ECGs will be collected. PR, RR, and QT will be measured, and QT interval will be corrected for heart rate using Fridericia's formula (QTcF).

5.3.6. Immunogenicity

Blood samples will be collected to test for presence and titer of ADAs to ALXN1210 in serum prior to study drug administration. Further characterization of antibody responses may be conducted as appropriate, including binding and neutralizing antibodies, PK/PD, safety, and activity of ALXN1210.

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 analysis.

6.2. PK Analysis Set and PD Analysis Set

The PK analysis set will consist of all patients in the Safety Set who have evaluable PK data used to derive PK parameters for ALXN1210. The PK analysis set will be used for PK summaries. The PD analysis set will consist of all patients in the Safety Set who have evaluable PD data. The PD analysis set will be used for all PD summaries.

6.3. Full Analysis (FAS)

The Full analysis set (FAS) will consist of all patients in the Safety Set with a baseline and 1 secondary endpoint measurement post-first ALXN1210 dose.

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 by naïve, previously eculizumab-treated patients and total; for continuous variables, descriptive statistics (n, mean, median, standard deviation [SD], minimum, maximum) will be presented by naïve, previously eculizumab-treated patients and total.

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.

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. The TTH samples from the central lab will be defined as having serum potassium $\geq$ 6 mmol/L and LDH $\geq 2 \times$ ULN.

A small portion of the data may not go through source data verification (SDV) process due to the COVID-19 pandemic. The non-SDV' d data will be flagged in listings.

7.1. Study Patients

7.1.1. Disposition of Patients

A summary of patient disposition for all 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 Primary Evaluation period or discontinued/withdrew from the study through the end of the Primary Evaluation 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

Important protocol deviations will be determined per the standard operating procedure (SOP) "Identification, Handling, and Documentation of Protocol Deviations" (SOP-G-CL-0044). The number and percent of patients with specific protocol deviations will be summarized for all enrolled patients by major deviations.

A by-patient listing of inclusion/exclusion criteria, as well as protocol deviations will be presented, separately.

7.1.3. Demographics, Disease Characteristics, and History

All demographic and baseline characteristics information will be summarized using the FAS Set. Summary statistics will be presented by naïve, previously eculizumab-treated patients and total.

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 study drug infusion: descriptive statistics (n, mean, median, SD, minimum, maximum) and frequency of patients in the following categories: ≤ 12, > 12 years
- Baseline Weight: descriptive statistics (n, mean, median, SD, minimum, maximum) and frequency of patients in the following categories in kg: ≥ 5 to < 10, ≥ 10 to < 20, ≥ 20 to < 30, ≥ 30 to < 40, ≥ 40 to < 60, ≥ 60 to < 100 and ≥ 100.
- Baseline Height
- Baseline Body Mass Index (BMI)
- Patients of Japanese Descent

7.1.3.2. Characteristics and PNH Medical History

The following PNH disease characteristics will be summarized.

- Age (years) at PNH diagnosis.
- Age (years) at first eculizumab infusion.
- Method of PNH diagnosis.
- Years from PNH diagnosis to informed consent.
- PNH clone size at screening.
- Packed red blood cell (pRBC) transfusion requirements in the year prior to receiving ALXN1210 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.
- 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. 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 will be classified by System Organ Class (SOC) and Preferred Term (PT) using the latest available version of standardized (MedDRA) and will be summarized by naïve, previously eculizumab-treated patients and total for the Safety Set. Likewise, baseline physical examination information will be summarized by naïve, previously eculizumab-treated patients and total for the Safety Set.

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, and vaccination history for *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* from birth. 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. A by-patient listing of meningococcal, Hib and *S pneumoniae* from birth vaccinations will be produced showing the date of vaccinations for each patient.

7.2. Efficacy Analyses

All pharmacokinetic analyses will be conducted on the PK Analysis Set. Pharmacodynamic analyses will be conducted on the PD Analysis Set. Analysis of secondary efficacy will be performed on the Full Analysis Set (FAS).

7.2.1. Primary Analysis

This study is descriptive in nature and not statistically powered for hypothesis testing due to the rarity of disease in pediatric patients. Analyses will be conducted separately for naïve and previously eculizumab-treated patients.

Sparse PK and PD (free C5) samples will be collected over the course of the study. Individual serum concentration data will be used to derive PK parameters for ALXN1210. Graphs of mean serum concentration-time profiles will be constructed. Graphs of serum concentration-time profiles for individual patients may also be generated. Actual dose administration and sampling times will be used for all calculations. Descriptive statistics (mean, SD, CV, median, minimum, maximum, geometric mean, and geometric %CV) will be calculated for serum concentration data at each sampling time, as appropriate.

Descriptive statistics will be presented for all ALXN1210 PD endpoints at each sampling time. The PD effects of ALXN1210 administered IV will be evaluated by assessing the absolute values and changes and percentage changes from baseline in total and free C5 serum concentrations and change from baseline in cRBC hemolysis over time, as appropriate.

7.2.1.1. Handling of Dropouts or Missing Data

Missing data for secondary 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 9.4.

7.2.1.2. Subgroup Analysis

Summaries will be presented as indicated for the specific analysis by naïve, previously eculizumab-treated patients and total. 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

This study is descriptive in nature and not statistically powered for hypothesis testing. Estimates of treatment effect on some of the efficacy parameters will be accompanied by two-sided 95% confidence intervals, as indicated for the specific analysis.

7.2.1.5. Sensitivity Analyses

Presented in Section 7.2.2 last observation carried forward (LOCF) will be the sensitivity analyses for the secondary efficacy endpoints if applicable.

7.2.2. Secondary Analyses

Descriptive statistics for the secondary endpoints will be produced for each visit where applicable, by naïve, previously eculizumab-treated patients and total.

- Percentage change in LDH from baseline to Day 183 (Week 26)
  - Absolute LDH levels, and the change and percent change from baseline, will be summarized at all study visits up to Day 183 (Week 26) by both observed case (OC) and LOCF. Baseline is defined as the average of all assessments analyzed by the central laboratory prior to first study drug administration.
  - The number (%) of patients achieving LDH levels at or below 1.0 times upper limit of normal (1.0 × ULN) and levels at or below 1.5 × ULN will be displayed.
  - Mean (±95% CI) of absolute LDH levels, and the change and percent change from baseline will be plotted over time, by naïve and previously eculizumab-treated patients.
- Transfusion avoidance (TA)
  - Point estimates and 2-sided 95% exact CIs will be computed. Patients who withdraw from the study due to lack of efficacy during the Primary Evaluation Period will be considered as non-responders and will be counted in the group

needing transfusion. For patients who withdraw from the study for any other reason during the Primary Evaluation Period, their data up to the time of withdrawal will be used to assess TA.

  - A summary of the number of pRBC transfusion requirements up to Day 183 study will be presented including number of transfusion episodes and units transfused.

- Change in quality of life (QoL), as measured by Pediatric FACIT-Fatigue questionnaire from baseline to Day 183 (Week 26)
  - The scoring guideline for the Pediatric FACIT-Fatigue instrument will be used to calculate a FACIT-Fatigue score. Please refer to Section 9.4 for a more detailed description of the Pediatric FACIT-Fatigue score and the scoring methods.
  - Absolute scores, change from baseline, and percent change from baseline in FACIT-Fatigue scores will be summarized by both OC and LOCF at baseline and at the study visits where this assessment is collected up to Day 183 (Week 26).
  - At each study visit, the proportion of patients who showed an improvement of at least 3 points for the Pediatric FACIT-Fatigue scores will be summarized by point estimates and 2-sided 95% exact CIs.
- Proportion of patients with stabilized hemoglobin
  - Point estimates and 2-sided 95% exact CIs will be computed. Patients who withdraw from the study due to lack of efficacy during the Primary Evaluation Period will be considered as non-responders and will be counted in the group who did not meet the stabilized hemoglobin definition. For patients who withdraw from the study for any other reason during the Primary Evaluation Period, their data up to the time of withdrawal will be used to assess stabilized hemoglobin.
- Percentage change in free hemoglobin from baseline to Day 183 (Week 26)
  - Absolute free hemoglobin values, and the change and percent change from Baseline, will be summarized by both OC and LOCF at all study visits up to Day 183 (Week 26). Baseline is defined as the last non-missing assessment value prior to the first study drug infusion.
  - Mean (±95% CI) of free hemoglobin, and the change and percent change from baseline will be plotted over time, by naïve and previously eculizumab-treated patients.
- Proportion of patients with breakthrough hemolysis
  - Point estimates and 2-sided 95% exact CIs will be computed. Patients who withdraw from the study due to lack of efficacy during the Primary Evaluation Period will be considered as non-responders and will be counted in the group with breakthrough hemolysis. For patients who withdraw from the study for any other reason during the Primary Evaluation Period, their data up to the time of withdrawal will be used to assess breakthrough hemolysis.
  - The number of any treatment emergent MAVEs (n) and number of patients with events (n, %) will be displayed. Each of the MAVE categories will be similarly

summarized. Patients having multiple MAVEs within a category will be counted once in that category.

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

7.2.3. Pharmacokinetic and Pharmacodynamic Analyses

This section describes the PK/PD analyses in addition to those specified in Section 7.2.1. The assessment of population-PK may be considered using data from this study or in combination with data from other studies. Assessments of ALXN1210 PK/PD relationships may be explored using data from this study or in combination with data from other studies. Total C5 serum concentrations will be evaluated in the same way as free C5 serum concentrations.

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 183 will be provided in patient listings.

7.3.1. Study Duration, Treatment Compliance, and Exposure

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

- Number of infusions from Day 1 to Day 183
- Number of patients receiving 1, 2, etc maintenance doses prior 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 Primary Evaluation Period/Day 183 (ie, study duration = date of completion/discontinuation - date of informed consent+ 1).
- Total time on study treatment (days) calculated as the time in days from first study drug infusion date until the last study drug infusion date from the Primary Evaluation Period (ie treatment duration=last study drug infusion date from the Primary Evaluation Period - first study drug infusion date + 1). Note that dosing on Day 183 represents the start of the Extension Period and will not be included in these calculations.

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

This will be calculated as follows:

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

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

7.3.2. Adverse Events (AEs)

Adverse Events (AEs) will be classified by System Organ Class (SOC) and Preferred Term (PT) using the latest available version of MedDRA and will be reported by naïve, previously eculizumab-treated patients and total. 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 9.3. 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 naïve, previously eculizumab-treated patients and total. 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.

Adverse events 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.

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. 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 and related. If a patient has more than one occurrence of an AE, the strongest relationship to study treatment will be used in the summary table. Serious adverse events will be summarized similarly.

7.3.2.4. AEs by 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, and Grade 5). If a patient has more than one occurrence of an AE, the highest grade will be used in the summary table.

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

A listing of patient deaths will be produced, if applicable.

An important identified risk in this study is meningococcal infections. The adverse event of special interest (AESI) will be summarized by naïve, previously eculizumab-treated patients, and total.

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 naïve, previously eculizumab-treated patients, and total. 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 normal, low, or high based on normal range values. 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, haptoglobin, hematocrit, reticulocytes, LDH, bilirubin, direct bilirubin, creatinine, AST, ALT, and GGT.

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

7.3.3.2. Physical Examination, Vital Signs, and Growth

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

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 naïve, previously eculizumab-treated patients, and total. Baseline is defined as the last non-missing assessment value prior to the first ALXN1210 infusion. The same method will be used to summarize height, weight, and head circumference (the latter only for patients $\leq$ 3 years of age).

By-patient data listings will be provided.

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.

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

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

7.3.3.4. Immunogenicity

All immunogenicity analyses will be conducted on the Safety Set. The number and percentage of patients developing ADA and anti-drug neutralizing antibodies, where applicable, will be summarized by naïve, previously eculizumab-treated patients, and total.

7.3.3.5. Non-Drug Therapies and Procedures

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

8. REFERENCES

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9. APPENDICES

9.1. Protocol Schedule of events

Refer to the protocol for a schedule of events.

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

This study is descriptive in nature and not statistically powered for hypothesis testing due to the rarity of disease in pediatric patients. Approximately 13 patients will be enrolled to ensure at least 10 evaluable patients complete the 26-week period, which is expected to be sufficient to adequately describe PK/PD in pediatric patients with PNH.

9.3. Sample Size, Power, and Randomization

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 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

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

Definition of Baseline Values

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

Change From Baseline

Change in values from baseline will be calculated as follows:

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

Percent Change in Assessments From Baseline

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

% Change in Value = Change in Value/ Baseline value × 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

Study visits will be defined through the use of windows based on the list of visits described in the schedule of assessments of the protocol. For all assessments, the number of days from baseline will be calculated using the following formula: (date of assessment) - (date of first study treatment) + 1. This number of days will be used to assign analysis visits. This may not always correspond to the electronic case report form (eCRF) visit.

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

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

For example, for an assessment with a scheduled visit on Day 127, and a prior scheduled visit on Day 99 and subsequent scheduled visit on Day 155, the window will start at 113 days from baseline and will go to 140 days from baseline.

If only 1 record is within an analysis visit window, the data from that record will be used in the analysis. If more than 1 record is within the same analysis visit window, the record closest to the midpoint of the interval will be used in the analysis. If 2 records are "tied" before and after the middle of the interval, the earlier record will be used in the analysis.

Please refer to the following table for visit window definitions.

Table 4: Visit Window

Endpoint	Visit	Nominal Day	Start (Day)	End (Day)
Chemistry/Hematology/ Vital Signs	Screening		-28	0
	Day 1	1	1	1
	Day 15	15	8	28
	Day 43	43	29	56
	Day 71	71	57	84
	Day 99	99	85	112
	Day 127	127	113	140
	Day 155	155	141	168
	Day 183	183	169	196
FACIT Fatigue/Urinalysis	Screening		-28	0
	Day 1	1	1	1
	Day 15	15	8	42
	Day 71	71	43	98
	Day 127	127	99	154
	Day 183	183	155	210
PNH Clone	Screening		-28	0
	Day 1	1	1	1
	Day 71	71	36	126
	Day 183	183	127	266

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 group including naïve, previously eculizumab-treated patients and total.

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

9.4. Additional details on Statistical Methods

9.4.1. Pediatric FACIT-Fatigue (FACIT-Fatigue) Calculations

The Pediatric 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 pF2 and pF3 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.