TITLE PAGE

Protocol Title: 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) Patients as Monotherapy

Protocol Number: ACH228-110

Amendment Number: 5.0

Compound: ALXN2050 (ACH-0145228)

Study Phase: 2

Short Title: Study of the Oral Factor D (FD) Inhibitor ALXN2050 in PNH Patients as Monotherapy

Sponsor Name: Alexion Pharmaceuticals Inc.

Legal Registered Address: 121 Seaport Blvd, Boston, MA 02210 USA

Regulatory Agency Identifier Number(s)

Registry	ID
EudraCT	2019-003830-17
WHO UTN	U1111-1241-2441
ClinicalTrials.gov	NCT04170023

Release Date: 24 May 2023

Sponsor Signatory:

[redacted] _____ _____

Date

Medical Monitor Name and Contact Information can be found in study contact list.

INVESTIGATOR'S AGREEMENT

I have read the study protocol amendment and agree to conduct the study in accordance with this protocol amendment, all applicable government regulations, the principles of the ICH E6 Guidelines for Good Clinical Practice, and the principles of the World Medical Association Declaration of Helsinki. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol amendment.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	01 Oct 2019
Global Amendment 1.0	06 Apr 2020
Local Amendment 1.1 (UK)	20 Jul 2020
Global Amendment 2.0	07 Jan 2021
Global Amendment 2.1	12 Apr 2021
Global Amendment 3.0	03 May 2021
Local Amendment 3.1 (France)	09 Sep 2021
Local Amendment 3.2 (Germany)	10 Sep 2021
Global Amendment 4.0	07 Oct 2021
Local Amendment 4.1 (New Zealand)	09 Sep 2022
Global Amendment 5.0	24 May 2023

Amendment 5.0 (Global) 24 May 2023

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union

Overall Rationale for the Amendment:

This global amendment was initiated to provide an option for continued access of treatment with ALXN2050 beyond the study duration. Patients who in the opinion of the treating physician would clinically benefit from continued treatment with ALXN2050 and will not have alternative treatment options will have the option to transition to an Alexion-sponsored Roll Over Study (ROSY); Study ALXN2050-ROSY-401.

In addition, with this global amendment, all patients not already receiving 180 mg bid, will be dose escalated to 180 mg bid.

This amendment also includes:

Section # and Name	**Description of Change**	**Brief Rationale**
Throughout the protocol	Change in version number and document date; updated to summarize changes.	Administrative change.
Synopsis, Intervention Groups and Duration Section 1.3 Schedule of Activities – Table 1 footnotes, Section 4.2 Scientific Rationale for Study Design, Section 6.7 Dose Modification of ALXN2050	The following terminology "12 weeks of treatment" was replaced with "**12-week Treatment Period**".	Editorial change for consistency.

Section # and Name	Description of Change	Brief Rationale
Synopsis, Overall Design Section 4.2 Scientific Rationale for Study Design	The following text was updated: This is a multiple-center […] (previously ACH-0145228) monotherapy in **adult** patients **(≥ 18 years of age) diagnosed** with PNH.	To align with the current Alexion protocol template.
Synopsis, Overall Design Section 1.2 Schema Section 4.1 Overall Design	*The following enrollment text has been deleted.* ~~*Group 1 will be enrolled in all countries except the US. Group 2 will be enrolled in all countries. Group 3 will be enrolled in countries where Study ACH471-103 is being conducted.*~~	Updated to remove country-specific information. US sites were not able to participate in the study.
Synopsis, Overall Design Section 1.3 Schedule of Activities - Table 1 footnotes Section 4.2 Scientific Rationale for Study Design Section 6.7 Dose Modification of ALXN2050 Section 6.7.4 Dose escalation or Modification at Other Time Points for All Patient Groups	Text pertaining to dose escalation to 180 mg bid in patients who are not already receiving 180 mg bid, after the 12-Week Treatment Period, was added.	Updated based on available interim data.
Section 1.3 Schedule of Activities Table 3 footnotes Section 4.2 Scientific Rationale for Study Design Section 4.4 End of Study Definition	The following text was updated: "If the patient has entered the LTE Period and discontinues from the study to enroll in Study ALXN2050-ROSY-401 (see Section 6.9), the patient will complete the Week 160/ET visit assessments. The patient will not need to taper or attend the Follow-up Visit as described above."	To enable patients to transition to Study ALXN2050-ROSY-401 for continued access of treatment.
Section 4.4 End of Study Definition	The following text was updated: " OR The patient decides not to transition to Study ALXN2050 ROSY 401; ET/Week 160 must be completed at any time during the LTE, with a dose taper (See Section 7.2) and Follow-up Visit (see Section 7.3)."	To clarify end of study definition for patients not transitioning to Study ALXN2050-ROSY-401.
Section 1.3 Schedule of Activities Table 1 and Table 3, and associated footnotes Section 8.3.4 Clinical Safety Laboratory Assessments Section 8.6 Pharmacokinetics	Addition of breakthrough hemolysis assessment and supporting text.	To include testing for breakthrough hemolysis at scheduled and unscheduled visit days.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities, Table 3	Addition of ± 3-day visit window for ET/Week 160 visit.	To align with the visit windows of other visits during the LTE Period.
	Added "interim" in Footnote 10.	To include urine pregnancy testing at interim visit days.
	Updated collection details of plasma/serum samples for additional nongenetic biomarker testing in Footnote 11.	To align with the scheduled collection time points found in Table 3.
Section 2.2.2 Paroxysmal Nocturnal Hemoglobinuria	Text pertaining to pegcetacoplan added.	To include approved treatments for PNH.
Section 2.3.1 Risk Assessment	The following text was added: "In Study ALXN2050-HV-107, EEG recordings revealed no evidence of epileptiform activity for any patient at any of the ALXN2050 doses tested (120, 240, or 360 mg bid)." The following text was updated: "A 24-hour EEG monitoring of the 2 highest dose cohorts in ~~the MAD study~~ **Study ACH228-002** (120 mg and 200 mg orally (PO) bid) was conducted"	Update made to include safety data for ALXN2050.
Section 2.3.1 Risk Assessment	Deleted text pertaining to risk of liver enzymes elevation.	To align with IB Edition 09 (20 Jan 2022). Update made as liver enzyme elevation is not considered an important potential risk. Liver enzyme changes observed in toxicology studies were reversible and non-adverse with minimal toxicologic significance for human risk assessment.
Section 4.3 Justification for Dose	Text pertaining to safety margins for tablet formulation at doses 120 mg bid and 180 mg bid was added.	To align with IB Edition 10 (14 Feb 2023).
	Section updated with interim efficacy and safety data for the current study.	To support dose escalation to 180 mg bid in all patients).

Section # and Name	Description of Change	Brief Rationale
Section 5.1.1 Inclusion Criteria Section 10.5 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	Section updated to include details on acceptable method of contraception.	Based on the large maternal safety margins at the NOAEL in most recent EFD toxicity studies, and absence of genotoxic potential, Alexion considers ALXN2050 to have an unlikely risk of human teratogenicity/fetotoxicity . The ALXN2050 IB, Edition 10 was updated accordingly.
Section 6.2 Preparation/Handling/Storage/ Accountability	Text pertaining to handling and storage conditions was updated.	To align with stability data and IB Edition 10 (14 Feb 2023).
Section 6.9 Intervention After the End of the Study	The following text was updated: "~~Study medication will not be provided to patients after the last scheduled dosing~~. **As described in Section 4.4, the end of study is defined as the date the last patient completes the last visit or last scheduled procedure (including follow up) in the study, as shown in the SoA.** **If the Treating Physician is of the opinion that a patient may clinically benefit from continued treatment with ALXN2050, a patient in the LTE may transition to the Alexion Roll Over Study (ROSY), Study ALXN2050-ROSY-401, without treatment interruption (no taper or Follow up Visit are required), as soon as possible after completing the ET/Week 160 Visit assessments.** **Eligible patients will be provided with a new informed consent form if they decide to participate in Study ALXN2050-ROSY-401."**	To enable patients to transition to Study ALXN2050-ROSY-401 for continued access of treatment.

Section # and Name	Description of Change	Brief Rationale
Section 8.1.1 Screening for All Patients Section 8.3.1 Physical Examinations	The following text was updated: A ~~complete~~**full** physical examination will be performed at Screening, Baseline, at Week 12, the LTE (as needed) and at the ET/Week 160 Visit and will include an assessment of general appearance and a review of body systems. Additional brief, **full** ~~complete~~, or symptom-driven physical examinations may be conducted at the discretion of the Investigator or designee and/or when patients present with AEs.	Updated for internal consistency.
Section 8.3.1 Physical Examinations	Text was shuffled within the same section.	Update made for better readability and clarity.
Section 8.3.2 Vital Signs Section 8.3.5 Blood Collection	Updated to include the term "sitting" position during collection time.	Vital signs and blood collection were updated to include sitting position in addition to supine.
Section 8.5 Treatment of Overdose	The following text was added: **Capture and forward the event, with or without associated AEs, to Alexion Global Patient Safety via email or facsimile (clinicalsae@alexion.com or + 1.203.439.9347) using the Alexion Clinical Study Overdose Report Form within 24 hours of awareness.**	To align with the current Alexion protocol template.
Synopsis Ethical Considerations and Benefit-Risk Assessment Section 4.4 End of Study Definition Section 8.3.6 Medication Error, Drug Abuse, and Drug Misuse Section 10.1.1 Regulatory and Ethical Considerations Section 10.1.4 Data Protection Section 10.3.13 Unexpected Events Section 10.4 Medication Error, Drug Abuse, and Drug Misuse	Incorporation of template changes for EU Clinical Trials Regulation 536/2014 within the amendment.	To align with the current Alexion protocol template.

Section # and Name	Description of Change	Brief Rationale
Section 10.1.6 Data Quality Assurance Section 10.6 Appendix 5: Genetics	Duration of retention of genetic samples was increased to 25 years.	To align with Alexion processes for retention of genetic samples.
Section 10.3.8 Reporting Serious Adverse Events and Pregnancies	Updated: US / Canada: 1-866-91-AXIOM (29466) International: 647-799-4015 Email: achillion@axiom.cc.	Updated contact information for SAE reporting.
Section 10.13 Appendix 12 Protocol Amendment History	Protocol Amendment History was moved from the Summary of Changes section to Section 10.13 Appendix 12.	To align with the current Alexion protocol template.
General/All Sections	Minor editorial and formatting changes throughout the document, including minor spelling corrections and updating the list of abbreviations and table of contents.	For clarity and completeness.

Abbreviations: AE = adverse event; bid = twice daily; EEG = electroencephalogram; EFD = embryo-fetal developmental; ET = early termination; IB = investigator's brochure; LTE = long-term extension; NOAEL = no-observed-adverse-effect-level; PNH = paroxysmal nocturnal hemoglobinuria; ROSY = Roll Over Study; SAE = serious adverse event; USPI = United States Prescribing Information.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: 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) Patients as Monotherapy

Short Title: Study of the Oral Factor D (FD) Inhibitor ALXN2050 in PNH Patients as Monotherapy

Rationale: This is a study to evaluate the efficacy and safety of ALXN2050 monotherapy in treatment naïve PNH patients, in PNH patients currently treated with eculizumab who still experience anemia and reticulocytosis, and in PNH patients currently treated with ALXN2040 (danicopan) as monotherapy.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of ALXN2050 based on improvement in hemoglobin (Hgb)	• Change in Hgb relative to baseline at Week 12
Secondary	
• 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 patients with paroxysmal nocturnal hemoglobinuria (PNH)	• Number of patients who have transfusion avoidance (defined as patients remaining transfusion-free and not requiring transfusion as per protocol-specified guidelines) during 12-week Treatment Period with ALXN2050 • Number of RBC units transfused and transfusion instances during 12-week Treatment Period as compared with transfusion data prior to screening • Change in LDH relative to baseline at Week 12 • Change in absolute reticulocyte count and direct and total bilirubin from baseline at Week 12 • Change in PNH RBC clone size and C3 fragment deposition on PNH RBCs from baseline at Week 12
• To evaluate the safety and tolerability of ALXN2050	• Incidence of TEAEs, SAEs, and events leading to discontinuation of study medication
• To evaluate maintenance of response of ALXN2050 during the LTE period.	• Change in Hgb relative to baseline • Change in LDH relative to baseline

Objectives	Endpoints
• To evaluate the effect of ALXN2050 on Functional Assessment of Chronic Illness Therapy-Fatigue scale (FACIT) scores	• Change in FACIT Fatigue scale (Version 4) scores from baseline at Week 12 and at Week 160.
Exploratory	
• To characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of ALXN2050	• Change in circulating complement biomarkers, including Bb fragment of complement factor B (Bb) concentrations at Week 12 relative to baseline • Change in serum alternative pathway (AP) activity at Week 12 relative to baseline • Plasma concentrations of ALXN2050 over time
• To evaluate other health-related quality of life (QOL) in patients with PNH based on patient-reported outcome instruments and their evolution over the course of ALXN2050 treatment	• Change in the European Organisation 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 160 • Change in EuroQoL-5-Dimensions, 3-level version (EQ-5D-3L) scores from baseline at Week 12 and at Week 160.

Overall Design

This is a multiple-center, open-label multiple dose study to assess the efficacy, safety, pharmacokinetics (PK), and pharmacodynamics (PD) of the oral factor D (FD) inhibitor ALXN2050 (previously ACH-0145228) monotherapy in adult patients (≥ 18 years of age) diagnosed with PNH.

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

- Group 1: PNH patients who are treatment naïve
- Group 2: PNH patients 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 patients who have received danicopan monotherapy during Study ACH471-103, and who will switch to ALXN2050 in this study

To mitigate the potential risk of meningococcal infection, all patients must be vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating the study medication.

After signing the informed consent form (ICF), patients will enter the Screening Period. During the Screening Period, eligibility and screening assessments will be performed. Screened patients who continue to meet eligibility criteria will enter the Treatment Period and will receive their first dose of the study medication during the Baseline Visit (Day 1) in this study. Eligible patients will be enrolled in the study and will receive ALXN2050 at a dose of 120 mg twice daily (bid) for 12 weeks, with potential escalation to 180 mg bid based on clinical response and tolerability as defined in the dose escalation section (Section 6.7). At the end of Week 12, patients will enter the 148-week Long-term Extension (LTE) Period. During the course of the study, all patients will return to the clinic for safety and other assessments as shown in Table 1 to Table 3.

For Group 1: PNH treatment naïve study patients will receive their first dose of ALXN2050 on Day 1 (Baseline Visit).

For Group 2: Patients switching from eculizumab to ALXN2050 monotherapy will receive their first dose of ALXN2050 (Day 1) 7 (± 1) days after the last dose of eculizumab.

For Group 3: Patients who are rolling over from Study ACH471-103 will receive their last danicopan dose the evening prior (Day -1) to the first dose (approximately 8 hours) of ALXN2050 (Day 1) in this study.

Patients will have the option to have selected visits performed via the visiting healthcare service provided by Sponsor. With this service, the patient does not physically visit the investigative site. Instead, a healthcare provider visits the patient at the patient's residence to perform protocol-specified assessments with appropriate documentations.

Withdrawals and Discontinuation

If the patient withdraws from the study prior to Week 12, the patient will be encouraged to complete the Week 12/Early Termination (ET) Visit as soon as possible and should take the study medication per protocol until that time. After the ET Visit is completed, ALXN2050 will be tapered over 6 days. Additionally, a safety Follow-up Visit will be conducted 30 (+ 7) days after the last dose of ALXN2050.

If the patient has entered the LTE Period and discontinues from the study, the patient will be encouraged to complete the ET Visit, and the dose of ALXN2050 will be tapered over a 6-day period. The patient will attend a Follow-up Visit as described above.

Disclosure Statement: This is a multiple-center, open-label, multiple-dose study with 3 patient groups.

Number of Patients: Approximately 26 patients which will include approximately 10 patients in Group 1, approximately 10 patients in Group 2, and approximately 6 patients in Group 3.

Intervention Groups and Duration: ALXN2050 will be administered orally, 120 mg bid, with the option for dose escalation to 180 mg bid during the 12-Week Treatment Period according to the protocol specified dose escalation guidance for the 3 planned patient groups.

The study consists of a 60-day Screening Period, a 12-week Treatment Period, and a 148-week LTE Period, followed by a 6-day taper and a 30-day safety follow-up after the last dose. The total duration of the study will be approximately 173 weeks.

Data Monitoring Committee: No

Ethical Considerations and Benefit-Risk Assessment

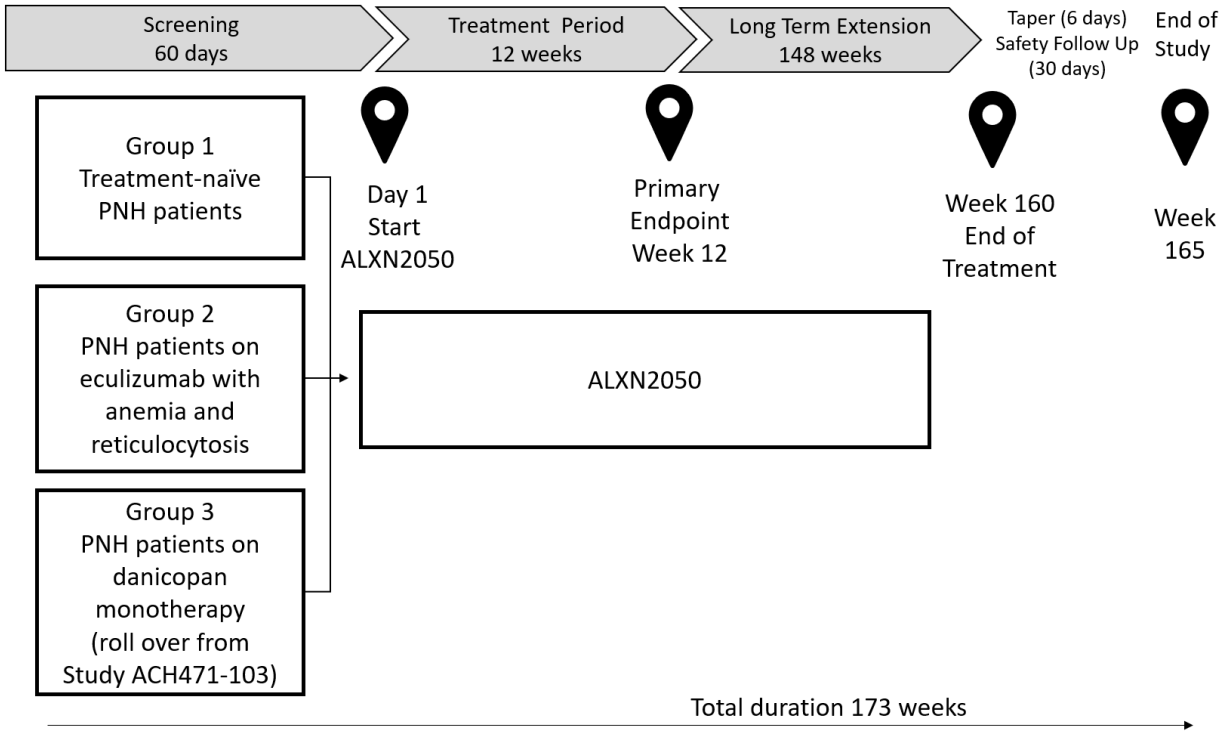
This study will be conducted as specified in this protocol and in accordance with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

A thorough benefit-risk assessment has been performed for ALXN2050. Measures will be taken to minimize risk to study patients. The potential risks identified in association with ALXN2050 are justified by the anticipated benefits that may be afforded to patients with PNH.

1.2. Schema

Figure 1: Study Design Schematic



Abbreviations: PNH = paroxysmal nocturnal hemoglobinuria.

1.3. Schedule of Activities

Table 1: Schedule of Activities: Screening and Treatment Periods

	Screening[1]	Treatment									
Visit	**Day -60 to -1**	**Baseline[1] (1st Day Dosed)**	**Wk 1 (± 1 day)**	**Wk 2 (± 1 day)**	**Wk 3 (± 1 day)**	**Wk 4 (± 1 day)**	**Wk 6 (± 3 days)**	**Wk 8 (± 3 days)**	**Wk 10 (± 3 days)**	**Wk 12/ET[2] (± 3 days)**	**Post-escalation[3]**
Day Number			**7**	**14**	**21**	**28**	**42**	**56**	**70**	**84**	
Clinic visit days	X	X		X		X		X		X	X
Visiting healthcare visit[4]			X		X		X		X		
Last eculizumab/danicopan dose[5]	X										
General assessments											
Informed consent	X										
Inclusion/exclusion criteria	X	X									
Medical history[6]	X	X									
Demographics	X										
Review patient safety card[7]		X	X	X	X	X	X	X	X	X	X
Vaccination history	X										
Height	X										
Neisseria meningitidis vaccinations	X		Administer according local/national guidelines								
ALXN2050 dispensing[8]		X		X		X		X		X	
Study medication accountability				X		X		X		X	

Table 1: Schedule of Activities: Screening and Treatment Periods

	Screening[1]	Treatment									
Visit	**Day -60 to -1**	**Baseline[1] (1st Day Dosed)**	**Wk 1 (± 1 day)**	**Wk 2 (± 1 day)**	**Wk 3 (± 1 day)**	**Wk 4 (± 1 day)**	**Wk 6 (± 3 days)**	**Wk 8 (± 3 days)**	**Wk 10 (± 3 days)**	**Wk 12/ET[2] (± 3 days)**	**Post-escalation[3]**
Day Number			**7**	**14**	**21**	**28**	**42**	**56**	**70**	**84**	
Clinical assessments											
Physical examination[9]	X	X		X		X		X		X	
Vital signs	X	X	X	X	X	X	X	X	X	X	
Weight[10]	X	X				X		X		X	
Single 12-lead ECG	X	X								X	X
PRO assessments[11]		X		X		X		X		X	
RBC transfusion review[6]	X	X		X		X		X		X	
AE/SAE	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Laboratory assessments[12]											
FSH[13]	X										
Urine drug screen	X										
Serology for hepatitis C, B and HIV	X										
Genetic biomarker testing (optional)		X									
Direct Coombs	X	X				X				X	
Hematology and chemistry	X	X	X	X	X	X	X	X	X	X	X

Table 1: Schedule of Activities: Screening and Treatment Periods

	Screening[1]	Treatment									
Visit	**Day -60 to -1**	**Baseline[1] (1st Day Dosed)**	**Wk 1 (± 1 day)**	**Wk 2 (± 1 day)**	**Wk 3 (± 1 day)**	**Wk 4 (± 1 day)**	**Wk 6 (± 3 days)**	**Wk 8 (± 3 days)**	**Wk 10 (± 3 days)**	**Wk 12/ET[2] (± 3 days)**	**Post-escalation[3]**
Day Number			**7**	**14**	**21**	**28**	**42**	**56**	**70**	**84**	
Urinalysis	X	X		X		X		X		X	
Pregnancy test[14]	X	X		X		X		X		X	
Coagulation (PT/PTT/INR), D-dimer	X	X				X		X		X	
Free Hgb, haptoglobin	X	X		X		X		X		X	
Iron studies (Iron, Transferrin, Ferritin Serum)[15]	X										
Trough PK samples[16]		X		X				X		X	
PK samples[17]		X				X					X
Bb, AP activity (APH)[17]		X		X		X		X		X	X
FD, C3, CH50[17]		X				X				X	
Plasma/Serum samples for additional nongenetic biomarker testing[17]		X				X		X		X	X
Breakthrough hemolysis[18]	Monitor continuously										
Flow cytometry: clone size	X	X				X				X	

Table 1: Schedule of Activities: Screening and Treatment Periods

	Screening[1]	Treatment									
Visit	**Day -60 to -1**	**Baseline[1] (1st Day Dosed)**	**Wk 1 (± 1 day)**	**Wk 2 (± 1 day)**	**Wk 3 (± 1 day)**	**Wk 4 (± 1 day)**	**Wk 6 (± 3 days)**	**Wk 8 (± 3 days)**	**Wk 10 (± 3 days)**	**Wk 12/ET[2] (± 3 days)**	**Post-escalation[3]**
Day Number			**7**	**14**	**21**	**28**	**42**	**56**	**70**	**84**	
Flow cytometry: C3 fragment deposition		X				X				X	
UGT1A1 (Gilbert's)	At any time – Test only if history or family history suggestive of Gilbert's syndrome										

1. Screening will be performed for Group 1 and Group 2 patients. For Group 3 patients rolling over from Study ACH471-103 study, a Screening visit is not required but informed consent and documentation of eligibility to participate in this study must be obtained and documented. Group 3 patients will begin study participation at the Baseline visit. The Baseline visit should be delayed if the patient has active bacterial or viral infection, a body temperature > 38°C on 2 consecutive days, or other evidence of infection at Baseline, or history of febrile illness within 14 days prior to first study medication administration.
2. If the patient withdraws from the study prior to Week 12, the patient should complete the Week 12/ET visit as soon as possible prior to tapering. Patients should take study medication per protocol until the tapering period begins. ALXN2050 will be tapered over 6 days and a Follow-up Visit will be conducted 30 + 7 days after the last dose. Patients must return any left-over ALXN2050 medication on the Follow-up Visit. Refer to Table 3 and Table 4 for details regarding taper and Follow-up Visit.
3. Intensive PK/PD sampling (refer to Table 2) should be obtained at the next clinic visit after dose escalation as feasible, but no sooner than 4 days after the dose escalation has occurred. For sites that cannot perform the intensive PK/PD sampling, a predose and a 2.5-hour postdose sample obtained at the next clinic visit, but no less than 4 days after dose escalation occurred is acceptable. In the event of breakthrough hemolysis, a serum sample for PK/PD analysis will be collected.
4. Laboratory samples will be collected by a visiting healthcare service provided by the Sponsor or site clinic for hematology, chemistry, and urinalysis assessments. If the visiting healthcare service is used, the site will call patient within 1 to 3 days to confirm that the visiting healthcare visit occurred and assess AEs, SAEs, and concomitant medications. If needed, site may ask about AEs, SAEs, and concomitant medications over the phone.
5. For Group 2, patients will receive their first dose of ALXN2050 (Day 1) 7 (± 1) days after last dose of eculizumab. For Group 3, patients will receive their last danicopan dose the evening prior (Day -1) to the first dose (approximately 8 hours) of ALXN2050 (Day 1). All patients will receive their first dose of ALXN2050 on Day 1.
6. Medical history must include at least 24 weeks and up to 52 weeks (if available) of RBC transfusion history. See Section 6.8 for transfusion guidelines before and during the study.
7. Patients are instructed to carry patient safety card at all times and bring to scheduled visits. Review signs and symptoms of infections using the safety card.
8. Patients will be provided with sufficient study medication to last until their next appointment. After the 12-Week Treatment Period, all patients who are not already receiving 180 mg bid (see Section 4.3) will be dose escalated to receive 180 mg bid. Patients may need to return to the clinic in between visits or a visiting healthcare visit could be made into a clinic visit to be dispensed ALXN2050 and new dosing instructions.

Table 1: Schedule of Activities: Screening and Treatment Periods

[9] A full physical examination will be performed at Screening, at Baseline and at Week 12 and will include an assessment of general appearance, a review of body systems, and a neurologic examination (refer to Section 8.3.1). Height will be recorded at Screening only. Abbreviated physical examination will be collected at all other time points. A symptoms-based neurologic examination will be performed if the patient has any complaints or clinical findings attributable to the central nervous system and if positive for findings, full neurologic examination will need to be performed at each assessment time point.

[10] Weight will be measured and should be taken in light clothing or underwear and without shoes.

[11] PROs will include the FACIT-Fatigue, the EORTC QLQ-C30 and the EQ-5D-3L as described in Section 8.9. PROs should be performed as early as possible during the clinic visits. On Day 1, PROs must be obtained before the first dose of study medication.

[12] Patients should refrain from heavy exercise 24 hours before blood collection for laboratory assessments. Walking and light exercise are acceptable.

[13] Follicle stimulating hormone assessment for postmenopausal women only.

[14] Serum pregnancy test at Screening. Urine pregnancy test for women of childbearing potential only at all other clinic visit days. At Baseline, the predose urine pregnancy test must be negative to continue study participation. Any positive urine pregnancy test will be confirmed by a follow-up serum pregnancy test.

[15] If there is evidence of iron deficiency at Screening, patients will be enrolled if on a stable iron supplementation for at least 30 days.

[16] Trough PK samples should be collected predose.

[17] On Day 1, for all sites, one predose and one 2.5-hour postdose PK sample will be collected. In addition, one predose PD sample (for all biomarkers) will be collected. On Day 28 (Week 4) or if patient's dose is escalated after Week 4, refer to Table 2 for intensive PK/PD sampling. Sites should collect as many samples as possible during the 12-hour period. For those sites that cannot perform the intensive PK/PD sampling, a predose and a 2.5-hour postdose sample obtained at the next clinic visit, but no less than 4 days after dose escalation occurred, is acceptable. Following dose escalation to 180 mg bid (see Section 4.3), PK/PD sampling will occur (as outlined in Section 6.7.5) at the subsequent clinic visit.

[18] If a suspected event of breakthrough hemolysis occurs, LDH, PK, and PD samples for analysis will be collected. If the suspected event of breakthrough hemolysis does not occur at a scheduled visit, an unscheduled visit should occur for evaluation of the patient and collection of additional LDH, PK, and PD samples by the central laboratory.

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; APH = hemolytic alternative pathway activity; AST = aspartate aminotransferase; Bb = Bb fragment of complement factor B; C = complement component 3; CBC = complete blood count; CH50 = hemolytic classical pathway activity; ECG = electrocardiogram; ET = Early Termination; FD = factor D; FSH = follicle stimulating hormone; GGT = gamma glutamyltransferase; Hgb = hemoglobin; HIV = human immunodeficiency virus; INR = international normalized ratio; LDH = lactate dehydrogenase; PD = pharmacodynamic(s); PI = Principal Investigator; PK = pharmacokinetic(s); PT = prothrombin time; PTT = partial thromboplastin time; QoL = quality of life; RBC = red blood cell; SAE = serious adverse event; UGT1A1 = uridine diphosphate glucuronosyltransferase 1 family, member A1;Wk = week.

Table 2: Intensive Pharmacokinetic and Pharmacodynamic Blood Sampling

	Predose	Week 4 (Day 28), Week 28 (Day 196) and Postdose Escalation[1] Time After Dosing (Hour ± 10 min)								
Hour	**0**	**1**	**1.5**	**2**	**2.5**	**3**	**6**	**8**	**10**	**12**
PK plasma samples	X[2]	X	X	X	X[2]	X	X	X	X	X
APH, Bb	X				X					X
Plasma/serum samples for additional nongenetic biomarker testing	X									X

[1] Intensive PK/PD sampling may be performed, if feasible, without food restrictions. Samples should be obtained at the next clinic visit but not before 4 days after dose escalation has occurred. All patients will have a (Week 4) Day 28 and Week 28 (Day 196) intensive PK sampling regardless of whether their dose has been escalated. If an escalation occurs less than 4 days prior to the Week 4 and Week 28 visits, intensive PK sampling collection should be shifted accordingly so at least 4 days have lapsed since the dose escalation. Blood volumes are provided in the Study Laboratory Manual.

[2] Sites should collect as many samples as possible during the 12-hour period, with the last sample collected being a PK/PD sample before the patient leaves the site. For those sites that cannot perform the intensive PK/PD sampling, a pre-dose and a 2.5 hour postdose sample, obtained at the next clinic visit, but no less than 4 days after dose escalation occurred will be acceptable.

Abbreviations: APH = hemolytic alternative pathway activity; Bb = Bb fragment of complement factor B; ECG = electrocardiogram; PD = pharmacodynamic(s); PK = pharmacokinetic(s).

Table 3: Schedule of Activities: Long-term Extension Period, Taper, and Follow-up Periods

	Long-term Extension (LTE) Period				Taper		Follow-up (+ 7 days)
	Interim Visits[1]	Clinic Visits[2]	Postdose escalation[4]	ET / Week 160[12] (± 3 days)	T1[13]	T2[13]	F/U[14]
	Weeks 16 – 152 (± 3 days)	Weeks 20 - 144 (± 3 days)					
Clinic Visit		X	X[4]	X			X
Visiting healthcare service	X				X	X	
ALXN2050 dispensing[3]		X		X			
Study medication accountability	X	X		X	X	X	X
Review patient safety card[5]	X	X	X	X	X	X	X
Neisseria meningitidis vaccinations	Administer according to local/national guidelines						
Physical examination[6]		X		X			X
Vital signs		X		X	X	X	X
ECG			X	X			X
Weight		X	X	X			X
PRO questionnaires[7]		X		X		X	X
RBC transfusion review		X		X	X	X	X
AE/SAE	X	X	X	X	X	X	X
Breakthrough hemolysis[8]	Monitor continuously						
Concomitant medications/ protocol restrictions	X	X	X	X	X	X	X
Hematology and chemistry, and urinalysis[9]	X	X	X	X			
Pregnancy test[10]	X	X		X			X

Table 3: Schedule of Activities: Long-term Extension Period, Taper, and Follow-up Periods

	Long-term Extension (LTE) Period				Taper		Follow-up (+ 7 days)
	Interim Visits[1]	Clinic Visits[2]	Postdose escalation[4]	ET / Week 160[12] (± 3 days)	T1[13]	T2[13]	F/U[14]
	Weeks 16 – 152 (± 3 days)	Weeks 20 - 144 (± 3 days)					
Clinic Visit		X	X[4]	X			X
Coagulation (PT/PTT/INR), D-dimer		X		X			
Free Hgb, haptoglobin		X		X			
Direct Coombs		X					
PK samples[11]		X[11]	X[4]	X			
AP activity (APH); Bb[11]		X	X[4]	X			
FD, C3, CP activity (CH50)[11]		X		X			
Plasma/Serum samples for additional nongenetic biomarker testing[11]		X	X[4]	X			
Flow cytometry: clone size		X		X			
Flow cytometry: C3 fragment deposition		X		X			

1. Visiting healthcare service visits will occur every other visit, starting at Week 16 (ie, W16, W24, W32, W40, W48, W56, W64, W72, W80, W88, W96, W104, W112, W120, W136, and W152). A visiting homecare service will collect samples for hematology, chemistry, and urinalysis. The site will call the patient within 1 to 3 days to confirm that samples were collected and to assess AEs, SAEs, and concomitant medications. If needed, site may ask about AEs, SAEs, and concomitant medications over the phone.
2. Clinic visits will occur every other visit starting at Week 20 (ie, W20, W28, W36, W44, W52, W60, W68, W76, W84, W92, W100, W108, W116, W128, and W144).
3. Patients will be provided with sufficient study medication to last until their next appointment.

Table 3: Schedule of Activities: Long-term Extension Period, Taper, and Follow-up Periods

[4.] The postdose escalation visit is only applicable for patients that escalated from 120 mg to 180 mg. This visit ideally should occur at the next in-clinic visit but no less than 4 days after the beginning of the new dose. Depending on when dose is escalated, patients may need to return to the clinic in between visits to be dispensed ALXN2050 and new dosing instructions. Intensive PK/PD sampling, (refer to Table 2), is required to be obtained at the next clinic visit after the dose escalation, but no sooner than 4 days after the start of the new dose. For sites that cannot perform the intensive PK/PD sampling, a predose and a 2.5-hour postdose sample, obtained at the next clinic visit, but no less than 4 days after dose escalation occurred will be acceptable. Refer to Table 2 for intensive PK/PD sampling requirements.

[5.] Review signs and symptoms of infections using the patient safety card.

[6.] A full physical examination is required at the ET/WK 160 visit; At other clinic visits, an abbreviated physical examination is required, including a symptoms-based neurologic examination if the patient has any complaints or clinical findings attributable to the central nervous system and if positive for findings, full neurologic examination will need to be performed.

[7.] PROs will include the FACIT-Fatigue, the EORTC QLQ-C30 and the EQ-5D-3L as described in Section 8.9.These will be administered approximately every 6 months within the LTE (ie, W36, W60, W84, W108, W128, and W160) Period. PROs should be performed as early as possible during the clinic visits.

[8.] If a suspected event of breakthrough hemolysis occurs, LDH, PK, and PD samples for analysis will be collected. If the suspected event of breakthrough hemolysis does not occur at a scheduled visit, an unscheduled visit should occur for evaluation of the patient and collection of the an additional LDH, PK, and PD samples by the central laboratory.

[9.] Patients should refrain from heavy exercise 24 hours before blood collection. Walking and light exercise are acceptable.

[10.] Urine pregnancy test for women of childbearing potential at all interim and clinic visit days. Any positive urine pregnancy test will be confirmed by a follow-up serum pregnancy test.

[11.] Intensive PK/PD sampling will be collected at Week 28 (Refer to Table 2 for details). Predose PK and PD samples, AP activity, Complement Bb, CH50, FD, C3, and plasma/serum samples for additional nongenetic biomarker testing are to be collected within the LTE Period at W44, W60, W76, W92, W108, and ET/W160. In the event of breakthrough hemolysis, a serum sample for LDH, PK/PD analysis will be collected.

[12.] If the patient has entered the LTE Period and discontinues from the study to enroll in Study ALXN2050-ROSY-401 (see Section 6.9), the patient will complete the ET/Week 160 Visit assessments. The patient will not need to taper or attend the Follow-up Visit.

[13.] Any patient who discontinues study medication will need to have an ET visit completed, followed by a 6-day Tapering Period and a Follow-up Visit 30 (+ 7 days) after the last dose of ALXN2050. T1 and T2 may be done through VHA or via phone call on Day 3 and Day 6 of the Taper period.

[14.] Follow-up Visit (F/U) takes place 30 (+7) days after the last dose of study medication (ie, post Taper Period 2 completion). Patients will be instructed to bring back all unused study medication on this visit.

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AP = alternative pathway; APH = AP hemolysis; Bb = Bb fragment of complement factor B; C3 = complement component 3; CH50 = CP activity; CP = classical pathway; ECG = electrocardiogram; ET = Early Termination; FD = factor D; F/U = follow-up; GGT = gamma glutamyltransferase; Hgb = hemoglobin; INR = international normalized ratio; LDH = lactate dehydrogenase; LTE = Long-term Extension; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PT = prothrombin time; PTT = partial thromboplastin time; QoL = quality of life; RBC = red blood cell; SAE = serious adverse event; T = taper; W = week.

2. INTRODUCTION

ALXN2050 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.

The Sponsor has conducted a Phase 2 proof-of-concept Study ACH471-100 to evaluate danicopan monotherapy in patients with PNH with an ongoing LTE Study ACH471-103. Results from these studies demonstrate that danicopan at doses of 100 to 200 mg taken orally 3 times a day provides AP suppression, clinically significant improvements in Hgb and lactate dehydrogenase (LDH), increases in PNH red blood cell (RBC) Type III clone size, and patient-reported well-being.

This study will assess the efficacy and safety of ALXN2050 as monotherapy in the following patient groups:

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

A detailed description of the chemistry, pharmacology, efficacy, and safety of ALXN2050 is provided in the Investigator's Brochure.

2.1. Study Rationale

The purpose of this study is to establish safety and efficacy of ALXN2050 in PNH as monotherapy.

The C5 inhibitor monoclonal antibody, eculizumab, has been proven effective for the treatment of PNH, resulting in a sustained control of complement-mediated intravascular hemolysis (IVH). Although eculizumab treatment brings patients with PNH a significant clinical benefit, a low-level hemolysis still occurs in many eculizumab-treated patients, leaving approximately one-third of treated patients transfusion-dependent. The blockade of the complement cascade at C5 by eculizumab allows complement component 3 (C3) fragment deposition to proceed without hemolysis on PNH RBCs during C5 inhibitor treatment and is a likely cause for suboptimal response in the subset of patients with PNH who experience extravascular clearance of PNH RBCs coated by C3 fragments (Risitano, 2009).

By inhibiting the cleavage of FB, danicopan, the first-generation FD inhibitor, targets the control point for the amplification loop of the complement cascade, blocking C3 convertase formation and, therefore, significantly reduces the production of C3 cleavage fragments and downstream

membrane attack complex (MAC) formation ex vivo (Yuan, 2017). In addition, although FD inhibition does not inhibit components specific to the classical or lectin complement pathways, nor does it inhibit components of the terminal complement pathway, it will inhibit the AP-mediated amplification of complement activity initiated via the classical and lectin pathways. By inhibiting FD with danicopan, both IVH, mediated by the activation of the complement terminal pathway, and extravascular hemolysis (EVH), mediated by C3 fragment opsonization in eculizumab-treated patients, can be blocked or significantly attenuated.

Danicopan has been studied in patients with PNH as monotherapy (Study ACH471-100) with proof of concept established as evidenced by improvement in Hgb and decrease in LDH. Danicopan has also been studied in patients with PNH on background therapy with a C5 inhibitor, with proof of concept established (Study ACH471-101). Interim results from this study demonstrate clinically significant improvements in Hgb, a dramatic reduction in transfusion needs, and improvements in other clinical parameters of interest in PNH.

ALXN2050 is derived through optimization of danicopan for potency and for PK properties. ALXN2050 displays approximately 3-fold greater potency compared to danicopan and is able to achieve sustained potent inhibition of complement AP activity at bid dosing as opposed to danicopan's tid dosing. Given its optimized PK profile and its mechanistic advantage targeting the control point for the amplification loop of the complement cascade, ALXN2050 has the potential to provide a superior oral alternative for the treatment of patients with PNH by controlling IVH and EVH.

2.2. Background

2.2.1. Complement Factor D

One of 9 serine proteases in the complement system, FD is a highly specific enzyme with only one known substrate, FB. Of all the complement proteins, it is among the lowest abundance in serum with a concentration of approximately 2 µg/mL (Schnabolk, 2015), and it catalyzes the rate-limiting step of the AP activation (Figueroa, 1991; Volanakis, 1996). The FD is a low molecular weight protein (24 kDa) that is primarily produced by adipocytes, but can also be produced and secreted by monocytes/macrophages and astrocytes in humans (Figueroa, 1991; Schnabolk, 2015). Due to its small size, it is freely filtered at the glomerulus, and then taken up by the proximal tubule cell where it is catabolized with an estimated fractional catabolic rate of 60% per hour. It is this rapid catabolism that is responsible for maintaining low circulating FD levels. As a result, renal dysfunction is associated with elevated FD levels, which may lead to increased AP activity and inflammation (Kobayakawa, 1992; Miyata, 1991). The biochemical, physiological, and functional features of FD make it an attractive target for pharmacological inhibition, as this may prove useful in the treatment of a wide spectrum of complement-mediated diseases.

2.2.2. Paroxysmal Nocturnal Hemoglobinuria

Paroxysmal nocturnal hemoglobinuria is a rare disease that has a reported prevalence of approximately 16 per million people (Szer, 2012). Paroxysmal nocturnal hemoglobinuria may occur at any age; it has been reported in children as young as 2 years to adults as old as 83 years,

but is most frequently diagnosed in adults, with a median age at diagnosis of approximately 40 years. Men and women are affected equally, and no familial tendencies exist.

Paroxysmal nocturnal hemoglobinuria is caused by a somatic mutation in the phosphatidylinositol N acetylglucosaminyltransferase subunit A gene in one or more hematopoietic stem cells, resulting in the loss of glycosylphosphatidylinositol-anchored proteins, including the complement regulatory proteins CD55 and CD59, from the surface of mutant RBCs. This leaves these mutant RBCs vulnerable to MAC mediated IVH and to EVH, presumably mediated by C3 fragment opsonization, primarily due to constitutive activation of the complement AP via tickover mechanism (Schubert, 2015). In addition to anemia that can require frequent RBC transfusions, patients with PNH are at high risk for thrombotic events, which can be life-threatening and are the major cause of morbidity and mortality in untreated patients. Patients with PNH also experience smooth muscle dysfunction (eg, dysphagia, erectile dysfunction, and abdominal pain), presumably related to the liberation of intracellular Hgb and its consequent derangement of nitric oxide levels in the vasculature.

The only curative treatment for PNH is hematopoietic stem cell transplantation (HSCT) using allogeneic donors. Given the high transplant-related mortality, especially when using unrelated or mismatched donors, HSCT is generally not offered as initial therapy for most patients with classic PNH. Other supportive therapies include recombinant erythropoietin, corticosteroids, and androgens to stimulate erythropoiesis, anticoagulants to treat thrombotic complications, and immunosuppressive agents to stimulate hematopoiesis in the aplastic phase.

The only currently approved drugs to treat PNH are eculizumab or ravulizumab (in some countries), closely related monoclonal antibodies directed against complement C5, which prevent IVH by inhibiting formation of the terminal complement complex. However, approximately 30% of patients on eculizumab continue to have ongoing EVH (Hill, 2010).

More recently, the complement inhibitor pegcetacoplan, which targets C3 of the complement cascade, was approved to treat adult patients with PNH. However, a subset of patients with PNH who are treated with a C3 inhibitor experience breakthrough hemolysis requiring discontinuation or dose adjustment (Gerber, 2022; de Latour, 2022). The severity of breakthrough hemolysis in some patients on pegcetacoplan differs significantly from that observed in patients on C5 inhibition and more closely resembles the IVH, including LDH levels approximately 10 to 15 × ULN, seen in untreated patients with PNH (Ueda, 2021; Kulasekararaj, 2021). Therefore, there exists an unmet medical need in a subset of patients for a therapy to better control EVH and IVH.

Inhibition of FD with ALXN2050 is expected to prevent EVH and control IVH, given its potential mechanistic advantage over C5 inhibition. By inhibiting the cleavage of FB, ALXN2050 targets the control point for the amplification loop of the complement cascade, blocking C3 convertase formation and the production of C3 cleavage fragments, blocking opsonization in addition to significantly reducing the downstream terminal pathway which leads to MAC formation. As a result, ALXN2050 can prevent EVH (via C3 fragment opsonization) while also being able to control IVH (mediated by the terminal pathway).

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

Neisseria meningitidis

Since a primary function of the complement system is to fight infections, pharmacologic inhibition of the complement system could result in an increased risk of infections. As suggested by individual case reports of patients with complement system deficiencies, including FD, inhibition of the complement system may result in increased risk of infection, notably with *N meningitidis* (Biesma, 2001; Hiemstra, 1989; Sprong, 2006). However, this remains a theoretical risk since FD inhibition does not block the classical and lectin pathways of complement and appears to have little impact on opsonophagocytic killing or serum bactericidal activity in samples obtained from vaccinated or previously exposed patients (Konar, 2017).

To mitigate the potential risk of meningococcal infection, all patients must be vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study medication. Patients who initiate study medication treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Vaccines against serotypes A, C, Y, W135, and B, where available, are recommended to prevent common pathogenic meningococcal serotypes.

Patients must be vaccinated or revaccinated according to current national vaccination guidelines or local practice (eg, Advisory Committee on Immunization Practices [ACIP]) for vaccination use with complement inhibitors (eg, eculizumab, ravulizumab).

Vaccination may not be sufficient to prevent meningococcal infection. All patients should be monitored for early signs of meningococcal infection, evaluated immediately if infection is suspected, and treated with appropriate antibiotics, if necessary.

To increase risk awareness and promote quick disclosure of any potential signs or symptoms of infection experienced by patients during the course of the study, patients will be provided a Patient Safety Card to carry with them at all times. Additional discussion and explanation of the potential risks, signs, and symptoms will occur at specific time points as part of the review of the Patient Safety Card (Section 8.3.8) and throughout the study as described in the Schedule of Activities (SoA) (Section 1.3).

Seizures

Convulsions and/or electroencephalogram (EEG) abnormalities have been observed in the dog toxicity studies at doses of 75 mg/kg/day and higher, and the no observed adverse effect level (NOAEL) based on the dog 13-week toxicology study is 62.5 mg/kg/day. Convulsions were also observed in WT TgRasH2 mice at doses of ≥ 500 mg/kg/day, at approximately 5× higher systemic exposures than in Beagle dogs. The Beagle dog is the most sensitive species with a NOAEL of 62.5 mg/kg/day. In Study ALXN2050-HV-107, EEG recordings revealed no evidence of epileptiform activity for any patient at any of the ALXN2050 doses tested (120, 240, or 360 mg bid). A 24-hour EEG monitoring of the 2 highest dose cohorts in Study ACH228-002 (120 mg and 200 mg orally (PO) bid) was conducted; no EEG abnormalities were identified with dosing. Physical examinations and adverse event (AE) monitoring will be performed with special attention to any neurologic AEs.

The safety margins based on the nonclinical toxicity profile of ALXN2050 are specified in the Investigators Brochure.

Physical examinations (including neurologic examination) will be performed during this study (see SoA). In the event of a seizure, assessment recommendations are provided in Section 10.7, Appendix 6; Seizure Management Plan. Patients with a seizure history will be excluded from the study.

Coronavirus Disease 2019

The coronavirus disease 2019 (COVID-19) pandemic is active in many countries at the time of this protocol amendment. Given this unique circumstance, specific consideration has been given to the risks and benefits of the study as they relate to COVID-19, and the global and local changes that exist as a result of the pandemic. This assessment is described in Section 10.8, Appendix 7. The risk assessment for COVID-19 vaccination is described in Section 10.9 Appendix 8.

2.3.2. Benefit Assessment

Currently, no oral medicines for the treatment of PNH are available. Unmet needs in patients with PNH, not addressed by a C5 inhibitor, can be addressed by an oral FD inhibitor. Three groups of patients, whose disease cannot be adequately addressed with a C5 inhibitor, have been identified:

- Patients who have a suboptimal response to an approved C5 inhibitor, presumably largely due to EVH that is a result of C3-mediated opsonization. Eculizumab/ravulizumab treatment blocks the hemolytic destruction of PNH erythrocytes by the MAC (terminal stage of the complement pathway); however, neither of these C5 inhibitors prevents deposition of C3 fragments on PNH erythrocyte membranes, which results in opsonization of these red cells and subsequent destruction of these red cells in the spleen and liver (Hill, 2010). ALXN2050 has a potential mechanistic advantage since it acts upstream of C3 cleavage and has been shown to block C3 fragment deposition.
- Patients who only respond partially to eculizumab due to a genetic polymorphism in complement receptor 1 (CR1; eg, HindIII H/L and L/L genotypes [Rondelli, 2014]), which has been postulated to result in an increased proportion of C3-opsonized RBCs, may have an improved treatment response with FD inhibition.
- Rare patients (~1%) with no response to eculizumab due to mutations in C5 (eg, Arg885His) could also benefit from FD inhibition because it acts at a different target in the complement cascade and should be unaffected by a mutation in C5 (Harder, 2019).
- For treatment of treatment-naïve PNH patients, given that ALXN2050 has the potential to control IVH and prevent the development of EVH (Yuan, 2017).

2.3.3. Overall Benefit: Risk Conclusion

Considering the severity of the disease, the continuing anemia and reticulocytosis in some patients on C5 inhibitors, and the lack of an effective oral therapy alternative for PNH patients, there is a clear need for new therapies to improve PNH management. ALXN2050 is expected to provide improved efficacy based on its mechanism of action and optimized PK profile. Based on the preclinical and clinical data available to date, the benefit-risk profile remains favorable for advancing the development of ALXN2050 for the treatment of patients with PNH.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of ALXN2050 based on improvement in hemoglobin (Hgb)	• Change in Hgb relative to baseline at Week 12
Secondary	
• 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 patients with paroxysmal nocturnal hemoglobinuria (PNH)	• Number of patients who have transfusion avoidance (defined as patients remaining transfusion-free and not requiring transfusion as per protocol-specified guidelines) during 12-week Treatment Period • Number of RBC units transfused and transfusion instances during 12-week Treatment Period as compared with transfusion data prior to screening • Change in LDH relative to baseline at Week 12 • Change in absolute reticulocyte count and direct and total bilirubin from baseline at Week 12 • Change in PNH RBC clone size and C3 fragment deposition on PNH RBCs from baseline at Week 12
• To evaluate the safety and tolerability of ALXN2050	• Incidence of TEAEs, SAEs, and events leading to discontinuation of study medication
• To evaluate maintenance of response of ALXN2050 during the LTE period.	• Change in Hgb relative to baseline • Change in LDH relative to baseline
• To evaluate the effect of ALXN2050 on Functional Assessment of Chronic Illness Therapy-Fatigue scale (FACIT) scores	• Change in FACIT Fatigue scale (Version 4) scores from baseline at Week 12 and at Week 160
Exploratory	
• To characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of ALXN2050	• Change in circulating complement biomarkers, including Bb fragment of complement factor B (Bb) concentrations at Week 12 relative to baseline

Objectives	Endpoints
	• Change in serum alternative pathway (AP) activity at Week 12 relative to baseline • Plasma concentrations of ALXN2050 over time
• To evaluate other health-related quality of life (QOL) in patients with PNH based on patient-reported outcome instruments and their evolution over the course of ALXN2050 treatment	• Change in the European Organisation 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 160. • Change in EuroQoL-5-Dimensions, 3-level version (EQ-5D-3L) scores from baseline at Week 12 and at Week 160.

4. STUDY DESIGN

4.1. Overall Design

This is a multiple-center, open-label multiple-dose study to assess the efficacy, safety, PK, and PD of the oral FD inhibitor ALXN2050 (previously ACH-0145228) monotherapy in patients with PNH.

This study will assess ALXN2050 as monotherapy in the following patient groups:

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

4.2. Scientific Rationale for Study Design

This is a multiple-center, open-label, multiple-dose study to assess the efficacy, safety, PK, and PD of the oral FD inhibitor ALXN2050 (previously ACH-0145228) monotherapy in adult patients (≥ 18 years of age) diagnosed with PNH.

The first-generation FD inhibitor, danicopan, has been studied in patients with PNH, both as monotherapy and on top of background therapy with a C5 inhibitor, with proof of concept established (Studies ACH471-100 and ACH471-101, respectively). ALXN2050 is a second-generation FD inhibitor with increased potency and the improved convenience of an oral, bid dosing regimen. Therefore, FD inhibition should be an effective therapy for PNH. This study aims to establish both the safety and efficacy of ALXN2050 as monotherapy for PNH patients.

ALXN2050 is expected to address both intravascular and EVH in all PNH patients. The study will include patients who are PNH treatment naïve and patients who, despite treatment with eculizumab for a minimum of 6 months, continue to have anemia and reticulocytosis. The study design schematic is shown in Figure 1.

The study will enroll approximately 26 patients with PNH distributed across the 3 patient groups as follows:

- Group 1 (patients who are treatment naïve): approximately 10 patients
- Group 2 (patients switching from eculizumab to ALXN2050): approximately 10 patients
- Group 3 (patients rolling over from Study ACH471-103, switching from danicopan to ALXN2050): approximately 6 patients

The study consists of 3 periods: A 60-day Screening Period, a 12-week Treatment Period, and a 148-week LTE Period (up to Week 160) This is followed by a 6-day taper and 30-day safety follow-up giving a total duration of approximately 173 weeks.

Patients will be evaluated for history of vaccination. All patients must be vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study medication. See Section 6.5.3 for details.

To increase risk awareness and promote quick disclosure of any potential signs or symptoms of infection experienced by the patients during the course of the study, patients will be provided a Patient Safety Card to carry with them at all times (Section 8.3.8) and throughout the study as described in the SoA (Section 1.3).

The starting dose of ALXN2050 will be 120 mg bid. The dose for patients who are not already receiving 180 mg bid, will be escalated to 180 mg bid after the 12-Week Treatment Period (see Section 4.3).

For Group 1: PNH treatment naïve study patients will receive their first dose of ALXN2050 on Day 1 (Baseline Visit).

For Group 2: Patients switching from eculizumab to ALXN2050 monotherapy will receive their first dose of ALXN2050 (Day 1) 7 (± 1) days after the last dose of eculizumab.

For Group 3: Patients who are rolling over from Study ACH471-103 will receive their last danicopan dose the evening prior (Day -1) to the first dose (approximately 8 hours) of ALXN2050 (Day 1) on this study.

After signing the informed consent form (ICF), patients will enter the Screening Period. During the Screening Period, eligibility and screening assessments will be performed. Screened patients who continue to meet eligibility criteria will enter the Treatment Period and will receive their first dose of study medication during the Baseline Visit (Day 1) in this study. Eligible patients will be enrolled in the study and will receive ALXN2050 at a dose of 120 mg twice daily (bid), daily for 12 weeks, with potential escalation to 180 mg bid based on clinical response and tolerability as defined in the dose escalation section (Section 6.7). At the end of Week 12, patients will enter the 148-week Long-term Extension (LTE) Period. After the 12-Week Treatment Period, all patients who are not already receiving 180 mg bid, will be dose escalated to 180 mg bid. During the course of the study, all patients will return to the clinic for safety and other assessments as shown in Table 1 to Table 3.

Patients will have the option to have selected visits performed via the visiting healthcare service provided by Sponsor. With this service, the patient does not physically visit the investigative site. Instead, a healthcare provider visits the patient at the patient's residence to perform protocol-specified assessments with appropriate documentations.

If the patient withdraws from the study prior to Week 12, the patient will be encouraged to complete the Week 12/Early Termination (ET) Visit as soon as possible and should take the study medication per protocol until that time. After the ET Visit is completed, ALXN2050 will be tapered over 6 days. Additionally, a safety Follow-up Visit will be conducted 30 (+ 7) days after the last dose of ALXN2050.

If the patient has entered the LTE Period and discontinues from the study to enroll in Study ALXN2050-ROSY-401 (see Section 6.9), the patient will complete the Week 160/ET visit assessments. The patient will not need to taper or attend the Follow-up Visit as described above.

If the patient has entered the LTE Period and discontinues from the study, the patient will be encouraged to complete the ET Visit, and the dose of ALXN2050 will be tapered over a 6-day period. The patient will attend a Follow-up Visit as described above.

During the course of the study, all patients will return to the clinic for safety and other assessments as shown in Table 1 to Table 3.

4.3. Justification for Dose

Clinical PK and PD data have been generated for ALXN2050 in single ascending and multiple ascending doses in healthy volunteers (Studies ACH228-001 and ACH228-002, respectively). In these Phase 1 healthy volunteer studies, ALXN2050 PK exposures increased dose-proportionally following a single dose administration, and in a greater-than-dose-proportional manner following multiple doses at steady state over the dose range of 40 mg bid to 200 mg bid. Corresponding PD activity as determined by AP inhibition increased with increasing exposure.

In the multiple ascending dose Study ACH228-002, the dosage regimens of both 120 mg bid and 200 mg bid were safe and effective, showing approximately 10-fold or greater safety margins in both maximum plasma concentration (C_{max}) and the area under the concentration-time curve from time zero to 24 hours (AUC_{0-24}) over the exposures achieved at the no observed adverse effect level (NOAEL) from nonclinical chronic toxicology studies (see Investigator's Brochure). In addition, both dosage regimens provided complete (> 90%) and sustained inhibition of AP activity throughout the 12-hour dosing interval. Based on data from Phase 1 Study ACH228-004, the safety margins for the tablet formulation in clinically relevant doses (120 mg bid and 180 mg bid) are projected to have a ≥ 8-fold safety factor relative to C_{max} and AUC at the NOAEL from beagle dogs.

However, large variabilities were observed in the PK and PD data and in the established PK/PD relationship. Intersubject variability in PK and the PK/PD relationship indicated that a dosage higher than 120 mg bid, such as 180 mg bid, may be required to ensure more patients reach and maintain an ALXN2050 concentration above the threshold for 90% AP inhibition.

In the interim analysis for the current study (ACH228-110; Data cut-off date 30 Apr 2022), efficacy data from patients with PNH (N = 17, including 11 treatment naive patients and 6 danicopan roll-over patients) showed that hematologic responses increased in a dose-dependent manner with clinically meaningful responses at doses of 120 to 180 mg bid. In particular, the majority of patients (10 of 17 patients) dose escalated from 120 to 180 mg bid, based on the Principal Investigator's discretion (see Section 6.7). After dose escalation, meaningful improvements in Hgb levels were observed in most patients (8 of 10 patients), especially in treatment-naïve patients. Improvements or stabilization of other hemolysis markers, such as LDH and reticulocyte count, were also observed. Safety data from these 17 patients indicated that ALXN2050 at 120 and 180 mg bid, either tablet or capsule, was safe and well tolerated with no safety concerns observed.

ALXN2050 safety evaluations did not raise significant concerns within the studied doses ranging from 40 to 360 mg bid in healthy patients and patients with PNH regardless of prior therapy. Data from studies of healthy patients treated across the dose range of 40 to 180 mg bid, as well as interim safety data from patients with PNH treated with 120 mg and 180 mg bid, showed a favorable clinical safety and tolerability data; the PK and PD characterization of ALXN2050

available from these studies indicated that 180 mg bid ALXN2050 would be a safe and more efficacious dose in patients with PNH.

4.4. End of Study Definition

A patient is considered to have completed this study if:

- The patient decides to transition to Study ALXN2050-ROSY-401; ET/Week 160 visit must be completed at any time during the LTE, with no taper or Follow-up Visit needed for the transition.

OR

- The patient decides not to transition to Study ALXN2050-ROSY-401; ET/Week 160 must be completed at any time during the LTE, with a dose taper (See Section 7.2) and Follow-up Visit (see Section 7.3).

A patient is considered to early terminate from the study if the patient is discontinued from the study before completing all scheduled visits as per SoA, unless the patient transitions to Study ALXN2050-ROSY-401.

The end of the study is defined as the date the last patient completes the last visit or last scheduled procedure (including follow-up) in the study as shown in the SoA.

5. STUDY POPULATION

5.1. Eligibility Criteria for All Patients

5.1.1. Inclusion Criteria

All patients must meet **all** of the following conditions:

1. Diagnosis of PNH.
2. Male or female, ≥ 18 years of age (or minimum adult age in accordance with local legal requirements).
3. Documentation of vaccination for *N meningitidis*: all patients must be vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study medication. Patients who initiate study medication treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination.
4. Female patients of childbearing potential must agree to use a highly effective or acceptable method of contraception from the date of signing the ICF to 30 days after their last dose of study medication.
   - Female patients of childbearing potential must also have a negative serum pregnancy test during Screening and a negative urine pregnancy test at baseline prior to administration of the first dose.
   - Female patients of non-childbearing potential, as defined in Section 10.5, need not employ a method of contraception.
5. Non-sterile male patients must agree to use a highly effective or acceptable method of contraception with their partner(s) of childbearing potential from the first day of dosing through 90 days after their last dose of study medication.
   - Males who are surgically sterile need not employ additional contraception.
6. Capable of providing written informed consent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol amendment.
7. Patients who are on iron, folic acid, and/or vitamin B_{12} supplementation are eligible for the study. If patients are on iron, patients must be on stable iron supplementation for at least 30 days prior to Day 1.
8. Patients with aplastic anemia or bone marrow failure who meet the rest of the eligibility criteria and are currently treated with immunosuppressants may be eligible, only if on a stable regimen for at least 3 months prior to enrollment. The regimen of these medications must remain unchanged during the 12-week Treatment Period.

5.1.2. Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

1. History of a major organ transplant (eg, heart, lung, kidney, liver) or hematopoietic stem cell/marrow transplant (unless HSCT engraftment has failed).

2. Known aplastic anemia or other bone marrow failure that requires HSCT, or if these patients are on immunosuppressive agents for less than 24 weeks prior to enrollment.
3. Received another investigational agent other than danicopan within 30 days or 5 half-lives of the investigational agent prior to study entry, whichever is greater.
4. Known or suspected complement deficiency.
5. Known underlying bleeding disorders (eg, coagulation factor deficiencies, idiopathic thrombocytopenic purpura, Von Willebrand disease) or any other conditions leading to anemia not primarily associated with PNH.
6. Active bacterial or viral infection, a body temperature > 38°C on 2 consecutive daily measures, evidence of other infection, or history of any febrile illness within 14 days prior to first study medication administration.
7. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 and/or are on dialysis.
8. Laboratory abnormalities at screening, including:
   - Alanine aminotransferase (ALT) > 2 × ULN.
   - Direct bilirubin > 2 × ULN (unless due to EVH, in the opinion of the investigator).
9. History or presence of any risk factors for Torsades de Pointes (eg, heart failure/cardiomyopathy or family history of Long QT Syndrome), a screening QT interval corrected using Fridericia's formula (QTcF) > 450 msec for males and > 470 msec for females, or receiving medications known to significantly increase the corrected QT interval (QTc)
10. Any other clinically significant laboratory abnormality that, in the opinion of the Principal Investigator (PI), would make the patient inappropriate for the study or put the patient at undue risk.
11. Use of known cytochrome P450, family 3, subfamily A (CYP3A) sensitive substrates, moderate or strong CYP3A inducers, and/or moderate or strong CYP3A inhibitors, from 2 weeks or 5 half-lives, whichever is longer, prior to the first administration of study intervention on Day 1 (full list provided in Section 10.10).
12. History or presence of any clinically relevant co-morbidities that would make the patient inappropriate for the study (for example, is likely to result in deterioration of the patient's condition, affect the patient's safety during the study, or confound the results of the study).
13. History of seizures and/or current use of selected medications known to lower the seizure threshold and/or cause seizure (See Section 10.11).
14. Females who are pregnant, nursing, or planning to become pregnant during the study.
15. Patients with a female partner who is either pregnant, nursing, or planning to become pregnant during the study.
16. Evidence of hepatitis B (positive hepatitis surface antigen [HBsAg] or positive core antibody [anti-HBc] with negative surface antibody [anti-HBs]) or hepatitis C viral

infection (hepatitis C virus [HCV] antibody positive, except for patients with documented successful treatment and documented sustained virologic response [SVR]) at Screening.

17. Evidence of human immunodeficiency virus (antibody positive) infection at Screening.
18. Hypersensitivity to the investigational drug or any of its excipients.

In addition, specific eligibility criteria for the different patient groups are provided in the following sections.

5.2. Eligibility Criteria Specific for Group 1

In addition to the eligibility criteria in Section 5.1, this patient group must meet the following additional eligibility requirements:

1. PNH patients who have no history of treatment with any complement inhibitor at any dose
2. PNH Type III erythrocyte or granulocyte clone size ≥ 10%
3. Absolute reticulocyte count ≥ 100×10^9/L
4. Anemia (Hgb < 10.5 g/dL)
5. LDH ≥ 1.5 × ULN
6. Platelet count ≥ 30,000/µL without platelet transfusion
7. Absolute neutrophil count (ANC) ≥ 750/µL

5.3. Eligibility Criteria Specific for Group 2

In addition to the eligibility criteria in Section 5.1, PNH patients on stable eculizumab switching to ALXN2050 (Group 2) must meet the following criteria:

1. Stable background regimen of at least 24 weeks for eculizumab, without change in dose or interval for at least the past 8 weeks
2. Anemia (Hgb < 10 g/dL)
3. Absolute reticulocyte count ≥ 100×10^9/L
4. Platelet count ≥ 30,000/µL without the need for platelet transfusions
5. Absolute neutrophil count ≥ 750/µL

5.4. Eligibility Criteria Specific for Group 3

In addition to meeting the criteria listed in Section 5.1, patients in Group 3 need to fulfill the following criterion:

1. Patient received danicopan during Study ACH471-103.

5.5. Lifestyle Considerations

Certain foods such as grapefruit have been shown to be inhibitors of CYP3A4 enzyme activity. Patients should refrain from consuming these foods and beverages from 2 weeks prior to the first administration of study intervention on Day 1 until 2 weeks after the final dose of study intervention.

5.6. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently entered in the study. The Investigator must maintain a log of screen failure patients that includes, at a minimum, demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs) occurring after providing informed consent.

If the patient is unable to receive study medication within 60 days of screening, the patient may be rescreened once.

See details for rescreening in Section 8.1.

6. STUDY INTERVENTION

"Study medication" in this protocol refers to ALXN2050. All patients will receive the study medication.

In most countries, patients will take the capsule formulation of the study medication during the first 12 weeks of the study. A tablet formulation (described in Section 6.1 below) is being developed by the Sponsor. Once this tablet formulation is available, it will be introduced in this study, and the capsule formulation will be discontinued.

The study medication should be taken at approximately the same time each day and as close as possible to 12 hours apart with or without food. If a dose is missed, it should be taken within 4 hours of the originally scheduled time. After 4 hours, the missed dose should be skipped. In either case, the next dose should be taken according to the original dosing schedule.

6.1. Study Intervention Administered

Intervention Name	ALXN2050 (formerly ACH-0145228)	ALXN2050 (formerly ACH-0145228)
Type	Drug	Drug
Dose Formulation	Capsule	Tablet
Unit Dose Strength(s)	60 mg	60 mg
Dosage Level(s)	120 mg or 180 mg	120 mg or 180 mg
Route of Administration, (Frequency)	Oral (bid)	Oral (bid)
Use	Experimental	Experimental
IMP/NIMP	IMP	IMP
Sourcing	Provided by Sponsor	Provided by Sponsor
Packaging and Labeling	Study medication will be provided in bottles. Each bottle will be labeled as required per country requirement.	Study medication will be provided in bottles. Each bottle will be labeled as required per country requirement.

Abbreviations: bid = twice daily; IMP = investigational medicinal product; NIMP = non-investigational medicinal product

Details on the formulation of the study medication are provided in the Investigators' Brochure and Pharmacy Manual.

6.2. Preparation/Handling/Storage/Accountability

At the pharmacy, ALXN2050 capsules should be stored as provided at room temperature and tablets should be stored at 15°C to 30°C.

The PI or designee (eg, pharmacist) is responsible for ensuring storage as per the label on the drug product at the site and adequate accountability of all used and unused study medication.

This includes acknowledgment of receipt of each shipment of study medication (quantity and condition), patient dispensing records, and returned or destroyed drug. Dispensing records will document quantities received from the Sponsor and quantities dispensed to patients, including lot number, date dispensed, and patient identifier number. All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

Storage condition details for the drug product are described in the Pharmacy Manual provided by the Sponsor.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a single-arm, open-label study.

6.4. Study Medication Compliance

An interactive web response system will be used to monitor drug accountability. Patients will be required to bring their supply of study medication to each visit so that study site personnel may perform drug accountability. Site personnel will keep a record of all drug dispensed and returned at each visit. Drug dispensing records will be updated at each visit.

6.5. Concomitant Therapy

6.5.1. Concomitant Medications

Any medications that the patient is using during the study, including vitamins and/or supplements are considered concomitant medications.

New concomitant medications that need to be added to the patient's regimen during the study should be discussed between the PI and Sponsor before implementing, if possible. If this is not possible, the PI should evaluate the potential medication for interactions, taking into consideration the list of prohibited medications provided in this protocol, before implementing and inform the Sponsor as soon as feasible. If a new concomitant medication is started by another physician that is not associated with the study site without discussion with the PI, the PI should evaluate for interaction potential and inform the Sponsor.

Details of all concomitant medication use, including all medications administered for the treatment of AEs, must be recorded in the patient's case report form (CRF).

The use of concomitant medications during the study will be assessed at every visit, as indicated in Table 1.

The following are some general guidelines for concomitant medication use based on currently available data:

- Concomitant administration of folic acid and/or erythropoiesis-stimulating agents is permitted if on stable doses for at least 4 weeks prior to Baseline.
- Concomitant administration of steroids or other immunosuppressants is permitted if the dosage regimen is stable for at least 3 months before enrollment.

- Prophylactic antibiotics may be administered if deemed appropriate by local clinical practice and/or guidelines for treatment with a complement inhibitor. Because commercially available products will be used, information about any specific antibiotics administered can be found on the package inserts/product labels for those products.
- Gastric acid reducing agents should be avoided whenever possible.

6.5.2. Prohibited Medications

The use of the following medications is prohibited during the study:

- Known CYP3A sensitive substrates, moderate or strong CYP3A inducers, and/or moderate or strong CYP3A inhibitors are prohibited throughout the study, until 1 week after the final administration of study intervention (See Section 10.10 for a full list of these medications).
- Selected medications known to lower the seizure threshold and/or cause seizure (see Section 10.11 for a full list of these medications).
- Medications known to significantly prolong the corrected QT interval (QTc)

6.5.3. Vaccines

To mitigate the potential risk of meningococcal infection, all patients must be vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study medication. Patients who initiate study medication treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Vaccines against serotypes A, C, Y, W135, and B, where available, are recommended to prevent common pathogenic meningococcal serotypes.

Patients must be vaccinated or revaccinated according to current national vaccination guidelines or local practice for vaccination use with complement inhibitors (eg, ACIP). Vaccination may not be sufficient to prevent meningococcal infection. All patients should be monitored for early signs of meningococcal infection, evaluated immediately if infection is suspected, and treated with appropriate antibiotics, if necessary.

Any patient without sufficient history of these vaccines may be vaccinated or provided boosters, as appropriate. Vaccinations and/or boosters may be administered either during the Screening Period, after all other screening assessments have been completed, or once study medication treatment has commenced, according to national or local guidelines. For patients who will receive vaccinations, all other screening procedures must be completed, and patients must qualify for the study prior to vaccinations being administered. Female patients of childbearing potential who require vaccinations must also have a negative urine pregnancy test on the days of vaccination before any vaccine or booster is administered.

For any vaccines or boosters given as part of this study, full identifying information, including the brand, should be recorded in the patient's CRF.

6.6. Switching to ALXN2050

6.6.1. Switching from Eculizumab to ALXN2050

Patients switching from eculizumab to ALXN2050 monotherapy will receive their first dose of ALXN2050 (Day 1) 7 (± 1) days after last dose of eculizumab.

6.6.2. Switching from Danicopan to ALXN2050

Patients will receive the last dose of danicopan the evening before (approximately 8 hours) Day 1. On Day 1, patients will receive the first dose of ALXN2050 120 mg.

6.7. Dose Modification of ALXN2050

Dose escalation to 180 mg bid will be allowed in this study during the 12-week Treatment Period following the guidelines in Section 6.7.1 to Section 6.7.3. All patients will be dose escalated to 180 mg bid after the 12-Week Treatment Period.

The decisions to dose escalate patients will be made by the site PI based on each patient's individual data and guided by the dose escalation guidelines below. The PI should notify the Medical Monitor of any decision to proceed with dose escalation.

6.7.1. Dose Escalation for Treatment Naïve Patients (Group 1)

Patients in this group will be escalated if

- Hgb has not increased at least 1 g/dL by Week 4 relative to baseline, or
- Patient has received a blood transfusion, or
- LDH > 1.5 × ULN by Day 14 in 2 consecutive assessments

6.7.2. Dose Escalation for Patients Switched from Eculizumab (Group 2)

Patients in this group may be dose escalated if:

- Hgb by Week 4 has not increased at least by 1 g/dL relative to baseline, or
- Patient has received a blood transfusion, or
- LDH > 1.5 × ULN by Day 14 in 2 consecutive assessments

6.7.3. Dose Escalation for Patients Switched from Danicopan (Group 3)

Patients in this group will be escalated if

- Hgb by Day 14 has dropped by 1 g/dL or more, relative to baseline, and it is below the lower limit of normal, or
- Patient has received a blood transfusion, or
- LDH > 1.5 × ULN by Day 14 in 2 consecutive assessments

6.7.4. Dose Escalation or Modification at Other Time Points for All Patient Groups

Dose modification decisions can be made at any point in the study after Day 14, including during the LTE Period (through Week 160). The PI should notify the Medical Monitor of any decision to proceed with dose escalation. After the 12-week Treatment Period, all patients who are not already receiving 180 mg bid, will be dose escalated to 180 mg bid (see Section 4.3). At the subsequent clinic visit following dose escalation, PK/PD sampling will occur as outlined in Section 6.7.5.

Patients who have been dose-escalated may be dose reduced to a lower dose for safety or tolerability reasons based on the Investigator's judgement.

6.7.5. PK/PD Sampling During Dose Modification

Intensive PK/PD sampling may be performed, if feasible, without food restrictions. All patients will have a Week 4 (Day 28) and a Week 28 (Day 196) intensive PK sampling regardless of whether their dose has been escalated (see Table 2). Sites should collect as many samples as possible during the 12-hour period, with the last sample collected being a PK/PD sample before the patient leaves the site.

For sites that cannot perform the intensive PK/PD sampling, a predose and a 2.5-hour postdose sample will be acceptable. Samples for PK/PD and safety laboratory assessments should be performed at the next in-clinic visit and not sooner than 4 days after the dose escalation (refer to Table 2) since it will take at least 4 days to achieve steady-state conditions.

Patients who have been dose escalated may be dose reduced to a lower dose for safety or tolerability reasons following consultation between the Investigator and the Sponsor's Medical Monitor.

6.8. Transfusion Guidelines Before and During the Study

It is recommended to administer RBC transfusion when a patient has a:

1. Hemoglobin value of less than 7 g/dL regardless of presence of clinical signs or symptoms, or
2. Hemoglobin value of less than 9 g/dL with signs or symptoms of sufficient severity to warrant a transfusion.

In the event of life-threatening anemia, transfusion of ABO- and RhD-matched blood is appropriate. Further matching for Kell and JK Antigens can be conducted if this does not delay availability of blood for emergent transfusion. The reason for transfusion as well as signs or symptoms associated with the subject's need for transfusion will be documented on the electronic case report form (eCRF) for each individual subject. Typical anemia-related symptoms warranting transfusions include angina, change in mental status, syncope, light headedness, confusion, shortness of breath, and fatigue.

The Investigator will determine the appropriate number of units of RBCs to be transfused. In the event a transfusion is required, a blood sample for central lab is to be collected for assessments prior to transfusion. Administration of transfusion including the reason for transfusion (hemoglobin result, signs, and symptoms) and the number of units transfused, will be documented in the eCRF.

6.9. Intervention After the End of the Study

As described in Section 4.4, the end of study is defined as the date the last patient completes the last visit or last scheduled procedure (including follow-up) in the study, as shown in the SoA.

If the Treating Physician is of the opinion that a patient may clinically benefit from continued treatment with ALXN2050, a patient in the LTE may transition to the Alexion Roll Over Study (ROSY), Study ALXN2050-ROSY-401, without treatment interruption (no taper or Follow-up Visit are required), as soon as possible after completing the ET/Week 160 Visit assessments.

Eligible patient will be provided with a new informed consent form if they decide to participate in Study ALXN2050-ROSY-401.

7. DISCONTINUATION OF STUDY MEDICATION AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Medication

In rare instances, it may be necessary for a patient to permanently discontinue (definitive discontinuation) the study medication. If study medication is permanently discontinued, the dose of the patient will be tapered as described in Section 7.2, and the patient will remain in the study for 30 days after last dose of ALXN2050 to be evaluated for AEs.

A patient is free to withdraw from the study at any time without jeopardizing future medical care. In addition, the PI (or designee) may decide, for reasons of medical prudence or patient noncompliance or if C5 inhibitor is deemed necessary, to discontinue dosing of ALXN2050 for an individual patient. The Sponsor's Medical Monitor will be notified immediately, and if possible, before dosing is terminated.

Reasons for patient withdrawal include:

- Intercurrent illness that would, in the judgment of the Investigator, affect assessment of clinical status to a significant degree
- Unacceptable toxicity (including a clinically significant laboratory abnormality) necessitating discontinuation of study participation or that, in the judgment of the Investigator, compromises the ability to continue study-specific procedures, or it is considered not to be in the patient's best interest to continue the study
- Patient request to discontinue for any reason
- Pregnancy or planned pregnancy
- Patient noncompliance
- Lack of efficacy
- Development of seizures (see Section 10.7 Appendix 6: Seizure Management Plan)
- Discontinuation of the study at the request of the Sponsor, Regulatory Agency, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC)
- Any other condition or circumstance that that would jeopardize the welfare of the patient if s/he were to continue in the study
- Participation in other clinical studies with investigational products during this study

The reason for any patient's discontinuation and the date of withdrawal will be recorded in the patient's CRF. The patient's CRF, which will be completed up to the point of withdrawal, will be retained for the Sponsor. If a patient discontinues from the study for any reason, all protocol procedures as defined in Table 1 for treatment Week 12 should be performed as an ET visit if the patient discontinues prior to Week 12.

If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a patient withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.2. Dose Taper

If ALXN2050 is discontinued for any reason, the dose will be tapered over a 6-day period. The dosing taper regimen is described in Table 4. The taper schedule may be adjusted to allow for slower taper in a patient who is not tolerating discontinuation of the drug.

If dosing needs to be terminated for safety reasons (eg, development of a seizure), it may be done so immediately (without tapering), if it is considered to be in the best interest of the patient.

If the patient withdraws from the study, an ET visit must be completed, and the tapering schedule below should be followed.

Table 4: ALXN2050 Taper Schedule

Dose at Termination	Taper Period 1 (T1) (Taper Days 1 - 3)	Taper Period 2 (T2) (Taper Days 4 - 6)
120 mg bid	60 mg bid	60 mg qd
180 mg bid	120 mg bid	60 mg bid

T1 and T2 visits may done by visiting health care assessment or by phone call on Day 3 and Day 6, respectively.
T1 visit can be combined with the Early Termination visit if the patient discontinues prior to Week 12.
T1 should assess safety and give instructions to taper dosing. T2 should give instructions to terminate dosing.
Abbreviations: qd = once daily; bid = twice daily.

7.3. Follow-up Period

After completion of the Taper Period, patients will enter the Follow-up Period. Patients will be evaluated at the clinical site 30 days (+ 7 days) after the last dose of study medication. At this Follow-up Visit, physical examination and assessment of vital signs, AEs, and SAEs will be performed as specified in the SoA (Table 3).

7.4. Lost to Follow-up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.8.

8. STUDY ASSESSMENTS AND PROCEDURES

The required study assessments procedures are described in this section. The timeline for all procedures may be found in Section 1.3.

8.1. Screening Visit

8.1.1. Screening for All Patients

The PI or designee is responsible for administering and obtaining freely given consent, in writing, before the patient enters the study and before any study-related procedures are performed. Each patient will sign an ICF (see Section 10.1.3).

A window of up to 60 days is permitted for screening. Screening procedures may be spread over more than one visit. The screening clinic and laboratory procedures listed in Table 1 must be performed and documented. This will include a review of the inclusion and exclusion criteria. The patient's medical history will be reviewed, and a full physical examination will be conducted. The medical history must include at least 24 weeks and up to 52 weeks (if available) of RBC transfusion history. A urine drug screen will be performed during screening. The PI, in consultation with the Sponsor, will use professional judgment in allowing the patient to continue participation in the study when evaluating the results of the drug screen, if any positive results are obtained.

Iron studies must be performed as early as possible in the Screening Period to identify and initiate iron supplementation, if clinically indicated, in patients with iron deficiency. Patients on iron, folic acid, and/or vitamin B_{12} supplementation are eligible for the study. If patients are on iron, the dose should be stable for at least 30 days prior to Day 1.

All patients must meet all the overall as well as group-specific eligibility requirements listed in Section 5. It will be required that all female patients of childbearing potential have a negative serum pregnancy test to be eligible for the study.

If the patient is unable to receive study medication within 60 days of screening, they may be rescreened once.

For patients screened more than 60 days prior to the first dose of study medication, all screening assessments must be repeated to confirm eligibility. Patients will also be required to sign a new ICF and should be assigned the same patient number from the initial screening visit.

Repeating any screening laboratory test(s) may be permitted on a case-by-case basis with the approval of the Sponsor's Medical Monitor (or designee). In these instances, repeating a single laboratory test or a subset of the full panel may be acceptable.

As part of the screening process, patients will be evaluated to determine whether and which vaccinations are required (see Section 2.3).

8.1.2. Screening for Groups 1 and 2:

For newly identified patients with PNH (PNH treatment naïve; Group 1) and for patients switching from eculizumab (Group 2), prospective patients should be screened within 60 days prior to first administration of study medication. All evaluations must be completed before the

patient is enrolled into the study. If the patient is unable to receive study medication within 60 days of screening, the patient may be rescreened once.

8.1.3. Screening for Group 3:

If a patient is rolling over from Study ACH471-103, the patient enters the study at the Baseline Visit, ie, the Screening Visit is not needed, but informed consent and documentation of eligibility are required. Available laboratory data from Study ACH471-103 may be used to determine eligibility if they were performed within the 60-day screening window.

8.2. Efficacy Assessments

Blood will be collected according to the SoA (see Section 1.3) to assess the efficacy endpoints of change in Hgb, transfusion requirements, LDH, and other measures of hemolysis. Blood collection procedures are described in Section 8.3.5.

Transfusion data, including number of RBC units transfused during screening to the end of follow-up will be collected (from study site records and any other location where the patient receives any transfusions) and recorded in each patient's CRF.

Transfusion avoidance is defined as patients remaining transfusion-free and not requiring a transfusion through Week 12 as per protocol-specified guidelines in Section 6.8.

8.3. Safety Assessments

Safety will be evaluated by monitoring and assessment of AEs, clinical laboratory tests, physical examination findings, and vital signs measurements. Time points for all safety assessments are provided in Section 1.3. All findings must be recorded in the patient's source documents and CRF. Details on mandatory and recommended vaccinations are provided in Section 2.3.

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.3.1. Physical Examinations

A full physical examination will be performed at Screening, Baseline, at Week 12, the LTE (as needed) and at the ET/Week 160 Visit and will include an assessment of general appearance and a review of body systems.

A neurologic examination will be performed as part of the full physical examination at Screening, Baseline, at Week 12, and at ET/Week 160 Visit and will include the following:

- Mental status (orientation to person, place, and time),
- Cranial nerve examination (extraocular movements, facial muscles [raised 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 patient presents relevant symptoms.

A symptoms-based neurologic examination will be performed if the patient 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 time point.

Consideration for neurologic consultation and/or EEG testing is at the discretion of the Investigator in consultation with the Sponsor. See Section 10.7 (Appendix 6) for Seizure Management Plan.

An abbreviated physical examination will be conducted at all other time points, as indicated in Section 1.3. Additional brief, full, or symptom-driven physical examinations may be conducted at the discretion of the Investigator or designee and/or when patients present with AEs. Height will be collected at Screening only.

Weight will be measured and should be taken in light clothing or underwear and without shoes.

8.3.2. Vital Signs

Vital signs will include blood pressure, heart rate, and respiration rate at the visits indicated in Section 1.3. Vital signs will be measured in the supine or sitting position following a 5-minute rest.

Body temperature will be measured and collected using an oral or temporal thermometer at the visits indicated in Section 1.3.

8.3.3. Electrocardiograms

Electrocardiogram (ECG) measurements will be conducted at the times indicated in Section 1.3. All ECG recordings will be 12-lead and will be performed after the patient has rested quietly for at least 5 minutes in a supine position and before blood is drawn (whenever possible). 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.

In some cases, it may be appropriate to repeat an abnormal ECG to rule out improper lead placement that could contribute to ECG abnormality. It is important that the leads are placed in approximately the same positions each time in order to achieve precise ECG recordings.

All ECGs must be read by the PI or designee. All ECG parameters and assessments must be recorded or stored in the patient's source documents and CRF. Any clinically significant finding must be reported as an AE.

8.3.4. Clinical Safety Laboratory Assessments

See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency. If a suspected event of breakthrough hemolysis occurs, an unscheduled visit must take place at which an additional sample is collected for analysis of LDH and PK/PD by the central laboratory.

8.3.5. Blood Collection

Patients will be in a sitting or supine position during the blood collection. Specific instructions for sample collection, processing, and shipping will be provided in a separate laboratory manual.

If central laboratory tests results are not obtainable in a timely manner, samples may be collected at an unscheduled visit and analyzed locally. See the laboratory manual for additional information.

8.3.6. Medication Error, Drug Abuse, and Drug Misuse

8.3.6.1. Timelines

If an event of medication error, drug abuse, or drug misuse occurs during the study, then the Investigator or other site personnel will report to Alexion or designee immediately but no later than 24 hours of when they become aware of it.

The designated Alexion representative works with the Investigator to ensure that all relevant information is completed within 1 (initial fatal/life-threatening or follow-up fatal/life-threatening) or 5 (other serious initial and follow-up) calendar days if there is an SAE associated with the event of medication error, drug abuse, or misuse and within 30 days for all other events.

The full definitions and examples of medication error, drug abuse, and drug misuse can be found in Section 10.4.

8.3.6.2. Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an investigational medicinal product (IMP) or Alexion auxiliary medicinal product (AxMP) that either causes harm to the patient or has the potential to cause harm to the patient.

8.3.6.3. Drug Abuse

Drug abuse is the persistent or sporadic intentional, non-therapeutic excessive use of IMP or Alexion AxMP for a perceived reward or desired non-therapeutic effect.

8.3.6.4. Drug Misuse

Drug misuse is the intentional and inappropriate use of IMP or Alexion AxMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or Alexion non-investigational medicinal products (NIMPs), outside the intended use as specified in the protocol, including deliberate administration of the product by the wrong route.

8.3.7. Pregnancy

Details of any pregnancy in patients and/or partners of male patients that occurs or is confirmed within the timelines listed in Section 8.4.1 will be collected. If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.3, Appendix 3.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.8. Patient Safety Card

A Patient Safety Card will be provided to patients to carry with them at all times. The card is provided to increase patient awareness of the risk of meningococcal infection and promote quick recognition and disclosure of any potential signs or symptoms of infection experienced during the course of the study and to inform patients on what actions must be taken if they are experiencing signs or symptoms of infection.

At each visit throughout the study, the study staff will ensure that the patient has the Patient Safety Card and will review it with the patient at each visit as described in the SoA (Section 1.3).

8.4. Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs can be found in Section 10.3. All AEs will be reported to the Investigator or qualified designee by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study medication or study procedures, or that caused the patient to discontinue the study medication (see Section 7).

Procedures for recording, evaluating, follow-up, and reporting AEs and SAEs are outlined in Section 10.3 (Appendix 3).

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until 30 days after the last dose of study medication, at the time points specified in Section 1.3.

Medical occurrences that begin before the start of study medication but after obtaining informed consent will be recorded as pretreatment AEs. This does not include pretreatment or post-treatment complications that occur as a result of protocol-mandated procedures (eg, invasive procedures, such as venipuncture or biopsy), which should be reported as AEs. Pregnancy is not an AE. A pregnancy occurring after the start of study medication should be reported on the pregnancy forms, as described in Section 10.3, Appendix 3.

All SAEs will be recorded and reported to the Sponsor or the designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3 (Appendix 3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obliged to actively seek AE or SAE data after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study medication or study participation, the Investigator must promptly notify the Sponsor.

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3, Appendix 3.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow-up on each patient at subsequent visits/contacts. All SAEs will be followed-up until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.4.4. Regulatory Reporting Requirements for SAEs

Prompt notification of an SAE by the Investigator to the Sponsor is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study medication under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study medication under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ IECs, and Investigators.

Suspected unexpected serious adverse reactions (SUSARs) must be reported according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.5. Treatment of Overdose

For this study, any dose of ALXN2050 greater than that specified in the protocol will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose; general supportive measures are recommended.

In the event of an overdose or suspected overdose, the Investigator should:

1. Capture and forward the event, with or without associated AEs, to Alexion Global Patient Safety via email or facsimile (clinicalsae@alexion.com or + 1.203.439.9347) using the Alexion Clinical Study Overdose Report Form within 24 hours of awareness.
2. Contact the Medical Monitor immediately.
3. Assess the patient and determine the need for any monitoring in a medical setting; if the Investigator cannot see the patient or the patient cannot reach the Investigator, the patient should go to the emergency room.
4. Closely monitor the patient for any AE/SAE.

5. If necessary, based on consultation with the sponsor's medical monitor, obtain a plasma sample for PK analysis or safety labs.
6. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the patient.

8.6. Pharmacokinetics

Blood samples will be collected at the times outline in the SoA (Section 1.3) to determine plasma concentrations of ALXN2050.

ALXN2050 concentrations will be determined using validated bioanalytical methods. Single trough PK samples will be taken at other time points as outlined in Section 1.3.

The logistics of obtaining any intensive PK profile in this study will be discussed between the Sponsor and the PI. Sites should collect as many samples as possible during the 12-hour period. For those sites that cannot perform the intensive PK/PD sampling, a pre-dose and a 2.5-hour postdose sample obtained at the next clinic visit, but no less than 4 days after dose escalation occurred, will be acceptable. See also PK sampling during dose modification in Section 6.7.5.

The number of PK sampling time points for any given patient will not exceed the currently planned number of time points; in the event of breakthrough hemolysis, an additional PK/PD sample will be required.

Additional information on sample collection and shipping instructions will be provided in a separate laboratory manual.

8.7. Pharmacodynamics

Pharmacodynamics (Bb, APH, FD, C3, CH50) will be evaluated using serum or plasma collected during the study as outlined in Section 1.3. Additional information on sample collection and shipping instructions will be provided in a separate laboratory manual. Sponsor may store samples for other biomarker tests for future research.

8.8. Genetic Samples

If a patient provides separate informed consent via the optional genetic consent form, samples will be collected and retained for potential future genetic testing. Genetic analyses may be conducted: 1) if a patient does not respond to the study medication; 2) if a patient experiences drug-related toxicity; or 3) to further characterize PNH. Refer to Section 10.6, Appendix 5 for details.

8.9. Patient-Reported Outcomes

Patient reported outcomes will be captured using an electronic device. All patients enrolled in the study will complete the self-administered questionnaires for the FACIT-Fatigue (Version 4), EuroQoL 5 Dimensions, 3-Level version (EQ-5D-3L) scales and European Organisation for Research and Treatment of Cancer (EORTC) QoL Questionnaire-Core 30 scale (QLQ-C30),

Version 3.0, as indicated in Section 1.3. PROs should be administered as early as possible during clinic visits.

8.9.1. FACIT-Fatigue

The FACIT-Fatigue scale, Version 4.0, is a collection of QoL questionnaires pertaining to the management of fatigue symptoms due to a chronic illness. 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). Total scores range from 0 to 52, with higher score indicating better QoL.

8.9.2. EQ-5D-3L

The EQ-5D-3L is defined by 5 dimensions: mobility, usual activities, self-care, pain/discomfort, and anxiety/depression. Each of the EQ-5D dimensions may be summarized and analyzed as categorical variables. The visual analog scale results and EQ-5D-3L index may be summarized and analyzed as continuous variable. The EQ-5D index score (time trade off [TTO]) to determine the health state value will be based on the US population-based preference weights.

8.9.3. EORTC

The EORTC QLQ-C30, Version 3.0, is a questionnaire developed to assess the QoL of cancer patients. The questionnaire includes the following subscales: global health status, functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social activity), symptom scales (fatigue, nausea and vomiting, and pain), and single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Thirty questions related to QoL, with the first 28 questions scored on a 4-point scale (1 = not at all to 4 = very much) and the final 2 questions that probe the patient's overall health and QoL scored on a scale of 1 (very poor) to 7 (excellent). Each subscale has a range of 0 to 100%, with a high score representing a higher response level. Thus, a high score for a functional scale represents a high level of functioning but a high score for a symptom scale represents a high level of symptomatology/problem.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

No hypotheses will be formally tested in this study.

9.2. Sample Size Determination

The sample sizes are based on a pragmatic approach to study patients with PNH who are treatment-naïve, and patients with PNH who have received C5 inhibition treatment with eculizumab. Based on the results from the PNH monotherapy Studies ACH471-100 and ACH471-103, and the PNH combination therapy Study ACH471-101, it is anticipated that 10 patients in the treatment naïve group and 10 patients in C5 inhibitor switch group will be adequate to demonstrate the effectiveness of ALXN2050 as monotherapy in treating patients with PNH. For the primary endpoint of change from baseline to Week 12 in Hgb, the group of 10 patients each in treatment naïve cohort and eculizumab switch cohort will provide 87% power to detect the mean increase from baseline of 2 g/dL, assuming standard deviation of 1.8 g/dL and two-sided 0.05 significance level. The patients who switch from danicopan monotherapy in Study ACH471-103 will provide additional efficacy and safety data for ALXN2050 monotherapy.

9.3. Populations for Analyses

All patients who receive at least 1 dose of ALXN2050 will be included in the safety and efficacy analyses.

9.4. Statistical Analyses

Statistical methods described in this section will be further elaborated in a separate Statistical Analysis Plan (SAP).

9.4.1. General Considerations

Descriptive and exploratory statistical methods will be utilized to present results from data collected during 12-week Treatment Period with ALXN2050 and LTE period.

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 study design Section 4.

Patient listings will be provided for all efficacy, PK and PD, and safety parameters, including data from the LTE Period. Summary statistics will be computed for selected efficacy and safety parameters so that meaningful clinical interpretations can be made. Graphic presentations will also be produced for selected efficacy and safety parameters.

An SAP will be developed to describe the data analysis procedures and data presentations in detail.

9.4.2. Demographics and Baseline Characteristics

Demographic parameters (age, gender, race, weight, body mass index) and baseline PNH disease characteristics, including RBC transfusion history and baseline laboratory measurements, will be

summarized to provide an overall description of the study populations. Data will be presented by group and by total patients receiving ALXN2050. For the group switching from eculizumab or danicopan to ALXN2050, a summary of usage prior to screening will also be provided.

9.4.3. Efficacy Analyses

9.4.3.1. Analyses of Primary Efficacy Endpoints

The primary efficacy endpoint will be:

- Change in Hgb level from baseline measurement to Week 12

9.4.3.2. Analyses of Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Number of patients who have RBC transfusion avoidance during the 12-week Treatment Period with ALXN2050. Transfusion avoidance is defined as patients remaining transfusion-free and not requiring a transfusion through Week 12 as per protocol-specified guidelines (Section 6.8).
- Number of RBC units transfused and transfusion instances during the 12-week Treatment Period 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 160.

Similar to Hgb measurements, descriptive statistics and graphic presentations for the numeric secondary endpoints listed above will also be provided. Summary statistics for RBC transfusion units received during 12 weeks of dosing will also be provided.

9.4.4. Safety Analyses

The evaluation of safety during the 12-week Treatment Period with ALXN2050 and during the LTE Period will be based primarily on the frequency of AEs, clinical laboratory assessments, vital signs, and 12-lead ECG. Other safety data will be summarized as appropriate.

Descriptive statistics using summary statistics will be calculated for quantitative safety data, as well as for the difference to baseline measurement by visit, when appropriate.

Adverse events will be coded using the latest version of MedDRA. Treatment-emergent adverse events (TEAEs) (ie, those AEs that newly occur or worsen in severity during treatment) will be summarized by system organ class and preferred term. Tabulated listing of patients with SAEs and those who discontinue from the treatment due to an AE will be provided.

Shift tables may be provided for selected graded laboratory parameters, if clinically deemed meaningful.

Data on vital signs and ECGs will be examined through patient listings, and by summary statistics of selected parameters.

9.4.5. Pharmacokinetic Analysis

Pharmacokinetic analysis will be done using a validated computer program. The PK characteristics of ALXN2050 from patients, 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 patients, mean/geometric mean, SD, median, minimum, and maximum) will be used to summarize the calculated PK parameters.

$AUC_{0\text{-}12}$	Area under the curve
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

9.4.6. Pharmacodynamic Analysis

Pharmacodynamic analyses will be performed for all patients who receive at least 1 dose of ALXN2050 and who have evaluable baseline and postdose PD data. Descriptive statistics will be presented for all PD endpoints at each sampling time. The PD effects of ALXN2050 administered orally will be evaluated by assessing the absolute values and changes and percentage changes from baseline in serum or plasma concentrations over time, as appropriate. Assessments of ALXN2050 PK-PD relationships may be explored using data from this study or in combination with data from other studies.

9.4.7. Population PK/PD Analysis

Population PK modeling will be conducted using data from this study alone and/or in combination with data from other studies. In addition, the exposure response (PD markers and other clinical endpoints) relationship may be explored. Population PK/PD analysis results may be presented in a separate report.

9.4.8. Patient-Reported Outcome Measures Assessment

9.4.8.1. FACIT-Fatigue (Version 4)

The change in FACIT-Fatigue scores from baseline to Week 12 and end of LTE will be analyzed as a secondary outcome. FACIT-Fatigue data will be summarized at baseline and each postbaseline time point using descriptive statistics for continuous variables for the observed value as well as the change from baseline.

9.4.8.2. EQ-5D-3L

Both EQ-5D-3L Visual Analogue scale (VAS) and index score (TTO) will be calculated. The EQ-5D-3L TTO to determine the health state value will be based on the US population-based preference weights. The EQ-5D-3L data will be summarized at baseline and each postbaseline time point using descriptive statistics for continuous variables for the observed value as well as the change from baseline.

9.4.8.3. EORTC

Changes from baseline in EORTC-QLQ-C30 will be summarized by treatment group at baseline and at the study visits where this assessment is collected. Descriptive statistics for continuous variables for the observed value as well as the change from baseline will be presented.

9.5. Interim Analyses

Interim analyses are planned when either 6 patients in Group 1 or Group 2 complete the 12-week Treatment Period. The primary endpoint of change in Hgb levels at Week 12, as well as the secondary efficacy endpoints, will be evaluated. The interim analyses data will not be used to modify the design of the study. Results from the interim analyses may be used to inform design of next phase clinical studies. Additional interim analyses may be conducted and described in detail in the SAP.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
  - Promptly notifying Alexion of any (potential) serious breach of the protocol or regulations so that legal and ethical obligations are met. A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a patient or the reliability and robustness of the data generated in the clinical study.
- In certain regions/countries, Alexion has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches. Alexion will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and Investigators.
- The Investigator should have a process in place to ensure that:

  - The site staff or service providers delegated by the Investigator/institution are able to identify the occurrence of a (potential) serious breach
  - A (potential) serious breach is promptly reported to Alexion or delegated party, through the contacts (email address or telephone number) provided by Alexion.
- The Coordinating Investigator will be identified among the enrolling Investigators during the course of the study and will be responsible for reviewing the clinical study report (CSR) and confirming that it accurately describes the conduct and results of the study.

10.1.2. Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The Investigator, or his/her representative, will explain the nature of the study to the patient or his/her legally authorized representative, and will review the informed consent and answer any questions regarding the study. No study assessments or procedures will be performed until all the patient's questions have been answered and the patient has signed the ICF.

Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study, and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

If the ICF is revised, patients must be reconsented to the most current version of the ICF during their active participation in the study.

A copy of the ICF must be provided to the patient or the patient's legally authorized representative.

A patient who is rescreened is required to sign another ICF.

10.1.4. Data Protection

Patients will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The Sponsor as a data controller has implemented privacy and security controls designed to help protect patient personal data, including information security controls, firewalls, incident detection, and secure transfer measures.

In the event of any accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data ("breach"), the controller has implemented procedures and measures to promptly address and mitigate any risk to the data subject. In the event of a breach, the controller will notify the appropriate regulatory authorities and/or the data subject in accordance with applicable data protection law.

The contract between Alexion and study sites specifies responsibilities of the parties' related data protection, including handling of data security breaches and respective communication and cooperation of the parties.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.5. Dissemination of Clinical Study Data

Study-related information and study results may be posted on publicly accessible clinical study databases (eg, the US website www.clinicaltrials.gov or the EU website www.clinicaltrialsregister.eu), as appropriate, and in accordance with national, regional, and local regulations.

All information contained in this protocol and the study results are considered to be confidential. The Investigator agrees to use this information for purposes of conducting this study. It is understood that the Sponsor may use data derived from this study for the purpose of research and development. The data may be disclosed by the Sponsor to other Investigators, the US FDA, other government agencies, or foreign drug regulatory authorities, or to the public. No publication of study design or results is permitted without specific Sponsor's approval. To gain approval, a copy of the manuscript for review must, therefore, be sent to the Sponsor 60 days before submission for publication.

10.1.6. Data Quality Assurance

All patient data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy, methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Medical Monitoring, Safety Monitoring and Global Monitoring Plans.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations [CRO]).

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the last marketing application approval, or if not approved, 2 years following the discontinuance of the study medication, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.7. Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.8. Study and Site Start and Closure

The Sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the Investigator
- Discontinuation of further study medication development

10.1.9. Publication Policy

All information contained in this protocol and the study results will be considered confidential. The Investigator agrees to use this information for purposes of conducting this study. It is understood that the Sponsor may use data derived from this study for the purpose of research and development. The data may be disclosed by the Sponsor to other Investigators, the FDA, other government agencies, or foreign drug regulatory authorities, or to the public. No publication of study design or results is permitted without specific Sponsor approval.

- Where possible, primary manuscripts reporting results of the primary efficacy endpoint or the final results will be submitted for publication within 12 to 18 months of the primary evaluation date or end of study, whichever is earlier.
- Investigators who participate as authors in manuscripts derived from Alexion sponsored studies will agree to the prerequisites as outlined in the Sponsor author engagement agreement prior to engaging in manuscript development.
- The Investigator agrees to submit proposals for new manuscripts (whether or not the proposed analyses are derived from protocol-specified endpoints) to the Sponsor for review and consideration. All manuscripts or abstracts emanating from approved proposals are to be submitted to the Sponsor for review before submission to the journal/society. This allows the Sponsor to protect proprietary information and to provide comments.
  - The proprietary nature of some development work may preclude publication. In some cases, it may be necessary to delay a publication to allow the Sponsor to ensure protection of intellectual property.
- In general, primary publications, including congress and journal publications, containing the protocol-specified results of a study should occur prior to the publication of individual study site results or case reports. Alexion's policy prohibits duplicate publication, whereby the same results must not be published in multiple peer-reviewed journal manuscripts.
  - Encore congress publications may be appropriate to allow communication of research findings to relevant audience and geographical regions.
- Alexion will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, Alexion will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements and per the Alexion Publication Policy.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 5 will be performed by the central and/or local laboratory. Protocol-specific requirements for inclusion or exclusion of patients are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations. Investigators must document their review of each laboratory report.

Table 5: Protocol-Required Laboratory Assessments[1]

Hematology	Chemistry	Urine	Other Assessments

Complete blood count (CBC), including:
- RBC count
- White blood cell (WBC) count
- WBC differential (absolute and percent):
  - neutrophils
  - lymphocytes
  - monocytes
  - eosinophils
  - basophils
- Hematocrit (Hct)
- Hemoglobin (Hgb)
- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Mean platelet volume (MPV)
- Platelet count
- Red cell distribution width (RDW)
- Reticulocyte count (absolute and percent)
	Alanine aminotransferase (ALT)
	Albumin
	Alkaline phosphatase
	Aspartate aminotransferase (AST)
	Bicarbonate (HCO3)
	Bilirubin (fractionated)[2]
	Blood urea nitrogen (BUN)
	Calcium
	Calculated eGFR[3]
	Chloride
	C-reactive protein (CRP)
	Creatine kinase[4]
	Creatinine
	Gamma-glutamyl transferase
	Glucose[5]
	LDH
	Lipid profile including:
	- Cholesterol/HDL ratio
	- High-density lipoprotein cholesterol (HDL-C)
	- Low-density lipoprotein
		Urinalysis and microscopy:
		- Bilirubin
		- Color
		- Glucose
		- Hgb
		- Ketones
		- Leukocytes
		- Nitrite
		- Occult blood
		- pH
		- Protein
		- Specific gravity
		- Urobilinogen Microscopic examination of sediment
		Urine pregnancy test[6]
		Urine drug screens:
		- Cocaine
		- Amphetamines,
		- Barbiturates
		- Benzodiazepines
		- Cannabinoids
		- Opiates
		- Phencyclidine
		- Propoxyphene
		- methadone
			Hemolytic alternative pathway activity (APH)
			Bb
			C3
			C3 fragment deposition
			Hemolytic classical pathway activity (CH50)
			D-dimer
			Direct Coombs
			Factor D
			Free hemoglobin
			Follicle stimulating hormone (FSH)
			Haptoglobin
			Plasma/serum samples for additional nongenetic biomarker testing
			PNH clone size
			Coagulation (PT/PTT/INR)
			Pregnancy (serum)[6]
			Iron studies:
			- Serum ferritin
			- Serum iron
			- Serum transferrin
			- Transferrin saturation (TSAT)

Table 5: Protocol-Required Laboratory Assessments[1]

Hematology	Chemistry	Urine	Other Assessments
	cholesterol (LDL-C) - Non-HDL-C - Total cholesterol - Triglycerides - Very low-density lipoprotein cholesterol (VLDL-C) Potassium Sodium Total protein Uric acid		- Total iron binding capacity (TIBC) Serology: - HCV Ab - HbsAg - HbcAb - HIV Ab - UGT1A1 (Gilbert's)[7] Genetic biomarkers (optional) PK

1. Check the Schedule of Activities for specific times when these tests should be done.
2. Fractionate and obtain measurements of direct and indirect bilirubin for all patients.
3. Provide eGFR based on Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) creatinine equation (2009) for patients ≥ 19 years of age and based on the "bedside Schwartz" equation (2009) for patients < 19 years of age.
4. Perform at baseline, and then subsequently only as a reflex if AST > ULN.
5. If glucose is > ULN, reflexively test HbA1c.
6. Any positive urine pregnancy test will be confirmed by a serum pregnancy test.
7. Test only if history or family history suggestive of Gilbert's Syndrome.

Abbreviations: APH = alternative pathway activity; AST = aspartate aminotransferase; Bb = Bb fragment of complement factor B; CH50 = classical pathway activity; eGFR = Estimated glomerular filtration rate; HbsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; HIV Ab = human immunodeficiency virus antibody; INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; ULN = upper limit of normal.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of Adverse Event

Adverse events must be assessed for the investigational product(s) in this study. An investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in the study, whether blinded or unblinded. The term "adverse event" is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered to be drug related. An AE can arise with any use of the drug (eg, off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

Medical occurrences that begin before the start of study medication but after obtaining informed consent will be recorded as pretreatment AEs. This includes pre- or posttreatment complications that occur as a result of protocol-mandated procedures (eg, invasive procedures, such as venipuncture or biopsy). While pregnancy itself is not considered an AE, for the purposes of safety, a pregnancy occurring after the start of study medication should be reported on the pregnancy forms.

A 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 investigational product until 30 days after the last dose of study medication will be considered treatment-emergent, as defined in Section 10.3.5. All TEAEs will be recorded and reported.

An AE (including a TEAE) can be one or more of the following:

- Any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug and does not imply any judgment about causality.
- Any new disease or exacerbation of an existing disease.
- Recurrence of an intermittent medical condition (eg, headache) not present at baseline.
- Any case of abuse of alcohol, illicit drugs, or prescription drugs; abuse of study medication(s) or protocol-specified drug(s); addiction.
- Laboratory test or other clinical test (eg, ECG or X-ray) with a clinically significant abnormality (as defined below).
- An effect of the study medication, including comparator.
- Any dose of medication (study medication or other concomitant medication) that is taken at a dose higher than the prescribed dose (ie, an overdose). Overdose should be reported as an AE, only if it is associated with any symptoms or signs.

The following are not considered to be AEs:

- Medical or surgical procedures (eg, surgery, endoscopies, tooth extraction, transfusion) – the condition which leads to the procedure is the AE.

- Preexisting diseases or conditions or laboratory abnormalities present or detected prior to the screening evaluation that do not worsen.
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions).

Clinically significant changes in objective findings (eg, laboratory, ECG, physical examination) should be considered AEs only if they meet one or more of the following criteria:

- Associated with accompanying symptoms
- Require medical/surgical intervention
- Lead to a change in study medication dosing or discontinuation from the study
- Lead to significant additional concomitant drug treatment, or other therapy
- Lead to any of the outcomes included in the definition of a serious adverse event
- Are considered clinically significant by the Investigator

Whenever possible, the etiology of the abnormal finding (rather than the abnormal finding itself) should be documented as the adverse event. Repeated additional tests and/or other evaluations required to establish the significance and etiology of an abnormal result should be obtained when clinically indicated.

Any abnormal test result that is determined to be an error does not require reporting as an AE.

Surgical procedures themselves are not AEs but are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an adverse event, if it occurs, or is detected during the study period. Planned surgical measures permitted by the clinical study protocol (if any) and the condition(s) leading to these measures are not AEs, if the condition(s) was (were) known before the start of the study treatment and documented in the patient's medical record. In the latter case, the condition should be reported as medical history.

All patients who have AEs, whether considered to be associated with the use of the Investigational product or not, must be monitored to determine the outcome of the event(s). The clinical course of the AE will be followed according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found, or the Investigator considers it medically justifiable to terminate follow-up.

10.3.2. Criteria for Assessing Seriousness

All AEs must be evaluated as potential SAEs. If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met. An SAE is any untoward medical occurrence that occurs at any dose and meets at least one of the following criteria:

- Results in death
- Is life-threatening ie, the patient was at immediate risk of death from the AE as it occurred. (This does not include an event that, had it occurred in a more severe form, or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization for the AE

- The following types of hospitalizations are not considered SAEs for regulatory reporting purposes:
  - Hospitalization(s) for planned (pre-scheduled) medical procedures known at the time of screening
  - Protocol-specific hospital admission
  - Respite care
  - Admission for the treatment of pre-existing condition (known at the time of screening) not associated with the development of a new AE or with the worsening of the pre-existing condition
  - Observation/same day/ambulatory procedure
- Is a persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect (in the child of a patient who was exposed to the study medication)
- Is an important medical event or reaction

10.3.3. Documentation and Reporting of Adverse Events

Adverse events, including TEAEs, may be spontaneously reported to the Investigator by a patient or his/her representative, or elicited during questioning and examination of a patient. All AEs will be assessed by the Investigator and documented regardless of apparent causality from use of the study treatment(s). For each AE, the Investigator will evaluate and report the date of onset and resolution, outcome, severity, relationship to study treatment(s), action taken, additional treatments required to manage the event, and determination of seriousness. All identified AEs occurring during the study and follow-up period must be fully recorded and described on the appropriate CRF page. The AE will be reported in standard medical terminology. Whenever possible, the AE should be evaluated and reported as a diagnosis, rather than as individual signs or symptoms. A cluster of signs and symptoms that results from a single cause will be reported as a single diagnosis (eg, fever, elevated WBC, cough, and abnormal chest X-ray can all be reported as “pneumonia”).

If a definitive diagnosis is not possible, the individual symptoms and signs will be individually recorded. Documentation must be supported by an entry in the patient’s medical record. The relationship to study medication or study procedures will be assessed using the definitions in Section 10.3.7.

10.3.4. Treatment and Follow-Up of Adverse Events

All AEs will be followed up (including obtaining relevant laboratory tests) until they have returned to baseline status or stabilized. If a clear explanation is established, it should be recorded. Follow-up of AEs will continue through the last day on study (including the follow-up period) or until the events have resolved or stabilized to the satisfaction of the PI and the sponsor Medical Monitor (or designee). The Sponsor may request that certain AEs be followed until resolution or stabilization.

10.3.5. Timeframe for Collection of Adverse Events

Adverse events include events that appeared or worsened during the course of the clinical study. AEs may also include pre- or post-treatment complications that occur as a result of protocol-mandated procedures (eg, invasive procedures, such as venipuncture or biopsy).

Any AE (ie, a new event or an exacerbation of a preexisting condition) with an onset date after the patient provides informed consent through the 30 days following the patient's last study medication dose will be recorded as an AE on the appropriate CRF page(s).

All SAEs, regardless of cause or relationship, occurring within 30 days of last study medication dose will be documented and reported. Follow-up of SAEs will continue through the last day on study or until the event has resolved or stabilized to the satisfaction of the PI and the Sponsor's Medical Monitor (or designee).

Investigators are not obligated to actively seek out SAEs beyond the follow-up period. However, if the PI (or designee) learns of an SAE occurring after completion of the final Follow-up Visit, and the SAE is deemed by the PI (or designee) to be related to the study medication(s), the PI (or designee) will promptly document and report the event to the Sponsor.

10.3.6. Severity and Grading of Adverse Events

Assessment of Intensity
The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories from National Cancer Institute CTCAE v5.0, published 27 Nov 2017: • Grade 1: Mild (awareness of sign or symptom, but easily tolerated) • Grade 2: Moderate (discomfort sufficient to cause interference with normal activities) • Grade 3: Severe (incapacitating, with inability to perform normal activities) • Grade 4: Life-threatening • Grade 5: Fatal An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

The PI (or designee) should determine the severity of the AE based on the overall clinical importance or significance of the finding for that individual patient. If a lab abnormality is deemed to be clinically significant, according to the criteria described in Section 10.3.1, it will be reported as an AE, and the AE grade reported should correspond to the grade of the laboratory abnormality on the CTCAE grading scale.

If an AE that was reported during the study increases or decreases in severity, then that AE is given a resolution date and time and a new record initiated with the new severity. If the severity of an AE remains the same, the AE will be kept open through to resolution.

An event is defined as "serious" when it meets at least 1 of the pre-defined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

10.3.7. Assessment of Causality

Assessment of Causality

- The Investigator is obligated to assess the relationship between the study intervention and each occurrence of each AE or SAE. An Investigator causality assessment must be provided for all AEs (both nonserious and serious). This assessment must be recorded in the CRF and on any additional forms, as appropriate. The definitions for the causality assessments are as follows:
  - Not related: There is no reasonable possibility the study intervention caused the AE.
    - The AE has a more likely alternative etiology; it may be due to underlying or concurrent illness, complications, concurrent treatments, or effects of another concurrent drug.
    - The event does not follow a reasonable temporal relationship to administration of the study intervention.
  - Related: There is a reasonable possibility the study intervention caused the AE.
    - The AE has a temporal relationship to the administration of the study intervention.
    - The event does not have a likely alternative etiology.
    - The event corresponds with the known pharmaceutical profile of the study intervention.
    - There is improvement on discontinuation and/or reappearance on rechallenge.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to Alexion. However, it is very important that the Investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to Alexion.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.3.8. Reporting Serious Adverse Events and Pregnancies

Alexion has requirements for the expedited reporting of safety events meeting specific requirements to worldwide regulatory authorities; therefore, Alexion must be notified immediately regarding the occurrence of any SAE and/or pregnancy that occurs during the study (time frames outlined in Section 10.3.5).

The procedures for reporting all SAEs and/or pregnancies, regardless of causal relationship, are as follows:

- SAE
  - Record the SAE within 24 hours of becoming aware of the event by logging into the EDC system (Fusion) and completing an initial SAE report.
  - This will trigger an email notification to the Axiom and Alexion Pharmaceuticals distribution lists.
- Pregnancy
  - Record the pregnancy within 24 hours of becoming aware of the event into the EDC system (Fusion) and complete the pregnancy form.

This will trigger an email notification to the Axiom and Alexion Pharmaceuticals distribution lists.

Contact information is provided below.

SAE CONTACT

Report all SAEs and/or pregnancy events into Axiom Fusion EDC

In the event of system failure, or for questions about completing the forms in EDC:

SAE Telephone Number and email:

Axiom Real-Time Metrics

US / Canada: 1-866-91-AXIOM (29466)

International: 647-799-4015

Email: achillion@axiom.cc

For fatal or life-threatening events, provide redacted copies of hospital discharge reports, autopsy reports, and other documents, as applicable. The Sponsor may request additional information from the PI to ensure the timely completion of accurate safety reports.

Any follow-up information collected on any report of an SAE and/or pregnancy must be reported by the Investigator within 24 hours of becoming aware of information.

In the case of a medical emergency, the Medical Monitor should be contacted.

10.3.9. Investigator Reporting Requirements for Suspected Unexpected Serious Adverse Reactions

Alexion is responsible for ensuring that Investigators and central IECs/IRBs are notified of all AEs that are serious, unexpected, and considered related, probably related, or possibly related to the Investigational product. A CRO may be designated to perform this notification. This notification will be in the form of a MedWatch/CIOMS report. The PI will notify the local IECs or IRBs as per IEC or IRB requirements. Upon receiving such notices, the PI must review and retain the notice. The Sponsor, Investigator, and EC or IRB will determine if the informed consent requires revision. The PI should also comply with IEC or IRB procedures for reporting any other safety information.

10.3.10. Concomitant Medication Assessments

Details of all prior (within 90 days of the screening evaluation) and concomitant medication use, including all medications administered for the treatment of AEs as well as prior administration of danicopan from previous Sponsor studies, will be recorded in the patient's CRF at each study visit.

10.3.11. Monitoring Patient Safety

The safety of patients will be monitored by Investigators and by a Medical Monitor (or designee) at the Sponsor on an ongoing basis while patients are receiving investigational product.

10.3.12. Removal of Patients from the Study or Study Medication

A patient is free to withdraw from the study at any time without jeopardizing future medical care. The PI (or designee) may decide, for reasons of medical prudence or patient noncompliance, to discontinue dosing in a patient. The Sponsor's Medical Monitor should be notified immediately, and if possible, before dosing is terminated.

If dosing is to be terminated, it may be done so immediately, or a taper can be implemented as described in Section 7.2, whichever is considered to be in the best interest of the patient. When dosing is terminated, study participation is not necessarily immediately terminated. Instead, whenever possible, the patient should complete all activities in the Taper and Follow-up Periods (if tapered) or in the Follow-up Period (if discontinued immediately), as described in Section 7.

The criteria for patient withdrawal are listed in Section 7.1.

The reason for any patient's discontinuation and the date of withdrawal will be recorded in the patient's CRF. The patient's CRF, which will be completed up to the point of withdrawal, will be retained for the Sponsor.

10.3.13. Unexpected Events

Apart from the reporting of SUSARs, there may be other events which are relevant in terms of benefit-risk balance and which should be reported in a timely manner according to regional and national requirements, eg, EU CTR 536/2014 (48). It is important for patient safety that, in addition to SAEs and reactions, all unexpected events that might materially influence the benefit-risk assessment of the study intervention or that would lead to changes in the administration of the study intervention or in overall conduct of a clinical study should be reported. Examples of

such unexpected events include an increase in the rate of occurrence of expected serious adverse reactions which may be clinically important, a significant hazard to the patient population, such as lack of efficacy of a medicinal product, or a major safety finding from a newly completed animal study (such as, carcinogenicity).

Under the EU CTR 536/2014 (49), where unexpected events require an urgent modification of a clinical study, it should be possible for Alexion and the Investigator to take urgent safety measures without awaiting prior authorization. If such measures constitute a temporary halt of the clinical study, Alexion should apply for a substantial modification before restarting the clinical study.

10.4. Medication Error, Drug Abuse, and Drug Misuse

Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or Alexion AxMP that either causes harm to the patient or has the potential to cause harm to the patient.

Any events of medication error, with or without associated AEs, are to be captured and forwarded to Alexion Global Patient Safety via email or facsimile (clinicalsae@alexion.com or + 1.203.439.9347) using the Alexion Clinical Study Medication Error Report Form.

A medication error is not lack of efficacy of the drug, but rather a human or process-related failure while the drug is in control of the study site staff or patient.

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before the patient received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the patient
- Drug not administered as indicated, eg, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the refrigerator when it should be at room temperature
- Wrong patient received the medication (excluding Integrated Response Technology [IRT]/Randomization and Trial Supply Management [RTSM] errors)
- Wrong drug administered to patient (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which led to one of the above listed events that would otherwise have been a medication error
- Patient accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or Alexion AxMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the Alexion Global Patient Safety via email or facsimile (clinicalsae@alexion.com or + 1.203.439.9347) using the Alexion Clinical Study Drug Misuse or Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study patient or if the drug abuse involves a person not enrolled in the study (such as a relative of the study patient).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study patient or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study patient) of IMP or Alexion AxMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or Alexion AxMPs, outside the intended use as specified in the protocol, including deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the Alexion Global Patient Safety via email or facsimile (clinicalsae@alexion.com or + 1.203.439.9347) using the Alexion Clinical Study Drug Misuse or Drug Abuse Report Form. This form should be used both if the drug misuse happened in a study patient or if the drug misuse involves a person not enrolled in the study (such as a relative of the study patient).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person.
- The drug is sold to other people for recreational purposes.
- The drug is used to facilitate assault in another person.
- The drug is deliberately administered by the wrong route.
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole.
- Only half the dose is taken because the study patient feels that he/she is feeling better when not taking the whole dose.
- Someone who is not enrolled in the study intentionally takes the drug.

10.5. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.5.1. Definition: Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study medication, additional evaluation should be considered.

Women in the Following Categories Are Not Considered WOCBP

1. Premenarchal
2. Premenopausal female with one of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.

3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state.

Females on hormonal replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective or acceptable contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2. Contraception Guidance

10.5.2.1. Contraception for Male Patients

All non-sterile male patients must use highly effective or acceptable contraception with their partner(s) of childbearing potential from the first day of dosing (baseline) through 90 days (a spermatogenesis cycle) after their last dose of study medication.

Sterile is defined as having bilateral orchiectomy.

Highly effective contraception for males is defined as any of the following:

- Vasectomy with confirmed medical assessment of surgical success

- Condom plus use of one of the following by partner(s) of child-bearing potential:
  - Oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
  - Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation
  - Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
  - Bilateral tubal occlusion
- Sexual abstinence, defined as completely refraining from heterosexual intercourse during the entire period. Periodic abstinence (eg, calendar, symptothermal, postovulation methods) is not an acceptable method of contraception. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. If a patient is usually not sexually active but becomes active, they, with their partner(s), will comply with the contraceptive requirements described in this section.

An acceptable method of contraception for males is as follows:

- Agrees to use a male condom when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.
- Refrain from donating fresh unwashed semen
- PLUS, either:
  - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

    OR

  - Agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person

10.5.2.2. Contraception for Female Patients

Female patients of childbearing potential must use a highly effective or acceptable method of contraception from the moment of ICF signature through 30 days after their last dose of study medication.

Highly effective contraception for females is defined as any of the following:

- Oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
- Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion

- Vasectomized partner(s) with confirmed medical assessment of surgical success
- Sterile partner(s) (bi-lateral orchiectomy)
- Sexual abstinence, defined as completely refraining from heterosexual intercourse during the entire period. Periodic abstinence (eg, calendar, symptothermal, postovulation methods) is not an acceptable method of contraception. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. If a patient is usually not sexually active but becomes active, they, with their partner(s), must comply with the contraceptive requirements described in this section.

Female patients of childbearing potential may also use the following acceptable methods (considered effective, but not highly effective means failure rate of ≥ 1% per year) of contraception:

- Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide
- Cervical cap, diaphragm, or sponge with spermicide
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods). If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Female patients of childbearing potential must have a negative serum pregnancy test in order to enter the study and must have urine pregnancy tests throughout the study at the intervals defined in the SoA.

Female patients of nonchildbearing potential need not employ a method of contraception.

10.5.2.3. Collection of Pregnancy Information

Any pregnancy, including female partner pregnancies of male patients, that occurs or becomes confirmed during a clinical study will be reported to the Sponsor (or designee) within 24 hours of first knowledge of the pregnancy, as described in Section 8.3.6. The report will be provided on the pregnancy form. While pregnancy itself is not considered an AE, for the purposes of tracking, it should be reported on the pregnancy forms.

All pregnancies temporally related to taking study medication should be followed and discussed with the Medical Monitor as follows:

- The Investigator will follow up with the patient approximately every 3 months throughout the pregnancy to collect information on the status of the pregnancy. Generally, follow up will not be required for longer than 3 months beyond the estimated delivery date.
- The Investigator will report any information on the status of the pregnancy to the Sponsor (or designee) using the pregnancy forms.

The final outcome of the pregnancy will be reported to the Sponsor (or designee) using the pregnancy forms. Any termination of pregnancy will be reported, regardless of fetal status (ie, presence or absence of anomalies) or indication for the procedure.

Any SAEs related to the pregnancy (see below), or occurring during the pregnancy, or after delivery, must be documented and reported to the Sponsor (or designee) on both the SAE form and the pregnancy forms. Serious adverse events occurring in the child (eg, congenital anomalies or other conditions present at birth, whether genetically inherited or occurring in utero) must also be documented on both the SAE form and the pregnancy forms.

Reportable SAEs associated with pregnancy include, but are not limited to:

- Pregnancy losses (eg, spontaneous abortion, late fetal death)
- Life-threatening developments (eg, placental abruption, fetal distress)
- Congenital anomalies
- Neonatal or maternal death
- Any event resulting in maternal or neonatal hospitalization/prolonged hospitalization

10.6. Appendix 5: Genetics

Provision of genetic sampling is optional. If a patient provides separate informed consent via the optional genetic consent form, samples will be collected and retained for potential future genetic testing. Genetic analyses may be conducted if a patient does not respond to the Investigative drug, to better understand a potential drug-related toxicity, or to further characterize the underlying disease. Genes which may be sequenced include (but are not limited to):

- Complement component C3
- Complement factor H-related proteins (CFHR1, CFHR3, CFHR4, CFHR5)
- Complement factor B
- Complement factor D
- Complement factor H
- Complement factor I
- Membrane co-factor protein/cluster of differentiation 46 (MCP/CD46)
- Thrombomodulin (THBD)
- CR1

All genetic samples will be stored for a maximum of 25 years after completion of the study. During that time, samples may be retested if other mutations are discovered that may be associated with PNH or a drug safety signal. Patients may withdraw their consent for genetic testing and withdraw their samples from further genetic testing at any time by notifying the study Investigator verbally and in writing. After the 25-year storage period defined above, the sample will be destroyed. Any data already generated from the sample may continue to be used for the purposes of this study and future research.

10.7. Appendix 6: Seizure Management Plan

Convulsions and/or EEG abnormalities have been observed in dog and mouse repeated dose toxicology studies. The dog is the most sensitive species studied, and the NOAEL based on the dog 13-week toxicology study is 62.5 mg/kg/day.

Seizures are considered a potential risk that is to be closely monitored in patients. Seizures are defined as a transient occurrence of clinical signs and/or symptoms that are due to abnormal excessive or synchronous neuronal activity in the brain.

Should a suspected seizure occur during the study, the following procedures should be performed:

- Patients and family members should be instructed to call an ambulance or report to a medical facility if the patient experiences a seizure. In general, most seizures are self-limiting and do not require acute intervention
- For seizures that are not self-limiting, the patient should be treated medically according to local protocols for ongoing seizure.
- Patients and family members should be instructed to call the investigator to inform them of the seizure
- Treatment with ALXN2050 should be suspended until a complete work up is performed
- The following assessments are recommended for all patients with suspected seizure:
    - Blood samples should be taken to evaluate electrolytes (including calcium and magnesium), glucose, complete blood count, renal function tests, liver function tests, creatine kinase, toxicology screen, ethanol level, serum lactate, and any other tests or investigations determined to be pertinent (eg. brain imaging, blood and urine cultures).
    - An EEG should be performed.
    - Blood samples should be taken to evaluate ALXN2050 PK levels.
- If the seizure is confirmed, ALXN2050 will be withdrawn, and the patient will be discontinued from the study.

Any event of seizure or suspected seizure must be reported to Alexion within 24 hours of the Investigator's awareness as an SAE. The following clinical information in addition to the above recommended assessments should also be collected:

- Seizure start date and time
- Description of the seizure
    - The type of seizure (eg, generalized tonic-clonic seizure, partial seizure, etc)
    - A detailed description of what the patient was doing before, during, and after each seizure. If possible, describe all aspects from start to end
    - What was the earliest sign of seizure onset?

  - Duration of seizure(s)
  - Was the patient unconscious, unaware, or confused?
  - Evidence of bowel or bladder dysfunction?
  - Post-ictal period duration and signs.
  - Abnormal findings on neurologic examination?
  - Evidence of injury from the seizure (eg, tongue bites, bruises, or other injuries)
  - How did the patient recover after the seizure?
- Document identifiable seizure triggers
  - Was there any recognizable trigger that may have provoked the seizures for this person? Please include any recent medication changes, illness, or sleep deprivation.
- Past medical and surgical history review
  - Relevant medical history?
- Document concomitant medications

10.8. Appendix 7: COVID-19 Risk Assessment

PNH can cause irreversible morbidity and even mortality, if untreated. As such, and due to the limited number of available treatment options, the benefit a patient may receive from joining an investigational study with a therapeutic treatment is potentially significant. Given that treatment for PNH does involve immunosuppression, there is a theoretical concern that the risk for infection may be higher than in patients not receiving immunosuppressants. However, there is no specific data to further inform this risk. The site Investigator will therefore balance the risk/benefit considerations in the study patient taking these factors into account.

The potential risks identified and mitigation measures put in place in light of the COVID-19 pandemic are provided in Table 6.

Table 6: Potential Risks and Mitigation Measures due to COVID-19

Risks category	Summary of Data/ Rationale for Risk	Mitigation Strategy
Potential risks		
Healthcare institution availability for non-COVID-19 related activities	COVID-19 pandemic may impact the workload of healthcare institutions globally and may reduce staff availability to perform non-urgent activities and non-COVID-19 related activities.	During the time that the COVID-19 pandemic is active, Alexion will not open study sites or enroll new patients at sites unless the sites have the resources and capabilities to implement the study per protocol.
Data quality and integrity	Lack of availability of site personnel to perform study assessments and capture study specific data in a timely manner and to maintain adequate quality standards. Lack of availability of site personnel to ensure adequate and continuous chain of custody, storage conditions, and monitoring for investigational product and biological samples. Inability of study monitors and quality personnel to conduct in-person visits to exercise adequate oversight of study execution at investigational sites. Missing data (COVID-19 pandemic may impact study visit schedules and increase missed visits and/or patient study discontinuations inadvertently resulting in missing data [eg, for protocol-specified procedures]).	During the time that the COVID-19 pandemic is active, Alexion will only open study sites that report enough personnel capacity to sufficiently conduct clinical study-related activities. During this timeframe, patients eligibility as well as site capacity will be reviewed by the site Investigator and the study Medical Monitor prior to Screening. Each site is also evaluated for the capacity to perform remote monitoring visits and remote source data verification. During the time that the COVID-19 pandemic is active, it will be important to capture specific information in the electronic case report

Table 6: Potential Risks and Mitigation Measures due to COVID-19

Risks category	Summary of Data/ Rationale for Risk	Mitigation Strategy
		form that explains the reason the data is missing (eg, missed study visits or patient study discontinuations due to COVID-19).

Abbreviation: COVID-19 = SARS-CoV-2 coronavirus disease 2019.

10.9. Appendix 8: COVID-19 Vaccine Risk Assessment

Following a review of the available COVID-19 vaccine data (eg, Pfizer/BioNTech, Moderna, AstraZeneca, Johnson & Johnson), it is unlikely that the immune response to a COVID-19 vaccine (and therefore the efficacy of the vaccination) would be diminished with concomitant ALXN2050 administration, based on ALXN2050's mechanism of action. There is currently no information available evaluating the safety and efficacy of COVID-19 vaccines in patients treated with ALXN2050. Same precautions should be taken as described in Section 6.5.3.

Vaccination may further activate complement. As a result, patients with complement-mediated diseases may experience increased signs and symptoms of their underlying disease. Therefore, patients should be closely monitored for disease symptoms after recommended vaccination

Because vaccines may activate complement, if possible, consider vaccination when the underlying complement mediated disease is clinically controlled and subsequent complement blockade is relatively high, shortly after administration.

Local and national guidelines should be consulted for recommendations related to COVID-19 vaccination.

The potential risks identified and mitigation measures put in place in light of the COVID-19 vaccination rollout are provided in Table 7.

Table 7: Potential Risks and Mitigation Measures due to COVID19 Vaccine

Risks category	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential risks		
Data quality and integrity	Missing data due to appointments for COVID-19 vaccination or side effects of COVID-19 vaccine may impact study visit schedules and increase missed visits and/or patient study discontinuations, inadvertently resulting in missing data (eg, for protocol-specified procedures).	Capture specific information in the eCRF that explains the reason the data is missing (eg, missed study visits due to appointments for COVID-19 vaccination or side effects of COVID-19 vaccine)

Abbreviation: COVID-19 = coronavirus disease 2019.

10.10. Appendix 9: List of Inhibitors, Inducers, and Substrates of CYP3A

Table 8: List of Prohibited Inducers, Inhibitors, and Substrates of CYP3A

Classification	Medication	Table Number[a]
Strong CYP3A inhibitors	boceprevir, cobicistat, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, telithromycin, troleandomycin, voriconazole, clarithromycin, idelalisib, nefazodone, and nelfinavir	3-2
Moderate CYP3A inhibitors	aprepitant, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, and verapamil	3-2
Strong inducers of CYP3A	apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, and St. John's wort	3-3
Moderate inducers of CYP3A	bosentan, efavirenz, etravirine, phenobarbital, and primidone	3-3
Sensitive substrates of CYP3A	alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, everolimus, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, vardenafil, budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir, lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan	3-1

Note: This list is complete as of 25 Jan 2021. Please visit the link below for the most up-to-date information.
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.

[a] Table number from FDA Table of Clinical CYP Inhibitors and Inducers.

Abbreviation: CYP3A = cytochrome P450, family 3, subfamily A.

Source: FDA Drug Development and Drug Interactions, 2022

10.11. Appendix 10: Selected Medications Known to Lower the Seizure Threshold and/or Cause Seizure

The following medications are PROHIBITED while on the study:

- Meperidine/pethidine
- Tramadol
- Typical (first generation) antipsychotics
- Clozapine
- Olanzapine
- Lithium
- Tricyclic antidepressants
- Bupropion
- Aminophylline/theophylline

10.12. Appendix 11: Abbreviations

Abbreviation	Definition
ACH-0144471	ALXN2040; danicopan
ACH-0145228	ALXN2050, study medication for this study
ACIP	Advisory Committee on Immunization Practices
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AP	alternative pathway
APH	alternative pathway hemolysis’
AST	aspartate aminotransferase
AxMP	auxiliary medicinal product
Bb	Bb fragment of complement factor B
bid	twice daily
C3	complement component 3
C5	complement component 5
CFHR	complement factor H-related protein
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum plasma concentration
CNS	central nervous system
COVID-19	coronavirus disease 2019
CP	classical pathway
CRF	case report form
CR1	complement receptor 1
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CYP3A	cytochrome P450, family 3, subfamily A
ECG	electrocardiogram
EDC	electronic data capture
eCRF	electronic case report form
EEG	electroencephalogram
eGFR	estimated glomerular filtration rate
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-3L	EuroQoL 5 Dimensions, 3-Level version

Abbreviation	Definition
ET	early termination (visit)
EVH	extravascular hemolysis
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue scale (Version 4.0)
FB	(complement) factor B
FD	(complement) factor D
FSH	follicle stimulating hormone
F/U	follow-up (visit)
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GDS	Global Drug Safety
Hgb	hemoglobin
HRT	hormonal replacement therapy
HIPAA	Health Insurance Portability and Accountability Act
HSCT	hematopoietic stem cell transplantation
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	Integrated Response Technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IVH	intravascular hemolysis
LDH	lactate dehydrogenase
LTE	long-term extension (period)
MAC	membrane attack complex
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
NIMP	non-investigational medicinal product
NOAEL	no observed adverse effect level
PD	pharmacodynamic(s)
PI	Principal Investigator
PK	pharmacokinetic(s)
PNH	paroxysmal nocturnal hemoglobinuria
QLQ-C30	QoL Questionnaire-Core 30 scale

Abbreviation	Definition
QOL	quality of life
QT	interval between the start of the Q wave and the end of the T wave in an ECG
QTc	corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
RBC	red blood cell
RTSM	Randomization and Trial Supply Management
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SMS	short message service
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TTO	time trade off
UGT1A1	uridine diphosphate glucuronosyltransferase 1 family, member A1
ULN	upper limit of normal
WOCBP	woman of childbearing potential

10.13. Appendix 12: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents.

DOCUMENT HISTORY		
Document/Type of Amendment (Global or Country-specific)	**Date**	**Summary of Key Changes in the Amendment**
Protocol Amendment 4.1 (New Zealand)	09 Sep 2022	Extension of the Long-term Extension Period for an additional 52 weeks to collect additional long-term safety and efficacy data for patients in New Zealand
Protocol Amendment 4.0 (Global)	07 Oct 2021	Extension of the Long-Term Extension period for an additional 52 weeks to collect safety and efficacy data for longer term. Clarification on exclusion criteria and additional prohibited medications to align with exclusion criteria. Changes implemented in response to questions from the regulatory body in Germany (Protocol Amendment 3.2).
Protocol Amendment 3.2 (Germany)	10 Sep 2021	Germany-specific amendment to incorporate, changes made to address queries from the German Federal Institute for Drugs and Medical Devices (BfArM), in relation to – timeframe for reporting AE and SAE information after study is concluded; and – patient management after confirmed seizures
Protocol Amendment 3.1 (France)	09 Sep 2021	France-specific amendment to incorporate changes made to address queries from the regulatory bodies in France requesting clarification of the countries where each group will be enrolled.
Protocol Amendment 3.0 (Global)	03 May 2021	Removal of language from the dose-escalation instructions: “Dose escalation to 180 mg bid will be allowed once additional safety data from the currently ongoing Study ALXN2050-HV-107 is available.

DOCUMENT HISTORY		
Document/Type of Amendment (Global or Country-specific)	**Date**	**Summary of Key Changes in the Amendment**
		The Sponsor will inform study sites when dose escalation can be implemented." Preliminary data from Study ALXN2050-HV-107 are now available to support for the dose escalation to proceed. Inclusion of additional information regarding prohibited medications (ie, list of inhibitors, inducers, and substrates of CYP3A, and list of medications known to lower seizure threshold).
Protocol Amendment 2.1 (Global)	12 Apr 2021	Added text back pertaining to an exclusion criterion regarding history or presence of any risk factors for Torsades de Pointes, a screening QT interval corrected using Fridericia's formula (QTcF) > 450 msec for males and > 470 msec for females, or receiving medications known to significantly increase the corrected QT interval (QTc), which was inadvertently removed from Protocol Amendment 2.0. Added text to provide guidance on coronavirus disease 2019 (COVID-19) vaccine risk assessment.
Protocol Amendment 2.0 (Global)	07 Jan 2021	Aligned the patient population of this Phase 2 study with the expected Phase 3 populations and to explore the efficacy and safety of ALXN2050 as a monotherapy option for patients with paroxysmal nocturnal hemoglobinuria (PNH). The changes include updates to the study design, eligibility criteria and clarification of the endpoints. Changes were also made to further align the protocol with Alexion standards in all applicable sections, including serious adverse event (SAE) reporting, list of protocol-specific laboratory assessments, vaccination requirements and other safety monitoring and the statistical sections.

DOCUMENT HISTORY		
Document/Type of Amendment (Global or Country-specific)	**Date**	**Summary of Key Changes in the Amendment**
Protocol Amendment 1.1 (UK)	20 Jul 2020	UK-specific amendment to incorporate changes made to address queries from the Medicines and Healthcare products Regulatory Agency (MHRA).
Protocol Amendment 1.0 (Global)	06 Apr 2020	Updated to allow females of childbearing potential to participate in the study and to align the protocol with Alexion standards in all applicable sections. The changes include updates to the eligibility criteria, SAE reporting, list of protocol-specific laboratory assessments, vaccination requirements and the statistical sections.
Original Protocol	01 Oct 2019	Not applicable.

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