STATISTICAL ANALYSIS PLAN

PROTOCOL NUMBER: ACH228-110

A Phase 2 Open-Label Proof of Concept Study to Assess the Efficacy, Safety, and Pharmacokinetics of the Oral Factor D (FD) Inhibitor ALXN2050 (ACH-0145228) in Paroxysmal Nocturnal Hemoglobinuria (PNH) Subjects as Monotherapy

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Date: **29 Jun 2021**

Version: **1.0 Final**

1. APPROVAL SIGNATURES

[redacted]

29-Jun-2021 | 11:21:28 EDT

Date dd Mmm yyyy

[redacted]

07-Jul-2021 | 08:52:44 EDT

Date dd Mmm yyyy

[redacted]

29-Jun-2021 | 12:35:25 EDT

Date dd Mmm yyyy

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
TABLE OF CONTENTS 3
LIST OF TABLES 6
LIST OF FIGURES 6
3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 7
4. DESCRIPTION OF THE PROTOCOL 9
4.1. Changes from Analyses Specified in the Protocol 10
4.2. Changes from Analyses Specified in the Previous Version of the Statistic Analysis Plan 10
5. DEFINITIONS 11
5.1. Efficacy 11
5.1.1. Primary Endpoints 11
5.1.2. Secondary Endpoints 11
5.1.3. Exploratory Efficacy Endpoints 11
5.2. Pharmacokinetics/Pharmacodynamics 12
5.3. Safety 12
5.3.1. Adverse Events (AEs) 12
5.3.2. Laboratory Assessments 13
5.3.3. Vital Signs 13
5.3.4. Electrocardiogram 13
5.3.5. Physical Examination 13
6. DATA SETS ANALYZED (STUDY POPULATIONS) 15
6.1. Full Analysis (FA) Set 15
6.2. Per Protocol (PP) Set 15
6.3. Safety Set 15
6.4. Other Sets 15
7. STATISTICAL ANALYSIS 16
7.1. Study Subjects 16
7.1.1. Disposition of Subjects 16

7.1.2. Protocol Deviations 16
7.1.3. Demographics, Disease Characteristics, and Medical History 17
7.1.3.1. Demographics 17
7.1.3.2. Disease Characteristics 17
7.1.3.3. Medical / Surgical History 17
7.1.4. Prior and Concomitant Medications / Therapies 17
7.2. Efficacy Analyses 18
7.2.1. Primary Endpoint Analysis 18
7.2.1.1. Handling of Dropouts or Missing Data 19
7.2.1.2. Subgroup Analysis 19
7.2.1.3. Multicenter Studies 19
7.2.1.4. Hypothesis Testing and Significance Level 19
7.2.1.5. Sensitivity Analyses 19
7.2.2. Secondary Endpoint Analyses 19
7.2.2.1. FACIT Fatigue Scale (Version 4) 20
7.2.3. Other Efficacy Analyses 20
7.2.3.1. EORTC-QLQ-C30 (Version 3) 20
7.2.3.2. EQ-5D-3L 21
7.2.4. Pharmacokinetic and Pharmacodynamic Analyses 21
7.2.5. Adverse Events 22
7.2.5.1. Overall Summary of Adverse Events 23
7.2.5.2. AEs and SAEs by System Organ Class (SOC) and Preferred Term (PT) 23
7.2.5.3. AEs and SAEs by SOC, PT, and Relationship 23
7.2.5.4. AEs and SAEs by SOC, PT, and Severity 23
7.2.5.5. Deaths, Other SAEs, and Other Significant Adverse Events 23
7.2.6. Other Safety 24
7.2.6.1. Analyses for Laboratory Tests 24
7.2.6.2. Vital Signs 24
7.2.6.3. Electrocardiogram 24
7.2.6.4. Physical Examination 25
7.3. COVID-19 Related Analyses 25
8. INTERIM ANALYSES 26
9. REFERENCES 27

10. APPENDICES 28
10.1. Protocol Schedule of Assessments 28
10.2. Changes from Analyses Specified in the Previous Version of the SAP 28
10.3. Scoring the EORTC QLQ-C30 version 3.0 28
10.4. Scoring EQ-5Q-3L Health State Index 29
10.5. Technical Specifications for Derived Variables 30

LIST OF TABLES

Table 1. Abbreviations and acronyms 7
Table 2 Scoring of EORTC QLQ-C30 version 3.0 28
Table 3 Definition for variables used in calculating health state index using US population estimates 29
Table 4 Definition for variables used in calculating health state index using UK population estimates 30

LIST OF FIGURES

Figure 1: Study Design Schematic 10

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1. Abbreviations and acronyms

Abbreviation or acronym	Explanation
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase (SGOT)
ATC	Anatomical Therapeutic Chemical
AP	Alternative Pathway
APH	Alternative pathway hemolysis
Bb	Bb fragment of complement factor B
bid	twice daily
BMI	Body mass index
C3	Complement C3
C5	Complement C5
CH50	Classical pathway activity
CI	Confidence interval
cm	Centimeters
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EORTC	European Organiztion for Research and Treatment of Cancer
FA	Full analysis
GGT	Gamma-Glutamyltransferase (GGT)
Hgb	Hemoglobin
HR	Heart rate
kg	Kilogram
LDH	Lactate dehydrogenase
LTE	Long-term extension
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
PD	Pharmacodynamic(s)
PIC	Powder in capsule
PK	Pharmacokinetic(s)
PNH	Paroxysmal nocturnal hemoglobinuria
PR interval	Period that extends from the beginning of the P wave until the beginning of the QRS complex
PT	Preferred term (MedDRA)
pRBC	Packed red blood cell
QoL	Quality of life
QRS	Group of electrocardiogram waves comprising the Q, R, and S waves

Abbreviation or acronym	Explanation
QT interval	Period from deflection of QRS complex to end of T wave
QTcF	QT interval Fridericia correction formula
RBC	Red blood cells
RR	Respiration rate
RR interval	Period between QRS complexes
SAE	Serious adverse event
SD	Standard deviation
SAS®	Statistical Analysis Software®
SOC	System organ class (MedDRA)
TEAEs	Treatment-emergent adverse events
WHO	World Health Organization

4. DESCRIPTION OF THE PROTOCOL

This is a multiple-center, open-label multiple dose study to evaluate the efficacy, safety, pharmacokinetics (PK), and pharmacodynamics (PD) of the oral factor D (FD) inhibitor ALXN2050 monotherapy in PNH subjects.

ALXN2050 (formerly ACH-0145228) is a small molecule, orally administered FD inhibitor being developed for the treatment of complement-mediated diseases, such as PNH. A serine protease, FD catalyzes the cleavage of factor B (FB), a rate-limiting step in the alternative pathway (AP) of the complement cascade. By inhibiting FD, ALXN2050 potently and specifically inhibits AP activity.

ALXN2050 is a second-generation molecule. It has an identical mechanism of action (FD inhibition) as danicopan (ALXN2040), the first-generation molecule, but with increased potency, improved PK/PD profile, and associated incremental potential benefits in terms of monotherapy dosing and clinical efficacy.

This study will assess ALXN2050 as monotherapy in the following three different subject groups:

- Group 1: PNH subjects who are treatment naïve
- Group 2: PNH subjects who have received complement component 5 (C5) inhibition with eculizumab for at least 6 months, who continue to experience anemia (hemoglobin [Hgb] < 10 g/dL) and reticulocytes above the upper limit of normal (ULN), and who will switch to ALXN2050 in this study
- Group 3: PNH subjects who have received danicopan monotherapy during Study ACH471-103, and who will switch to ALXN2050 in this study

After signing the informed consent form (ICF), subjects will enter the Screening Period. During the Screening Period, eligibility and screening assessments will be performed. Eligible subjects will enter the Treatment Period and will receive their first dose of the study medication during the Baseline Visit (Day 1) in this study. At the end of Week 12, subjects will enter the 96-week Long-term Extension (LTE) Period. Figure 1 displays the study design schema.

Approximately 26 patients will be enrolled including approximately 10 patients in Group 1, approximately 10 patients in Group 2, and approximately 6 patients in Group 3.

ALXN2050 will be administered orally, 120 mg bid, with the option for dose escalation to 180 mg bid according to the protocol specified dose escalation guidance for the 3 planned patient groups.

The primary objective is:

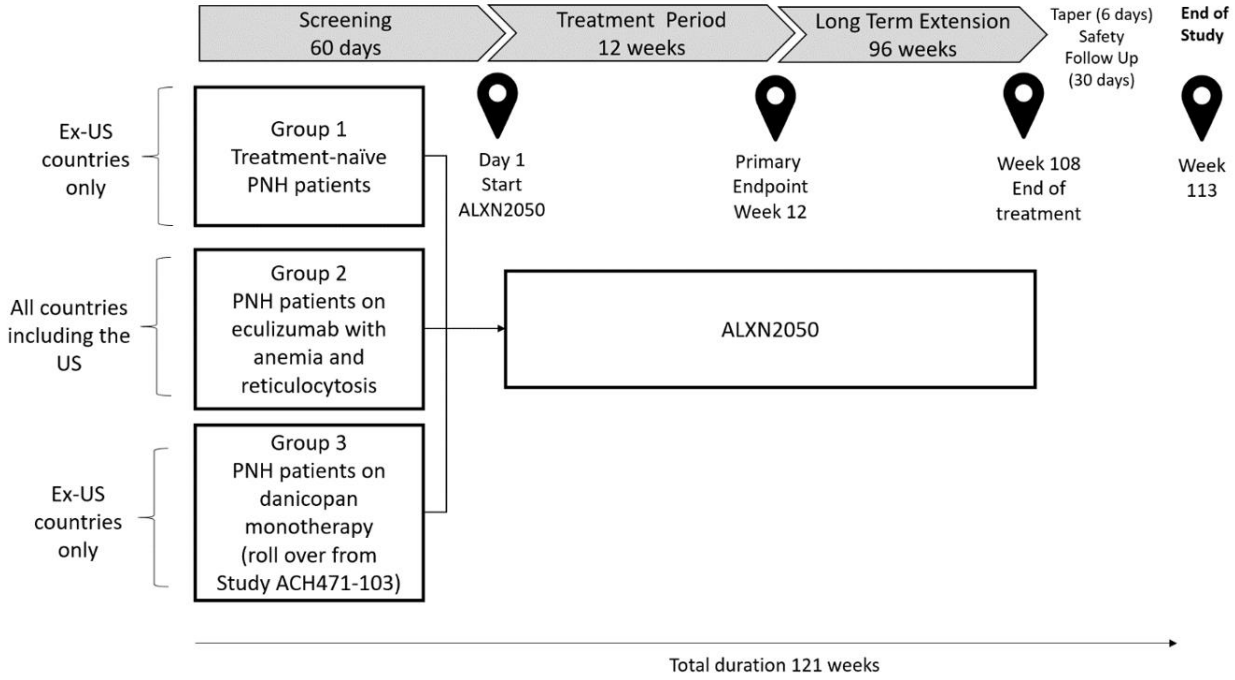
- To evaluate the efficacy of ALXN2050 based on improvement in hemoglobin (Hgb).

The secondary objectives include:

- To evaluate the efficacy of ALXN2050 based on reduction in transfusion requirements
- To evaluate the efficacy of ALXN2050 based on lactate dehydrogenase (LDH)
- To assess laboratory markers of hemolysis and other markers relevant in subjects with PNH
- To evaluate the safety and tolerability of ALXN2050

- To evaluate maintenance of response of ALXN2050 during the LTE period
- To evaluate the effect of ALXN2050 on Functional Assessment of Chronic Illness Therapy-Fatigue scale (FACIT) scores
- The exploratory objectives include:
- To characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of ALXN2050
- To evaluate other health-related quality of life (QoL) in subjects with PNH based on subject-reported outcome instruments and their evolution over the course of ALXN2050 treatment

Figure 1: Study Design Schematic



4.1. Changes from Analyses Specified in the Protocol

Not applicable.

4.2. Changes from Analyses Specified in the Previous Version of the Statistic Analysis Plan

Not applicable.

5. DEFINITIONS

5.1. Efficacy

5.1.1. Primary Endpoints

The primary efficacy endpoint is:

- Change in Hgb level from baseline at Week 12

5.1.2. Secondary Endpoints

The secondary safety endpoints will be included in Section 5.3.

The secondary efficacy endpoints are:

- Number of subjects with RBC transfusion avoidance (TA) during 12 weeks of treatment with ALXN2050
- Number of RBC units transfused and transfusion instances during 12 weeks of treatment as compared with transfusion data prior to screening
- Change in LDH level from baseline measurement at Week 12
- Change in absolute reticulocyte count and direct and total bilirubin from baseline measurement at Week 12
- Change in PNH RBC clone size and C3 fragment deposition on PNH RBCs from baseline measurement at Week 12.
- Change in FACIT-Fatigue score from baseline to Week 12 and Week 108.
- Change in Hgb relative to baseline at Week 108
- Change in LDH relative to baseline at Week 108

Transfusion avoidance is defined as subjects remaining transfusion-free and not requiring transfusion as per protocol-specified guidelines through the specified analysis period. For the analysis for this protocol, 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 transfusion guidelines:

It is recommended to administer packed red blood cells (pRBC) transfusion when a subject has a:

- hemoglobin value of less than 7 g/dL regardless of presence of clinical signs or symptoms, or
- hemoglobin value of less than 9 g/dL with signs or symptoms of sufficient severity to warrant a transfusion

5.1.3. Exploratory Efficacy Endpoints

Other efficacy endpoints include

- Change from baseline for the following biomarkers:
    - Free Hgb
    - Haptoglobin
    - D-dimer
    - Direct Coombs
- Change in the European Organization for Research and Treatment of Cancer (EORTC) QoL Questionnaire-Core 30 scale (QLQ-C30), Version 3.0 from baseline at Week 12 and at Week 108.
- Change in EuroQoL-5-Dimensions, 3-level version (EQ-5D-3L) scores from baseline at Week 12 and at Week 108.

5.2. Pharmacokinetics/Pharmacodynamics

Assessments for PK/PD are as follows:

- Change from baseline in circulating complement biomarkers, including Bb fragment of complement factor B (Bb) concentrations at Week 12
- Change from baseline in serum alternative pathway (AP) activity at Week 12
- Plasma concentrations of ALXN2050 over time

5.3. Safety

The safety and tolerability of ALXN2050 will be evaluated by incidence of adverse events (AEs), serious adverse events (SAEs) and events leading to discontinuation of study medication , laboratory assessments, vital signs, electrocardiograms (ECGs), and physical examinations.

5.3.1. Adverse Events (AEs)

The definitions of AEs and SAEs can be found in protocol Section 10.3. All AEs and SAEs will be collected from the signing of the ICF until 30 days after the last dose of study medication. A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during treatment, having been absent prior to treatment, or worsens relative to the pretreatment state. In this study, any AE first assessed after receipt of the first dose of ALXN2050 until 30 days after the last dose of study medication will be considered treatment-emergent. 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).

Each AE will be assessed regarding its seriousness, severity, and causal relationship (related, not related) with the study drug. The severity of an adverse event will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 or higher.

5.3.2. Laboratory Assessments

Blood and urine samples will be collected at protocol-specified visits for safety evaluation. The laboratory tests performed as hematology, chemistry, urinalysis, and other assessments are listed in the protocol Section 10.2.

5.3.3. Vital Signs

Vital sign measurements include blood pressure (BP), heart rate (HR), respiration rate (RR), body temperature, and weight at protocol-specified visits. Vital signs will be measured in the supine position on the dominant arm (if possible) following a 5-minute rest. Body temperature will be measured using an oral or temporal thermometer.

5.3.4. Electrocardiogram

Electrocardiogram (ECG) measurements will be conducted at the protocol specified time points. The following parameters and intervals will be assessed: heart rate, PR, RR, QRS, QT, and QTcF. The occurrence of depolarization or repolarization disorders, arrhythmic disorders, or other abnormalities will be noted. All ECG parameters and assessments must be recorded or stored in the subject's source documents and CRF. Any clinically significant finding must be reported as an AE.

5.3.5. Physical Examination

A complete physical examination will be performed at Screening, Baseline, at Week 12 and at the ET/Week108 Visits and will include an assessment of general appearance and a review of systems. An abbreviated physical examination will be conducted at other time points. Additional brief, complete, or symptom-driven physical examinations may be conducted at the discretion of the Investigator or designee and/or when subjects present with AEs.

A neurologic examination will be performed as part of the full physical examination at Screening, Baseline, at Week 12, and at ET/Week 108 Visit and will include:

- Mental status (orientation to person, place, and time)
- Cranial nerve examination (extraocular movements, facial muscles [raise eyebrows, eye closure, and smile])
- Upper and lower proximal and distal extremity strength
- Gait stability
- Coordination: finger to nose (looking for tremor) and arms outstretched looking for drift
- Sensory examination if subject presents relevant symptoms

A symptoms-based neurologic examination will be performed if the subject has any complaints or clinical findings attributable to the CNS and if positive for findings, full neurologic examination will need to be performed at each assessment timepoint.

6. DATA SETS ANALYZED (STUDY POPULATIONS)

6.1. Full Analysis (FA) Set

All subjects who receive at least one dose of ALXN2050 in this study will be included in the full analysis set (FAS). Efficacy analyses will be performed using the FAS.

6.2. Per Protocol (PP) Set

Not Applicable

6.3. Safety Set

All subjects who receive at least one dose of ALXN2050 in this study will be included in the safety set (SS). Safety analyses will be performed using the safety set.
Per the definitions, FAS and SS are identical in this study.

6.4. Other Sets

PK Analysis Set:
All subjects who receive at least one dose of ALXN2050 in this study and have evaluable PK data will be included in the PK analysis set.

PD Analysis Set:
All subjects who receive at least one dose of ALXN2050 in this study and have evaluable baseline and post-dose PD data will be included in the PD analysis set.

7. STATISTICAL ANALYSIS

Descriptive and exploratory statistical methods will be utilized to present results from data collected during 12 weeks of ALXN2050 Treatment Period and LTE period separately. Unless otherwise specified, all efficacy and safety data will be analyzed and presented separately by the three patient Groups 1 to 3 as specified in SAP Section 4 and overall.

In general, descriptive statistics for continuous variables will minimally include the number of participants, mean, median, standard deviation (SD), minimum, and maximum.

For categorical variables, frequencies and percentages will be presented. Summary statistics will be computed for selected efficacy and safety parameters so that meaningful clinical interpretations can be made.
Graphical displays will be provided as appropriate. For continuous endpoints, mean values over time will be plotted with standard deviation unless specified otherwise.

In general, baseline is defined as the last non-missing assessment value prior to first dose of study drug unless otherwise specified. For the analysis of numeric changes from baseline in laboratory parameters, only values from the central laboratory will be considered for baseline definition. For the analysis of change in Hgb, baseline is defined as the lowest Hgb value observed between and including screening and first dose date. Baseline for LDH is defined as the average of all available assessments prior to the first dose of study drug.

All data collected in this study will be presented in listings. Assessments from unscheduled visits will not be included in table summaries but be included in listings.

Analyses will be performed using the SAS® (Statistical Analysis Software®) software Version 9.4 or higher.

7.1. Study Subjects

7.1.1. Disposition of Subjects

A summary for the number of the screened patients (patients who signed informed consent of the study), screen failures, and treated patients (received at least one dose of study drug) will be tabulated. The number and percent of treated subjects who completed the week 12 and LTE and who discontinued the study will be summarized. For subjects who discontinued the study, the reason for discontinuation will be summarized.

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/exclusion criteria.

7.1.2. Protocol Deviations

All protocol deviations will be appropriately categorized, and the severity determined (major or minor) prior to the planned interim analysis or database lock. The number and percentage of subjects with major protocol deviations will be summarized overall, by protocol deviation category, and a listing with all protocol deviations will also be provided based on the FAS.

7.1.3. Demographics, Disease Characteristics, and Medical History

All demographic, baseline disease characteristics, physical exam findings, and medical history data will be summarized using descriptive statistics for the FAS. Listings will also be provided.

Data will be presented by group and by total patients receiving ALXN2050.

7.1.3.1. Demographics

The following demographic variables will be summarized:

- Age (in years) at Informed Consent
- Age category: <65, ≥65 years (65-74, 75-84, 85+)
- Gender
- Race
- Ethnicity
- Baseline Weight (kg)
- Baseline Height (cm)
- Baseline Body mass index (BMI, kg/m^2)

7.1.3.2. Disease Characteristics

Baseline disease characteristics will be summarized using descriptive statistics for the following parameters:

- Age (years) at PNH diagnosis
- Duration of PNH (Years from PNH diagnosis to informed consent)
- pRBC transfusion history including number of transfusion instances and units transfused during 24-week and 52-week prior to receiving study drug
- Packed RBCs transfused within 24 weeks and within 52 weeks prior to first dose of study drug (units)
- PNH clone sizes (RBC Type II and III, granulocyte)
- Absolute reticulocyte count (10^3/uL)
- Hemoglobin (g/dL)
- LDH
- FACIT-fatigue score at baseline

7.1.3.3. Medical / Surgical History

Medical history will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) available. Number and percentage of subjects with medical history findings will be summarized by system organ class (SOC) and preferred term (PT). Additionally, the MedDRA preferred term and verbatim text describing each diagnosis will be presented in a listing.

7.1.4. Prior and Concomitant Medications / Therapies

Concomitant medication/therapies are defined as medications/therapies received on or after the date of the first dose of the study drug (Day 1) through 30 days after the patient's last dose of study drug unless the patient transitions to an alternate treatment for PNH. If the start date of a

medication/therapy is partially or completely missing and the end date of the medication/therapy does not indicate that it ended prior to the first dose, then the determination of the concomitant status will be based on the following:

- If the start year is after the year of the first dose of study drug, then the medication/therapy is concomitant; else,
- If the start year is the same as the year of the first dose of study drug and
    - the start month is missing, then the medication/therapy is concomitant, else if
    - the start month is present and is the same or after the month of the first dose of study drug, then the medication/therapy is concomitant; else,
- If the start date is completely missing, then the medication/therapy is concomitant.

Medications/therapies received prior to Day 1 are considered Prior Medications/Therapies. The latest version of World Health Organization (WHO) Drug Dictionary available will be used to code the medications. Medications will be summarized by Anatomical Therapeutic Chemical (ATC) level 2 class and generic drug name.

Concomitant medications will be summarized for the Safety Set. The number and percentage of subjects receiving any medication will be summarized, as well as the number and percentage receiving any medication by ATC drug class and generic drug name. Subjects reporting use of more than one medication at each level of summarization (any medication received, ATC class, and generic drug name) will be counted only once. ATC class will be presented alphabetically followed by decreasing frequency of generic name. Concomitant medications will be presented in listings.

For the group switching from eculizumab or danicopan to ALXN2050, a summary of usage prior to the first dose of study drug will also be provided.

A separate by-subject listing of *N meningitidis* vaccinations during the study will be produced showing the date(s) and brand of vaccinations for each subject.

7.2. Efficacy Analyses

All efficacy analyses will be performed on the FAS. In general, when evaluating mean change from baseline in numeric laboratory parameters, only values reported by the central laboratory will be included in analysis.

In addition to the analyses described below, the observed values and changes from baseline of efficacy endpoints at each study visit will also be summarized by group using descriptive statistics.

For primary and continuous secondary endpoints during 12 weeks of treatment period, 2-sided 95% confidence interval (CI) will be provided based on the Student's t-statistics.

All endpoints (including the derived ones) will be presented in listings.

7.2.1. Primary Endpoint Analysis

The primary efficacy endpoint is:

- Change in Hgb level from baseline at Week 12

The primary objective is to evaluate the efficacy of ALXN2050 based on improvement in Hgb after 12 weeks of treatment. Transfusion is an intercurrent event that can occur during the treatment period and impact patient Hgb values. To address the impact of transfusion, Hgb values collected within 4 weeks after transfusion will not be included in the primary efficacy analysis.

Descriptive statistics and graphic presentations for Hgb level and change from baseline at Week 12 and other planned visits will be provided. Two-sided 95% CI will be provided based on the Student's t-statistics.

7.2.1.1. Handling of Dropouts or Missing Data

Analysis will be on observed values and no imputation will be applied.

7.2.1.2. Subgroup Analysis

No subgroup analysis is planned.

7.2.1.3. Multicenter Studies

Sample size is too small to warrant meaningful analysis to assess study site effect.

7.2.1.4. Hypothesis Testing and Significance Level

None

7.2.1.5. Sensitivity Analyses

Sensitivity analysis will be performed for the primary endpoint Hgb with exclusion of measures collected after major Protocol Deviations that affect efficacy. The analysis method is the same as described in Section 7.2.1.

7.2.2. Secondary Endpoint Analyses

Similar to Hgb measurement, other laboratory measurements (including LDH, absolute reticulocyte count, direct and total bilirubin, PNH RBC clone size, and C3 fragment deposition on PNH RBCs) and their changes from baseline (including LDH percentage of change from baseline) will be summarized using descriptive statistics and graphic presentations for each planned visit. Summary statistics for RBC transfusion units received and transfusion instances during 12 weeks of treatment and during 12 weeks prior to screening will also be provided.

Sensitivity analysis as described in Section 7.2.1.5 will be performed for LDH.

Transfusion avoidance is defined as patients who remained transfusion free and did not require a transfusion after the first dose of study drug.

Patients are included in the denominator for a visit only if they have data for that visit. For the 12- week duration of treatment, patients having at least one data for a visit will be included in the denominator and only visits with data will be used to assess transfusion avoidance. Those patients who withdraw due to a lack of efficacy will be counted as needing transfusion.

The number and proportion of patients who do not require a transfusion will be summarized over time by presenting the number and proportion of patients who remained transfusion free after the

first dose of study drug along with a 2-sided 95% CI for each applicable postbaseline time point. Additionally, this proportion will be summarized during 12 weeks of treatment, during the 12 weeks prior to screening, during the LTE and during the entire study. The above analyses of transfusion avoidance will be repeated only to count patients who didn't receive a transfusion.

7.2.2.1. FACIT Fatigue Scale (Version 4)

The FACIT-Fatigue scale is a collection of QoL questionnaires pertaining to the management of fatigue symptoms due to a chronic illness. The FACIT-Fatigue 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 scale: 0 (not at all) to 4 (very much). A total score will be calculated as below:

All negatively stated items (ie, all items except An5 and An7 from the CRF) are to be reversed by subtracting the response from 4. After reversing the proper items, all items are summed to obtain a score. The fatigue subscale score is then calculated by multiplying the sum of the item scores by 13, then dividing by the number of items answered. When there are missing data, prorating by subscale in this way is acceptable if 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.

FACIT total score and change from baseline will be summarized by study visit using descriptive statistics and graphic presentations.

7.2.3. Other Efficacy Analyses

Other efficacy endpoints to monitor and evaluate the long-term effects of ALXN2050 on PNH cells and complement AP components and function include the following:

- Free Hgb
- Haptoglobin
- D-dimer
- Direct Coombs

These measures and change from baseline will be summarized by study visit using descriptive statistics and graphic presentations.

7.2.3.1. EORTC-QLQ-C30 (Version 3)

There are 30 items in the EORTC-QLQ-C30 questionnaire. The 2 global health status items have 7 possible responses, with 1 being poor and 7 being excellent. All the other 28 items have 4 possible responses, with 1 being "Not at All" and 4 being "Very Much". These 30 items are composed of both multi-item scales and single-item measures, which include five functional scales, nine symptom scales/items, and one global health status/QoL scale as the following:

- Functional scales:
    - Physical functioning
    - Role functioning
    - Emotional functioning
    - Cognitive functioning
    - Social functioning

- Symptom scales/items:
  - Fatigue
  - Nausea and vomiting
  - Pain
  - Dyspnoea
  - Insomnia
  - Appetite loss
  - Constipation
  - Diarrhoea
  - Financial difficulties
- Global health status/QoL scale

All scales and single-item measures will be transformed into scores from 0 to 100. Details for transforming raw scores into scale scores for the scales and single-item measures are provided in SAP Section 10.3.
A high scale score represents a higher response level. A high score for a functional scale represents a high/healthy level of functioning, and a high score for the global health status/QoL represents a high QoL, while a high score for a symptom scale/item represents a high level of symptomatology/problems.
Scale scores and change from baseline for each QLQ-C30 scale/single-item measure will be summarized by study visit using descriptive statistics and graphic presentations.

7.2.3.2. EQ-5D-3L

The EQ-5D-3L essentially consists of 2 pages - the EQ-5D descriptive system (page 2) and the EQ visual analogue scale (EQ VAS; page 3).

The EQ-5D descriptive system uses 5 domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each with 3 response options (no problems, moderate problems, severe problems), defining a total of 243 unique health states (Rabin, 2001). For health state index, scoring algorithms derived for the U.S. general population will be applied using individual health profiles. Details for scoring algorithms are provided in SAP Section 10.4.

The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labelled 'The best health you can imagine' for 100 and 'The worst health you can imagine' for 0. Missing values will be coded as '999'. If there is a discrepancy between where the respondent has placed the X and the number written in the box, number in the box will be used for VAS.

The EQ-5D-3L scores (US index and VAS) and changes from baseline will be summarized by study visit using descriptive statistics and graphic presentations.

7.2.4. Pharmacokinetic and Pharmacodynamic Analyses

Pre-dose and post-dose PK and PD samples will be taken at the time points specified in the protocol schedule of assessments. Individual ALXN2050 plasma concentrations will be listed and summarized at each sampling time point. Descriptive statistics (number of non-missing observations (N), arithmetic mean, SD, median, coefficient of variation (CV%), minimum, maximum, geometric mean and geometric CV%) will be used to summarize ALXN2050

concentrations by dose level (120 mg and 180 mg) and formulation (PIC and tablet). Individual plasma concentration-time data on study day(s) with intensive PK sampling will be used to generate individual and mean concentration-time PK profiles. Mean concentration-time PK profiles will be presented for each dose level (120 mg and 180 mg) and formulation (PIC and tablet).

Pharmacokinetic analysis will be performed using Phoenix WinNonlin® Version 8.1 or higher. ALXN2050 PK parameters, including, but not limited to, the standard PK parameters outlined in the table below, will be derived from the individual plasma concentration-time data on study day(s) with intensive PK sampling. Descriptive statistics (number of non-missing observations (N), arithmetic mean, SD, median, coefficient of variation (CV%), minimum, maximum, geometric mean and geometric CV%) will be used to summarize the calculated PK parameters by dose level (120 mg and 180 mg) and formulation (PIC and tablet).

For the calculation of PK parameters, concentrations that are below the lower limit of quantification (BLQ) prior to the T_{max} will be set to 0 and those thereafter as missing. AUC values will be estimated using the linear trapezoidal rule and will require at least 3 post-dose concentration values that occur after and do not include T_{max}. Actual sampling times relative to dosing will be used in the calculation of PK parameters.

AUC(0-12)	Area under the concentration-time curve from time zero to the end of steady-state dose interval
C_{max}	Maximum plasma concentration
t_{max}	Time after administration of a drug when the maximum plasma concentration is reached
C(0)	Trough concentration at start of steady-state dose interval
C(12)	Trough concentration at end of steady-state dose interval

PD analyses of Bb, FD, C3, APH and CH50 will be performed for the PD Analysis Set. Descriptive statistics (number of patients, mean/geometric mean, coefficient of variation (CV%), SD, median, minimum, and maximum) and graphical presentations will be presented for all PD endpoints at each sampling time point, stratified by dose level (120 mg and 180 mg) and formulation (PIC and tablet). The PD effects of ALXN2050 administered orally will be evaluated by assessing the absolute values and changes and percentage changes from baseline in APH, CH50 and Bb concentrations over time (using descriptive statistics and graphical presentations), as appropriate.

7.2.5. Adverse Events

TEAEs will be summarized with number and percentage of subjects with AEs and event counts.

Patients having multiple TEAEs within a category (eg, 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 group and overall. Tables will be sorted by alphabetical order of SOC and by descending frequency of PT within SOC within the overall group. PTs with same frequency will be sorted in alphabetical order. Any TEAEs lasted across treatment periods will be only counted once in the treatment period the event started.

TEAE and Pre-Treatment Adverse Events (PTAEs) will be listed separately.

7.2.5.1. Overall Summary of Adverse Events

An overall summary of TEAEs for all subjects will summarize number of events and the number/percentage of subjects experiencing TEAEs in the following categories:

- Any TEAEs
- TEAEs related and not related to study drug
- TEAEs by CTCAE severity grade
- Serious adverse events
- TEAE leading to study drug withdrawal
- TEAE resulting in death if any

The above summary will also be performed to only include subjects with dose escalation to 180 mg bid, separately for the before-escalation and after-escalation periods.

A listing of all TEAEs by subject will be presented. Separate listings will be produced for SAEs, AEs leading to study drug withdrawal, and AEs resulting in death when applicable.

7.2.5.2. AEs and SAEs by System Organ Class (SOC) and Preferred Term (PT)

The number of TEAEs and the number and percentage of subjects with TEAEs will be presented by SOC and PT. Subjects will be counted once in each SOC and PT. Percentages will be based on the total number of subjects in the Safety set. SOC will be listed in alphabetical order, and PTs within a SOC will be listed in order of decreasing frequency, with ties broken alphabetically.

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

The number of TEAEs and the number and percentage of subjects with TEAEs will be presented by SOC, PT and relationship to study drug (related, not related). If a subject has more than one occurrence of an AE, the most related event to study treatment within one category will be counted in the summary table. Missing relationship to study drug will be assumed to be related.

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

The number of TEAEs and the number and percentage of subjects with events will be presented by SOC, PT and CTCAE toxicity grade. If a subject has more than one occurrence of an AE, the highest toxicity reported will be used. If toxicity is missing, the AE will be treated as 'Unknown'.

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

A listing of subject deaths will be produced.

Events of interest in this study include TEAEs of meningococcal infections and seizures. These events of interest will be summarized by group in tabular form. The AE MedDRA terms that will be considered for these summaries is listed below:

- Meningococcal infections: MedDRA preferred terms of Meningococcal bacteraemia, Meningitis meningococcal, Meningococcal infection, Meningococcal sepsis, Meningococcal carditis, Encephalitis meningococcal, Endocarditis meningococcal,

Myocarditis meningococcal, Optic neuritis meningococcal, and Pericarditis meningococcal.
- Seizures: MedDRA high level group term (HLGT) of seizures

In addition, a medical review will be performed to ensure that no relevant events were missed.

The event of breakthrough hemolysis will be summarized by group in tabular form.

7.2.6. Other Safety

7.2.6.1. Analyses for Laboratory Tests

Descriptive statistics for observed values and the change from baseline by study visit will be presented for each laboratory parameter by the scheduled visits, except those described in the efficacy analysis. Missing laboratory data will not be imputed, and only scheduled assessments at central laboratory will be included in by-visit summaries. Unscheduled assessments and local laboratory values will not be included in the by visit summary tables.

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.

For laboratory tests with CTCAE toxicity grades available, laboratory abnormalities will be summarized by worst treatment-emergent grade [treatment emergent (TE) lab abnormalities]. Note that the post-baseline laboratory value with the highest treatment-emergent toxicity grade will be reported for each test.

Box plots will be presented for the following central lab parameters by visit: Hemoglobin, absolute reticulocytes count, LDH, bilirubin (total and direct), haptoglobin, free hemoglobin, eGFR, AST, ALT, GGT, and D-dimer. Additionally, scatter plots of the worst value post first study drug versus baseline will be provided for the above-mentioned parameters.

All laboratory results as well as the associated normal ranges and high/low indicators of abnormal results will be presented in listings. Worst treatment emergent toxicity grade laboratory results will also be presented in a listing.

7.2.6.2. Vital Signs

Observed values and the change from baseline in vital signs (blood pressure, heart rate, respiratory rate, body temperature, and weight) at each visit will be summarized descriptively. Missing vital signs data will not be imputed and only scheduled assessments will be summarized in tables; unscheduled assessments will be presented in by-subject data listings. A listing of vital signs will be presented by subject, vital sign, and visit.

7.2.6.3. Electrocardiogram

All observed ECG data and changes from baseline in ECG data (heart rate, PR interval, RR interval, QRS duration, QT interval and QTcF) will be summarized descriptively by study visit.

At each planned visit with ECG, the number and percentage of subjects falling into the following treatment emergent ECG abnormality categories will be presented:

- PR interval: > 200 ms
- QTcF actual values: ≤450 ms, >450 to ≤480 ms, >480 to ≤500 ms, and >500 ms
- QTcF increases from baseline of >30 ms and >60 ms

All ECG data will be presented in a listing.

7.2.6.4. Physical Examination

Results of the abnormal physical examination results will be summarized and listed by scheduled visit.

7.3. COVID-19 Related Analyses

The following COVID-19 related data will be collected in this study:

- Modified and missed study visits (and COVID-19 related reasons)
- Discontinuation (impacted by COVID-19)
- COVID-19 Exposure
- TEAEs related to COVID-19
- Protocol deviations related to COVID-19

The number of subjects with modified study visits and the reasons for modified study visits (COVID related or other) will be summarized by groups and overall. Similarly, the number of subjects with missed study visits and the reasons for missed study visits (COVID-related or other) will be summarized by groups and overall.

The number of subjects with discontinuation status impacted by COVID-19 will be summarized by groups and overall.

Treatment compliance percentage will be summarized for subjects with COVID-19 exposure during the study by groups and overall.

An overall summary table of TEAEs related to COVID-19 will be presented. The number of TEAEs related to COVID-19 and the number and percentage of patients with TEAEs related to COVID-19 will be presented by SOC and PT.

Protocol deviations related to COVID-19 will be summarized as the overall protocol deviations specified in SAP Section 7.1.2.

8. INTERIM ANALYSES

Three interim analyses are planned: when 6 patients in Group 1, 6 patients in Group 2 and all patients complete the 12-week Treatment Period. All analyses in Section 7 will be performed.

9. REFERENCES

1. Dolan P. Modeling valuations for EuroQol health states. Med Care. 1997;35(11):1095-108. doi: 10.1097/00005650-199711000-00002.
2. Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group; The EORTC QLQ-C30 Scoring Manual (3rd Edition); European Organisation for Research and Treatment of Cancer, Brussels 2001.
3. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med. 2001;33(5):337-43. doi: 10.3109/07853890109002087.
4. Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. Med Care. 2005;43(3):203-20. doi: 10.1097/00005650-200503000-00003.

10. APPENDICES

10.1. Protocol Schedule of Assessments

Refer to the protocol for a schedule of activities.

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

Not applicable.

10.3. Scoring the EORTC QLQ-C30 version 3.0

The following Table 2. shows the component questions of QLQ-C30 included in each of the scales and single-item measures and their ranges (Fayers, 2001).

Table 2 Scoring of EORTC QLQ-C30 version 3.0

	Scale	Number of items	Item range*	**Version 3.0** Item numbers	Function scales
Global health status / QoL					
Global health status/QoL (revised)†	QL2	2	6	29, 30	
Functional scales					
Physical functioning (revised)†	PF2	5	3	1 to 5	F
Role functioning (revised)†	RF2	2	3	6, 7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social functioning	SF	2	3	26, 27	F
Symptom scales / items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14, 15	
Pain	PA	2	3	9, 19	
Dyspnoea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhoea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

* Item range is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving range = 3.
† Scales are those that have been changed since version 1.0, and their short names are indicated in this manual by a suffix "2" – for example, PF2.

Transforming responses to scale scores for each of the scales and single-item measures are as follows:

For all scales, the *RawScore*, is the mean responses of the component items:

$RawScore = (I_1 + I_2 + \ldots + I_n)/n$

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.

10.4. Scoring EQ-5Q-3L Health State Index

The EQ-5D descriptive system uses 5 domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each with 3 response options (no problems, moderate problems, severe problems), defining a total of 243 unique health states (Rabin, 2001).

For health state index, scoring algorithms derived for the U.S. general population will be applied using individual health profiles. This scoring algorithm was derived from time tradeoff assessments of EQ-5D health states made by a population sample of some 4,000 U.S. adults in face-to-face household interviews (Shaw, 2005). Health state index is to be calculated using the below equation with the US population-based sample estimates (Shaw, 2005). Variable definition is provided in Table 3.

$$Y=1 - 0.146*M2 - 0.558*M3 - 0.175*S2 - 0.471*S3 - 0.140*U2 - 0.374*U3 - 0.173*P2 - 0.537*P3 - 0.156*A2 - 0.450*A3 + 0.140*D1 - 0.011*I2^2 + 0.122*I3 + 0.015*I3^2$$

Table 3 Definition for variables used in calculating health state index using US population estimates

Variable	Definition
M2	1 if mobility is level 2; 0 otherwise
M3	1 if mobility is level 3; 0 otherwise
S2	1 if self-care is level 2; 0 otherwise
S3	1 if self-care is level 3; 0 otherwise
U2	1 if usual activities is level 2; 0 otherwise
U3	1 if usual activities is level 3; 0 otherwise
P2	1 if pain/discomfort is level 2; 0 otherwise
P3	1 if pain/discomfort is level 3; 0 otherwise

A2	1 if anxiety/depression is level 2; 0 otherwise
A3	1 if anxiety/depression is level 3; 0 otherwise
D1	The number of dimensions at level 2 or 3 beyond the first
I2	The number of dimensions at level 2 beyond the first
I3	The number of dimensions at level 3 beyond the first

In addition, the scoring algorithms derived from the UK population will also be applied to obtain the health state index, using the equation below (Dolan, 1997). Variable definition is provided in Table 4.

$$Y = 1 - 0.081*a - 0.069*MO - 0.104*SC - 0.036*UA - 0.123*PD - 0.071*AD - 0.176*M2 - 0.006*S2 - 0.022*U2 - 0.140*P2 - 0.094*A2 - 0.269*N3$$

Table 4 Definition for variables used in calculating health state index using UK population estimates

Variable	Definition
a	Constant: associated with any move away from full health
MO	1 if mobility is level 2; 2 if mobility is level 3; 0 otherwise
SC	1 if self-care is level 2; 2 if self-care is level 3; 0 otherwise
UA	1 if usual activities is level 2; 2 if usual activities is level 3; 0 otherwise
PD	1 if pain/discomfort is level 2; 2 if pain/discomfort is level 3; 0 otherwise
AD	1 if anxiety/depression is level 2; 2 if anxiety/dep. is level 3; 0 otherwise
M2	1 if mobility is level 3; 0 otherwise
S2	1 if self-care is level 3; 0 otherwise
U2	1 if usual activities is level 3; 0 otherwise
P2	1 if pain/discomfort is level 3; 0 otherwise
A2	1 if anxiety/depression is level 3; 0 otherwise
N3	1 if any dimension is level 3; 0 otherwise

10.5. Technical Specifications for Derived Variables

Missing and Partial 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 months 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. Should the date created with these imputation rules place it outside the possible range of values established by complete, known dates (such as the birth date, death date, or the ICF date for study procedures), the closest known date will be used. For example, a subject with a partial AE start date of June 2011 and a death date of June 5th 2011 would have the AE date imputed as June 5th 2011 instead of the 15th.

Analysis Relative Day

Analysis relative day is the day relative to the first dosing day. It will be calculated as: analysis date – first dose date + 1 if analysis date is after the first dose date, or else as: analysis date first - dose date.

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., 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).