Title Page

Protocol Title: A Phase 3 Study of Danicopan (ALXN2040) as Add-on Therapy to a C5 Inhibitor (Eculizumab or Ravulizumab) in Patients with Paroxysmal Nocturnal Hemoglobinuria Who Have Clinically Evident Extravascular Hemolysis (EVH)

Protocol Number: ALXN2040-PNH-301

Compound Number: ALXN2040 (previously ACH-0144471)

Study Phase: 3

Short Title: Pivotal study of danicopan as add-on therapy to a C5 inhibitor (eculizumab or ravulizumab) in patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) who have Clinically Evident EVH

Sponsor Name: Alexion Pharmaceuticals Inc.

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Sponsor Signatory:

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Date

[redacted]

Alexion Pharmaceuticals, Inc.
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Investigator's Signature(s)

Study Title:	A Phase 3 Study of Danicopan (ALXN2040) as Add-on Therapy to a C5 Inhibitor (Eculizumab or Ravulizumab) in Patients with Paroxysmal Nocturnal Hemoglobinuria Who Have Clinically Evident Extravascular Hemolysis (EVH)
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Version and Date	**Global Amendment** 6.3 (US) 08 Aug 2022

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 3 Study of Danicopan (ALXN2040) as Add-on Therapy to a C5 Inhibitor (Eculizumab or Ravulizumab) in Patients with Paroxysmal Nocturnal Hemoglobinuria Who Have Clinically Evident Extravascular Hemolysis (EVH)

Short Title: Pivotal study of danicopan as add-on therapy to a C5 inhibitor (eculizumab or ravulizumab) in patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) who have Clinically Evident EVH

Rationale: This is a registration study to evaluate the efficacy of danicopan as an add-on therapy to a C5 inhibitor (eculizumab or ravulizumab) to treat clinically-evident EVH.

Objectives and Endpoints:

Objectives	**Endpoints**
Primary	
• To evaluate the efficacy of danicopan as compared to placebo as add-on therapy to a C5 inhibitor at 12 weeks	• Change in hemoglobin (Hgb) relative to baseline after 12 weeks of treatment with danicopan compared to placebo
Secondary	
Key Secondary	
• To evaluate the efficacy of danicopan on Hgb improvement in absence of transfusion as compared to placebo as add-on therapy to a C5 inhibitor at 12 weeks	• Proportion of patients with Hgb increase of ≥ 2 g/dL at Week 12 in the absence of transfusion
• To evaluate the efficacy of danicopan as compared to placebo as add-on therapy to a C5 inhibitor on transfusion avoidance at 12 weeks	• Proportion of patients with transfusion avoidance (TA), defined as patients who remain transfusion-free and do not require a transfusion as per protocol-specified guidelines through Week 12
• To evaluate the effect of danicopan as compared to placebo as add-on therapy to a C5 inhibitor on Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue scores at 12 weeks of treatment	• Change from baseline in FACIT Fatigue scores at Week 12
• To evaluate the effect of danicopan as compared to placebo as add-on therapy to a C5 inhibitor on absolute reticulocyte count	• Change from baseline in absolute reticulocyte count at Week 12

Objectives	Endpoints
Other Secondary	
• To evaluate the efficacy of danicopan as add-on therapy to a C5 inhibitor on transfusion requirements at 24 weeks for those patients receiving 24 weeks of danicopan	• Change in the number of red blood cell (RBC) units transfused and transfusion instances during the 24 weeks of treatment with danicopan compared to the 24 weeks prior to initiation of treatment with danicopan • Percentage of patients who have transfusion avoidance through 24 weeks of treatment
• To evaluate the efficacy of danicopan as compared to placebo as add-on therapy to a C5 inhibitor on transfusion requirements at 12 weeks	• Change in the number of RBC units transfused and transfusion instances during the 12 weeks of treatment with danicopan compared to the 12 weeks while receiving placebo
• To evaluate the effect of danicopan as add-on therapy to a C5 inhibitor on Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue scores for 24 weeks of treatment	• Change from baseline in FACIT Fatigue scores at Week 24 in all patients
• To assess the efficacy of danicopan as add-on therapy to a C5 inhibitor on Hgb stabilization	• Percentage of patients with Hgb stabilization during the last 12 weeks of treatment in patients receiving 24 weeks of danicopan
• To evaluate the efficacy of danicopan on Hgb improvement in absence of transfusion as add-on therapy to a C5 inhibitor at 24 weeks	• Proportion of patients with Hgb increase of $\geq$ 2 g/dL at Week 24 in the absence of transfusion
• To assess additional laboratory markers relevant in PNH patients	• Change from baseline of danicopan treated patients compared to placebo in total and direct bilirubin at 12 weeks • Changes in PNH RBC clone size and C3 fragment deposition on PNH RBCs at 12 weeks of treatment with danicopan compared to placebo • Changes in lactate dehydrogenase (LDH) at 12 weeks • Percentage of patients with Hgb normalization at 12 weeks and 24 weeks

Objectives	Endpoints
Exploratory	
• To assess Patient-Reported Outcomes (PRO) and other health-related quality of life (QoL) measures during 24 weeks of treatment	• Change from baseline relative to placebo in Three-level EuroQoL 5 dimensions (EQ-5D-3L) scores at Week 12 • Change from baseline in EQ-5D-3L scores at Week 24 • Change from baseline relative to placebo in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 Scale (QLQ-C30) at Week 12 • Change from baseline in EORTC-QLQ-C30 scale at Week 24 • Change from baseline relative to placebo in Work Productivity and Activity Impairment Questionnaire: Anemic Symptoms (WPAI:ANS) at Week 12 • Change from baseline in WPAI:ANS scores at Week 24 • Change from baseline relative to placebo in Healthcare Resource Utilization (HRU) at Week 12 • Change from baseline in HRU scores at Week 24
• To characterize pharmacokinetics (PK) and pharmacodynamics (PD) of danicopan	• Plasma concentrations of danicopan over time • Changes from baseline in PD biomarkers
Safety	
• To evaluate the safety and tolerability of 24 weeks of treatment with danicopan as add-on therapy to a C5 inhibitor	• Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), laboratory abnormalities, and events leading to discontinuation of study drug during Treatment Periods 1 and 2.
• To evaluate the safety and tolerability of danicopan as add-on therapy to a C5 inhibitor during the long-term extension (LTE) Period	• Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), laboratory abnormalities, and events leading to discontinuation of study drug

Overall Design: This is a multiple-region, randomized, double-blind, placebo controlled, multiple-dose, Phase 3 study in patients with PNH who have clinically evident EVH on a C5 inhibitor (eculizumab or ravulizumab). This study will include approximately 84 patients who are receiving C5 inhibitor therapy according to the usual dose and schedule and continue to experience anemia with or without the need of transfusion support. At randomization, patients will be stratified by transfusion history (ie, > 2 or ≤ 2 transfusions within 6 months of Screening) and Hgb (ie, < 8.5 g/dL and ≥ 8.5 g/dL) at Screening, and Japanese patients (defined as patients enrolled from Japan)/non-Japanese patients.

Patients will be randomized to danicopan tid or placebo tid in a 2:1 ratio for 12 weeks (Treatment Period 1) in addition to their C5 inhibitor therapy (eculizumab or ravulizumab). At Week 12, patients randomized to receive placebo will be switched to danicopan for an additional 12 weeks (Treatment Period 2) and patients randomized to danicopan will continue on danicopan for an additional 12 weeks, while remaining on the ongoing C5 inhibitor therapy. At the end of the treatment periods (Week 24), patients may enter the Long-Term Extension (LTE) Period and continue to receive danicopan + their C5 inhibitor therapy.

In this study, patients will have been on a C5 inhibitor therapy for a time period sufficient to receive the full benefit of the therapy but still remain anemic. Prolonged therapy with a C5 inhibitor alone is not projected to have additional impact on their clinical response. Historical transfusion needs and pretransfusion hemoglobin levels will be captured for the 52 weeks prior to the Screening Visit. These historical data will be used to assess the efficacy and safety of combination therapy in this study.

The Screening Visit should occur no earlier than 4 weeks after a transfusion in order to minimize the effect of the transfusion on the screening Hgb level, which will be used for stratification purposes.

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 drug. Patients who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination.

The starting dose of danicopan or placebo is 150 mg tid. The dose may be escalated to 200 mg tid based on safety and clinical effect at any of the protocol-specified time points (Weeks 6, 12, and 18). All dose escalations will be made on a patient-by-patient basis at the discretion of the Principal Investigator, in consultation with the Sponsor based on the protocol dose escalation guidelines (see Section 6.6). Patients may not switch from their Day 1 C5 inhibitor to any other C5 inhibitor during the first 24 weeks of the study but may do so during the LTE Period. The only authorized switch is from eculizumab to ravulizumab.

The C5 inhibitor + placebo group will be dose-escalated in the same manner as the C5 inhibitor + danicopan group during the study to maintain the blind.

After Week 12, the C5 inhibitor + placebo group will switch from placebo to receive danicopan during Treatment Period 2.

All patients will return to the clinic for protocol specified assessments during the treatment periods and during the LTE Period as shown in Table 1 to Table 3.

Patients will have the option to have some selected visits in-clinic or via the home healthcare service provided by the 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.

Upon completion of Treatment Period 2 (Week 24), patients may enter the LTE Period at the same danicopan dose they were receiving at Week 24, plus their C5 inhibitor therapy. During the LTE Period, patients may be dose escalated, to a maximum of 200 mg tid, at the discretion of the Principal Investigator and in consultation with the Sponsor.

The LTE period will consist of a first year of LTE (Year 1) and a second year of optional LTE (Year 2). All patients will complete 72 weeks of LTE (Year 1) assessments as shown in Table 3. After Week 72 (at the end of the first year of LTE), patients have the choice to complete participation in this study or continue to the optional second year of LTE. Once Study ALXN2040PNH-303 opens for enrolment, all patients participating in the second optional year of LTE must transition without treatment interruption to Alexion study ALXN2040-PNH-303, completing the End of Treatment Period Visit as soon as possible (no taper or follow up visits are required), or complete participation in the current study by completing the End of Treatment Period Visit, plus Taper and Follow Up Visits as soon as possible. See Section 4.4 for definition of study completion.

If a patient discontinues from the study, dosing of danicopan or placebo should be tapered over 6 days (Taper Visit 1 and 2), and a Follow-up Visit will be conducted approximately 30 days after the last dose of study drug. Patients will continue to receive their C5 inhibitor therapy at the same dose and interval that they were receiving during the taper and follow-up visits.

Number of Patients: Approximately 84 patients on a C5 inhibitor will be enrolled and treated with danicopan or placebo (2:1 ratio).

Intervention Groups and Duration: Patients will be randomized to danicopan or placebo, in a 2:1 ratio, for 12 weeks (Treatment Period 1) in addition to their C5 inhibitor therapy. At Week 12, patients randomized to receive placebo will be switched to danicopan for an additional 12 weeks (Treatment Period 2), and patients randomized to danicopan will continue for an additional 12 weeks. At the end of the treatment periods (24 weeks), patients may enter the LTE Period at the same dose plus their C5 inhibitor therapy. Any patient discontinuing from the study at any time point should undergo a 6-day taper and will have a Follow-Up Visit approximately 30 days after the last dose during the Tapering Period.

The C5 inhibitor (eculizumab or ravulizumab) used in this study will be considered a background therapy. If patients switch from eculizumab to ravulizumab after completion of 24 weeks of treatment, the new medication used in this manner will also be considered a background therapy.

Inclusion Criteria:

1. Diagnosis of PNH
2. Clinically evident extravascular hemolysis (EVH) defined by:
   - Anemia (Hgb $\leq$ 9.5 g/dL) with absolute reticulocyte count $\geq 120 \times 10^9$/L.
3. Receiving an approved C5 inhibitor for at least 6 months prior to Day 1 in this study at an approved dose (or higher) and with no change in the prescribed dose or interval for

at least 24 weeks preceding Day 1. For those patients who recently switched from eculizumab to ravulizumab, they must have received at least the loading dose and 3 maintenance doses (minimum of 24 weeks) of ravulizumab preceding Day 1. Infusions outside the prescribed interval due to logistical reasons/patient convenience are not considered a change in the prescribed frequency and should be discussed with the Medical Monitor prior to randomization.

4. Platelet count ≥ 30,000/μL without the need for platelet transfusions.
5. Absolute neutrophil counts ≥ 500/μL.
6. Documentation of vaccination for *Neisseria meningitidis*: All patients must be vaccinated against meningococcal infections within 3 years prior to, or at the time of initiating study drug. Patients who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination.
7. Age 18 years or older (or greater than or equal to minimum adult age in accordance with local legal requirements).
8. Female patients of childbearing potential must agree to use a highly effective or acceptable method of contraception from the date of signing the informed consent until the specified duration after the last dose of their background C5 inhibitor as per the product labelling. Female patients of childbearing potential must also have a negative serum pregnancy test during Screening and negative urine pregnancy test on Day 1.
9. Female patients with documented evidence of non-childbearing potential need not employ a method of contraception.
10. Nonsterile 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 to 90 days after their last dose of study drug.
    - Males who are surgically sterile need not employ additional contraception.
    - Males must agree not to donate sperm while enrolled in this study and for 90 days after their last dose of study drug.
11. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form and in this protocol.
12. Must have access to emergency medical care.
13. Patients who are on iron, folic acid, and vitamin B_{12} supplementation are eligible for the study if on a stable dose for at least 30 days prior to Day 1. See Section 6.5.

Exclusion Criteria:

1. History of a major organ transplant (eg, heart, lung, kidney, liver) or hematopoietic stem cell transplantation (HSCT).
2. Known aplastic anemia or other bone marrow failure that requires HSCT or other therapies including anti-thymocyte globulin and/or immunosuppressants, unless the

dosage regimen of immunosuppressant has been stable for at least 12 weeks before Day 1 and patient is expected to remain on stable doses through Week 24 (see Section 6.5).

3. Received another investigational agent other than C5 inhibitors (eculizumab or ravulizumab) 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, etc.) or any conditions leading to anemia that are not primarily due to PNH.
6. Active bacterial or viral infection, a body temperature >38°C on two consecutive daily measures, evidence of other infection, or history of any febrile illness within 14 days prior to first study drug administration.
7. History or presence of any clinically relevant co-morbidities that would make the patient inappropriate for the study (e.g., 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).
8. Laboratory abnormalities at screening, including:
    - Alanine aminotransferase (ALT) > 2 × ULN (> 3 × ULN in the case of patients with documented liver iron overload defined by serum ferritin values ≥ 500 ng/mL). The inclusion of patients with documented iron overload and ALT > 2 × ULN will be done in a case by case basis, with prior discussion with the Medical Monitor.
    - Direct bilirubin > 2 × ULN, with the exception of:
        - patients who, in the opinion of investigator, have direct bilirubin > 2 × ULN due to EVH and/or
        - patients with documented Gilbert's syndrome (if Gilbert's syndrome is suspected, the patient will be tested for this condition at screening).
9. Any other clinically significant laboratory abnormality as judged by the Investigator that, in the opinion of the Principal Investigator, would make the patient inappropriate for the study or put the patient at undue risk.
10. Females who are pregnant, nursing, or planning to become pregnant during the study or within 90 days of study drug administration.
11. Current evidence of biliary cholestasis.
12. 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 (HCV antibody positive), except for patients with documented successful treatment and documented sustained virologic response (SVR) at Screening.
13. Evidence of human immunodeficiency virus (HIV antibody positive) infection at Screening.
14. Estimated glomerular filtration rate < 30 mL/min/1.73 m^2 and/or are on dialysis.

15. Hypersensitivity to the investigational drug (danicopan) or any of its excipients

Data Monitoring Committee (DMC):

An independent DMC comprising experts in relevant biomedical fields and one external statistician who have no direct relationship with the study will be appointed by the sponsor. The DMC will review and evaluate the accumulated study data for patient safety and make recommendations on continuing study drug administration. The DMC will review study information on a regular basis as outlined in the DMC charter, which is maintained separately from the study protocol. Final decisions regarding the conduct of the study will be made by the Sponsor after consultation with the DMC. All appropriate regulatory authorities and IRBs/IECs will be notified of any significant action.

Statistical Methods:

The null statistical hypothesis is the improvement in hemoglobin levels from baseline at Week 12 for danicopan treatment being similar to the improvement for placebo treatment; that is, the difference in mean changes from baseline between danicopan and placebo at Week 12 is zero.

Sample Size Determination:

The PNH literature indicates that patients with PNH who have received a C5 inhibitor (eculizumab or ravulizumab) but are still anemic have hemoglobin levels, on the average, of 10.5 g/dL. All patients entering this study will have a hemoglobin level of ≤ 9.5 g/dL. A minimum of 2 g/dL in difference between danicopan and placebo treatments in terms of mean improvement from baseline after 12 weeks of treatment is considered clinically meaningful.

A total of approximately 84 patients will be enrolled into this study to ensure an evaluable number of patients in each study arm. It is anticipated that approximately 10% of patients will discontinue prior to the primary endpoint. For the primary endpoint of change from baseline to Week 12 in hemoglobin level, the statistical power using a two-sample t-test is 99% to detect the difference in mean change from baseline of 2 g/dL (alternative hypothesis), assuming the statistical significance level of 0.05 (two-sided) and the standard deviation of 1.6 g/dL which is estimated from study ACH471-101. For the key secondary endpoint of patients with Hgb increase of ≥ 2 g/dL at Week 12 in the absence of transfusions, the study has >95% power assuming at least 35% of patients in the danicopan arm and 5% of patients in the placebo arm can meet the criterion.

For the key secondary endpoint of patients with transfusion avoidance (TA), the study has70% power for the TA endpoint, assuming 90% of patients in the danicopan arm and 64% of patients in the placebo arm will have TA. For the key secondary endpoint of change from baseline to Week 12 in FACIT-Fatigue score, the study has 91% power with two-sample t-test to detect a 9-point difference between treatment arms in mean change from baseline, which is considered clinically meaningful. The power calculation is based on the assumption of a standard deviation of 11 for the FACIT-Fatigue change, which was observed in Study ALXN1210-PNH-301 in PNH patients. The power is 80% based on the standard deviation assumption of 13, which was observed in Study ACH471-101.

Analysis populations are as follows:

- Intent-to-treat (ITT) population: All randomized patients; data will be analyzed by the treatment groups to which patients are randomly assigned, even if the patient does not take the assigned treatment, does not receive the correct treatment, or does not comply with the protocol.
- Per Protocol population: Intent-to-treat (ITT) patients who do not have protocol deviations expected to affect the primary efficacy endpoint (Week 12). Such protocol deviations will be prespecified in the statistical analysis plan prior to database lock.
- Safety population: All patients who take at least one dose of study drug.

If the ITT population and Per Protocol population have a similar number of patients (<5% difference), analyses will not be performed using the Per Protocol population.

Efficacy Analyses: Summary statistics for the baseline and post-baseline measurements, and changes from baseline will be presented by visit for all continuous efficacy variables to be analyzed.

The primary efficacy endpoint is the change in hemoglobin at Week 12 relative to baseline (defined as the lowest Hgb value, between and including screening and Day 1) between danicopan and placebo. The longitudinal changes from baseline in hemoglobin will be analyzed using a mixed model for repeated measures (MMRM) (Mallinckrodt, 2001, Mallinckrodt, 2004) which includes the fixed, categorical effects of treatment, study visit, and study visit by treatment group interaction as well as the continuous, fixed covariate of baseline hemoglobin value and the stratification randomization indicator of transfusion history in the model. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The primary test for statistical significance of the treatment group difference between the danicopan and placebo arms at Week 12 will be conducted via a re-randomization test at a 2-sided 0.05 significance level.

Longitudinal graphic presentations will also be provided to examine the hemoglobin profile throughout 12 weeks of treatment with danicopan or placebo, plus C5 inhibitor.

The primary efficacy analysis will be based on the ITT population. A supportive analysis will be carried out for the primary efficacy endpoint, changes in hemoglobin measurement, based on the Per Protocol population to examine the impact due to major protocol deviations.

Secondary efficacy analyses will be conducted on the ITT population. Key secondary efficacy endpoints will be analyzed using a hierarchical fixed sequence test procedure to determine the statistical significance at a level of 0.05 for each endpoint sequentially.

Safety Analyses: All safety analyses will be conducted on the Safety population. The evaluation of safety will be performed separately for the 12-week blinded Treatment Period 1, subsequent 12-week Treatment Period 2, and the LTE Period. The safety analysis will be based primarily on the frequency of adverse events, clinical laboratory assessments, vital signs, and 12-lead electrocardiogram (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 by visit, when appropriate. No inferential statistical analysis of safety data is planned.

Interim Analysis: An interim analysis may be conducted at the discretion of the study sponsor (based on enrollment progression) when approximately 75% of patients have been randomly assigned to study treatment and have had the opportunity to complete the 12-week Treatment Period 1 (information fraction = 0.75). The purpose of the interim analysis is to evaluate the study for stopping early for efficacy. If conducted, the primary endpoint of change in Hgb levels at Week 12, as well as the key secondary endpoints will be evaluated using the alpha-spending methods specified below to control family-wise error rate.

- The evaluation of primary endpoint at interim analysis will be using the gamma family alpha-spending function (Hwang, 1990) with parameter -4.
- The evaluation of key secondary endpoints at interim analysis will be using the gamma family alpha-spending function with parameter 1.

Due to the hierarchical nature of primary and key secondary endpoint, and proper alpha-spending function used to control error rate at one-sided 0.025 level for each endpoint, the overall family-wise error rate is controlled at one-sided 0.025 level across primary and key secondary endpoints among interim and final analyses (Glimm, 2010, Tamhane, 2010). The recommendation of stopping study enrollment and placebo-controlled Treatment Period 1 for efficacy can be made only if, at a minimum, the primary endpoint and the key secondary endpoints of proportion of patients with Hgb increase ≥ 2g/dL in the absence of transfusion and proportion of patients with transfusion avoidance through the 12week Treatment Period 1 meet the prespecified significance level. .

The interim analysis will be conducted under the auspices of an independent DMC. The final decision to stop the study enrolment and placebo-controlled Treatment Period 1 for efficacy will be done by the Sponsor based on the DMC recommendation. The DMC review of the data will be independent of the Sponsor as the Sponsor will remain blinded. Details of the DMC's responsibilities and logistics will be outlined in the charter before the dosing of the first patient.

1.2. Schedule of Assessments

Table 1: Schedule of Assessments Treatment Period 1: All Patients

	Screening	Treatment Period 1									
	Day -45 to -1	**Day 1**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 6**	**Wk 7[6]**	**Wk 8**	**Wk 10**	**Wk 12**
Clinic visit days[1]	X	X		X		X	X		X		X
Visiting healthcare assessment[2]			X		X			X		X	
***N. meningitidis* vaccinations[3]**	X	**Administer according to local/national guidelines**									
Study drug dispensing[4]		X				X	X		X		X
Drug accountability				X		X	X		X		X
Dose escalation decision day[5]							X				X
CLINICAL ASSESSMENTS											
Informed consent	X										
Inclusion/exclusion criteria	X	X									
Randomization		X									
Review safety card		X	X	X	X	X	X	X	X	X	X
Medical history	X	X									
Demographics	X										
Vaccination history	X										
Height	X										
Physical exam[7]	X	X		X		X			X		X
Vital signs	X	X		X		X			X		X
Weight	X	X		X		X			X		X
12-lead ECG (single)		X									X
PRO and QoL questionnaires[8]		X		X		X			X		X
RBC transfusion review	X	X		X		X			X		X
AE/SAE	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications/ protocol restrictions	X	X	X	X	X	X	X	X	X	X	X
FSH[9]	X										
HCV, HBs Ag, HIV	X										
Erythropoietin	X										
Sample for genetic testing (optional, white blood cells)		X									
Hematology, chemistry, and urinalysis[10]	X	X	X	X	X	X[5]	X	X	X	X	X[14]

Table 1: Schedule of Assessments Treatment Period 1: All Patients

	Screening	Treatment Period 1									
	Day -45 to -1	**Day 1**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 6**	**Wk 7[6]**	**Wk 8**	**Wk 10**	**Wk 12**
Pregnancy test[11]	X	X		X		X			X		X
PT/PTT/INR, D-dimer	X					X					X
Free hemoglobin, haptoglobin		X		X		X			X		X
Iron studies[12]	X										X
Direct Coombs	X	X				X					X
Flow cytometry: clone size		X				X					X
Flow cytometry: C3 fragment deposition		X				X					X
Bb, AP activity, FD, C3, CP activity, free C5[13]		X				X					X
PK samples[13]		X				X					X

Abbreviations: AE = adverse event; AP = alternative pathway; Bb = Bb fragment of complement factor B; C3 = complement protein 3; C5 = complement protein 5; CP = classical pathway; ECG = electrocardiogram; ET = early termination; FD = factor D; FSH = follicle-stimulating hormone; Hgb = hemoglobin; Hbs Ag = hepatitis B surface antigen; HCV = hepatitis C virus; HIV= human immunodeficiency virus; HRU = Healthcare Resource Utilization; INR = international normalized ratio; PD = pharmacodynamics; PK= pharmacokinetics; PRO = patient-reported outcome; PT = prothrombin time; PTT = partial thromboplastin time; QoL = quality of life; RBC = red blood cell; SAE = serious adverse event.; Wk = week.

[1] Visit window is ± 1 day for Weeks 1 through 12. A patient can discontinue from the study at any time and should complete all Week 24/ET assessments at final visit.

[2] Due to the time required to assign visiting nurses via the home healthcare provider, visiting healthcare assessments may not be available to patients. If not available, patients will need to get these assessments performed onsite. Availability of home healthcare visits will be patient- and location-specific and will be discussed with each site at the time of patient enrollment. The site will call the patient within 1 to 3 days to confirm that visiting healthcare assessment has occurred and AEs, SAEs, and concomitant medications have been assessed. If needed, site may ask about AEs, SAEs, and concomitant medications over the phone.

[3] Female patients of childbearing potential receiving vaccinations or boosters must have a negative urine pregnancy test on the days of vaccination before any vaccine or booster is administered.

[4] Patients will be provided with sufficient study drug to last until their next appointment. On the visits where PK/PD sampling will be done, the site will instruct the patient to take their study drug dose at the clinic. For in-clinic dosing, the kit dispensed at the corresponding visit (not the kit being returned from the previous visit) should be used. At dose escalation visits, patients will return to the clinic to be dispensed study drug and receive new dosing instructions.

[5] Weeks 6 and 12 are potential dose escalation time points. Hgb at Weeks 4 and 10 are to be used for dose escalation decisions at Weeks 6 and 12, respectively

Table 1: Schedule of Assessments Treatment Period 1: All Patients

[6] Week 7 visit is applicable only for patients who are dose escalated. If a dose escalation occurs, blood will be drawn for safety laboratory assessments by the visiting healthcare service or at the clinic 1 week after escalation.

[7] Full physical exam at Screening and Day 1. Brief physical exam at all other time points.

[8] PROs and QoLs should be performed as early as possible during the clinic visits. On Day 1, PROs must be obtained before the first dose of study drug. Refer to PRO and QoL questionnaires in Section 8.3. HRU will be administered at Day 1 and Week 12. If patient is to receive infusion of their C5 inhibitor agent on a clinic visit where PROs and QoLs will be obtained, it is recommended that patients fill out the PRO and QoL instruments before the C5 inhibitor infusion.

[9] FSH for postmenopausal women.

[10] Patients should refrain from heavy exercise 24 hours before blood collection. Walking and light exercise are acceptable. The screening hematology assessments should occur no earlier than 4 weeks if possible, after the occurrence of a transfusion in patients who require transfusion support in order to minimize the effect of transfusion on the screening Hgb level.

[11] Serum pregnancy test at screening. Urine pregnancy test for women of childbearing potential only. On Day 1, the pre-dose urine pregnancy test must be negative to continue. Any positive urine pregnancy test will be confirmed by a follow-up serum pregnancy test.

[12] If there is evidence of iron deficiency at Screening, patients will be enrolled if on stable iron supplementation for at least 30 days. See Section 6.5.

[13] Patients should have a snack and take their dose of study drug in the clinic 15 to 30 minutes post snack. Site should collect accurate information on the timing when patient takes the last 2 doses prior to the in-clinic dose, and the missing doses (morning, noon, or evening) in the last 2 days. Site will obtain a predose sample and a 2 ± 0.5 hours post dose PK sample. Samples for AP activity, Bb, FD, C3, CP activity, and free C5 should be taken at the same time as the PK samples (pre and post dose, as needed). Actual sampling time and the most recent dose time prior to sample collection should be recorded. See Table 4 for sample collection timing.

[14] A backup central hematology sample must be obtained at the Week 12 visit for all patients.

Table 2: Schedule of Assessments Treatment Period 2: All Patients

	Wk 13	Wk 14	Wk 15	Wk 16	Wk 18	Wk 19[6]	Wk 20	Wk 22	Wk 24/ET[11]
Clinic visit days[1]		X		X	X		X		X
Visiting healthcare assessement[2]	X		X			X		X	
***N. meningitidis* vaccinations[3]**	**Administer according to local/national guidelines**								
Study drug dispensing[4]				X	X		X		X
Drug accountability		X		X	X		X		X
Dose escalation decision[5]					X				
Review safety card	X	X	X	X	X	X	X	X	X
Brief Physical exam		X		X			X		X
Vital signs		X		X			X		X
Weight		X		X			X		X
12-lead ECG (single)									X
PRO and QoL questionnaires[7]		X		X			X		X
RBC transfusion review		X		X			X		X
AE/SAE	X	X	X	X	X	X	X	X	X
Concomitant medications/ protocol restrictions	X	X	X	X	X	X	X	X	X
Hematology, chemistry, and urinalysis[8]	X	X	X	X	X	X	X	X	X[12]
Pregnancy test[9]		X					X		X
PT/PTT/INR, D-dimer				X					X
Free hemoglobin, haptoglobin		X		X			X		X
Iron studies									X
Direct Coombs				X					X
Flow cytometry: clone size				X					X
Flow cytometry: C3 fragment deposition				X					X
Bb, AP activity, FD, C3, CP activity, free C5[10]				X					X
PK samples[10]				X					X

Table 2: Schedule of Assessments Treatment Period 2: All Patients

Abbreviations: AE = adverse event; AP = alternative pathway; Bb = Bb fragment of complement factor B; C3 = complement protein 3; C5 = complement protein 5; CP = classical pathway; ECG = electrocardiogram; EORTC QLQ30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Scale; ET= early termination; FD = factor D; Hgb = hemoglobin; HRU = Healthcare Resource Utilization; INR = international normalized ratio; PK= pharmacokinetics; PRO = patient-reported outcome; PT = prothrombin time; PTT = partial thromboplastin time; QoL = quality of life; RBC = red blood cell; SAE = serious adverse event; Wk = week; WPAI:ANS = Work Productivity and Activity Impairment Questionnaire: Anemic Symptoms.

[1] Visit window is ± 1 day for Weeks 13 through 24.

[2] The site will call patient within 1 to 3 days to confirm that visiting healthcare assessment has occurred and AEs, SAEs, and concomitant medications have been assessed. If needed, site may ask about AEs, SAEs, and concomitant medications over the phone.

[3] Female patients of childbearing potential receiving vaccinations or boosters must have a negative urine pregnancy test on the days of vaccination before any vaccine or booster is administered.

[4] Patients will be provided with sufficient study drug to last until their next appointment. At dose escalation visits, patients will return to the clinic to be dispensed study drug and receive new dosing instructions.

[5] Week 18 is a potential dose escalation time point. Hgb at Week 16 is to be used for dose escalation decision at Week 18.

[6] Week 19 is applicable only for patients who are dose escalated. If a dose escalation occurs, blood will be drawn for safety laboratory assessments by the visiting healthcare service or at the clinic 1 week after escalation.

[7] PROs and QoLs should be performed as early as possible during clinic visits. If patient is to receive infusion of their C5 inhibitor agent on a clinic visit where PROs and QoLs will be obtained, it is recommended that patients fill the PROs and QoL instruments before the C5 inhibitor infusion. Refer to PRO and QoL questionnaires in Section 8.3. Healthcare Resource Utilization (HRU), EORTC-QLQ30, and WPAI:ANS will be collected only at Week 24.

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

[9] Urine pregnancy test for women of childbearing potential only.

[10] Patients should have a snack and take their dose of study drug in the clinic 15 to 30 minutes post snack. Site should collect accurate information on the timing when patient takes the last 2 doses prior to the in-clinic dose, and the missing doses (morning, noon, or evening) in the last 2 days. Site will obtain a predose sample and a 2 ± 0.5 hours post dose PK sample. Samples for AP activity, Bb, FD, C3, CP activity, and free C5 should be taken at the same time as the PK samples (pre-and postdose, as needed). Actual sampling time and the most recent dose time prior to sample collection should be recorded. See Table 4 for sample collection timing.

[11] Patients will be instructed to bring back all remaining study drugs on this visit.

[12] A backup central hematology sample must be obtained at the Week 24 visit for all patients.

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

	Long-term Extension Year 1[1]		Optional Long-term Extension Year 2[1]		Post-escalation Visit[2]	End of Treatment Period Visit / Wk 72 or 120[1] / ET	Taper[4]		Follow Up
	VHA Visits[2]	Clinic Visits[3]	VHA Visits[2]	Clinic Visits[2]					
	Weeks 28, 36, 44, 52, 60, 68	Weeks 32,40, 48, 56, 64	Weeks 80, 96, 112	Weeks 88, 104			T1 Taper Days 1-3	T2 Taper Days 4-6	F/U[10]
Clinic visit days		X		X		X			X
Visiting healthcare assessment	X		X				X	X	
***N. meningitidis* vaccinations**	**Administer according to local/national guidelines**								
Study drug dispensing[5]		X		X		X			
Drug accountability		X		X		X	X	X	X
Review safety card	X	X	X	X	X	X	X	X	X
Brief physical exam		X		X		X			X
Vital signs		X		X		X			X
Weight		X		X		X			X
PRO and QoL questionnaires[6]		X		X		X			
RBC transfusion review		X		X		X			X
AE/SAE	X	X	X	X	X	X	X	X	X
Concomitant medications/ protocol restrictions	X	X	X	X	X	X	X	X	X
Hematology, chemistry, and urinalysis[7]	X	X	X	X	X	X			
Pregnancy test[8]	X	X	X	X		X			X
PT/PTT/INR, D-dimer		X		X		X			
Free hemoglobin, haptoglobin		X				X			
Direct Coombs		X				X			
Flow cytometry: clone size[9]		X				X			
Flow cytometry: C3 fragment deposition[9]		X				X			

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

Abbreviations: AE = adverse event; C3 = complement protein 3; EOS = end of study; ET = early termination; F/U = follow-up; INR = international normalized ratio; LTE = long term extension; PRO = patient-reported outcome; PT= prothrombin time; PTT = partial thromboplastin time; QoL = quality of life; RBC = red blood cell; SAE = serious adverse event; T = taper; VHA = visiting healthcare assessment.

[1] Week 72 and Week 120 visit window is ± 4 days. The LTE period will consist of a first year of LTE (Year 1) and a second year of optional LTE (Year 2). All patients will complete 72 weeks of LTE (Year 1) assessments. After Week 72 (at the end of the first year of LTE), patients have the choice to complete participation in this study or continue to the optional second year of LTE. Once Study ALXN2040PNH-303 opens for enrolment, all patients participating in the second optional year of LTE must transition without treatment interruption to Alexion study ALXN2040-PNH-303, completing the end of treatment period visit as soon as possible (no taper or follow up visits are required), or complete participation in the current study by completing the end of treatment period visit, plus taper and follow up visits as soon as possible. See Section 4.4 for definition of study completion.

[2] VHA visit window is ± 7 days. The site will call the patient within 1 to 3 days to confirm that samples were collected and AEs, SAEs, and concomitant medications have been assessed. If needed, site may ask about AEs, SAEs, and concomitant medications over the phone.

[3] Visit window is ± 4 days. If a dose escalation occurs, blood should be drawn for safety laboratory assessments by the visiting healthcare service or at the clinic 72 to 96 hours after escalation.

[4] Any patient who discontinues study drug will complete Taper and Follow-up Periods. T1 and T2 may be done through VHA or via phone call on Day 3 and Day 6 of the Taper Period. If a patient discontinues from the study for any reason, all early termination patients should follow Week 24/ET Visit assessments. See Section 7.2 for tapering instructions.

[5] Patients will be provided with sufficient study drug to last until their next appointment. At dose escalation visits, patients will return to the clinic to be dispensed study drug and receive new dosing instructions.

[6] PROs and QoLs should be performed as early as possible during clinic visits. If patient is to receive infusion of their C5 inhibitor agent on a clinic visit where PROs and QoLs will be obtained, it is recommended that patients fill the PROs and QoL instruments before the C5 inhibitor infusion. PRO and QoL questionnaires will be administered at Weeks 40, 56, and 72, and Weeks 88, 104, and 120, if applicable.

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

[8] Any positive test will be confirmed by a follow-up serum pregnancy test.

[9] Tests will be performed at Weeks 40, 56, 72 and Weeks 88, 104, and 120, if applicable.

[10] F/U: Clinic visit 30 (+ 7) days after the last dose of the study drug. Patients will be instructed to bring back all remaining study drugs on this visit. See Section 7.2.

Table 4: PK and PD Blood Sampling Schedule and Approximate Volumes

Test	Blood Collection on Day 1 Volume (mL)[1]	Blood Collection on Other Scheduled Visits Week 4, Week 12, Week 16, Week 24 (mL)[1]	Matrix Types
PK	2 mL predose 2 mL postdose	2 mL predose 2 mL postdose	Plasma
AP activity	1 mL predose 1 mL postdose	1 mL predose 1 mL postdose	Serum
FD	2 mL predose	2 mL predose	Plasma
Bb	2 mL predose 2 mL postdose	2 mL predose	Plasma
C3	1 mL predose	1 mL predose	Serum
CP activity	1 mL predose	1 mL predose	Serum
Free C5	1 mL predose	1 mL predose	Serum
Volume	15 mL	13 mL * 4 visits = 52 mL	
Total volume	67 mL[2]		

Predose = immediately prior to in-clinic dose administration; postdose = 2 ± 0.5 h after in-clinic dose administration
Abbreviations: AP = alternative pathway; Bb = Bb fragment of complement factor B; C3 = complement protein 3; C5 = complement protein 5; CP= classical pathway; FD = factor D; PD = pharmacodynamics; PK = pharmacokinetics.

[1] During PK/PD sampling visits, patients are instructed to bring their study drug to the clinic. Patients should have a snack and take their dose of study drug in the clinic 15 to 30 minutes post snack. Site should collect accurate information on the timing when patient takes the last 2 doses prior to the in-clinic dose, and the missing doses (morning, noon, or evening) in the last 2 days. Site will obtain a predose sample and a 2 ± 0.5 hours postdose PK sample. PD samples should be taken at the same time as the PK samples (pre- and postdose). Actual sampling time and the most recent dose time prior to sample collection should be recorded.

[2] Volumes may slightly vary depending on site and laboratory specifications. Details are provided in the study laboratory manual.

2. INTRODUCTION

Danicopan (ALXN2040, previously ACH-0144471), a small molecule, orally administered, factor D (FD) inhibitor, is being developed for the treatment of complement-mediated diseases, such as paroxysmal nocturnal hemoglobinuria (PNH) and C3 glomerulopathy (C3G). Factor D is a serine protease that catalyzes the cleavage of factor B (FB), a rate-limiting step in the alternative pathway (AP) of complement. By inhibiting FD, danicopan potently and specifically inhibits AP activity.

Interim data from a Phase 2 proof-of-concept study (ACH471-101) has demonstrated the efficacy of danicopan, in addition to eculizumab, a C5 inhibitor, at stable dose and regimen, to increase hemoglobin levels after 24 weeks of treatment in PNH patients. Results from this ongoing Phase 2 combination study demonstrates clinically significant improvements in both the primary and secondary endpoints. A mean increase in hemoglobin ≥ 2 g/dL was demonstrated, from a baseline mean of 7.9 g/dL. The efficacy was observed as early as Week 2 of treatment with danicopan for most patients.

This pivotal study will assess the efficacy and safety of danicopan in patients who have clinically evident extravascular hemolysis (EVH) on a C5 inhibitor (eculizumab or ravulizumab).

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

2.1. Study Rationale

This study is a pivotal study designed to demonstrate that danicopan can increase hemoglobin relative to baseline in patients being treated simultaneously with an approved C5 inhibitor.

C3 fragment deposition on PNH red blood cells (RBCs) during C5 inhibitor treatment is a likely cause for suboptimal response due to extravascular clearance of PNH RBCs coated by C3 fragments (Risitano, 2009). Danicopan inhibits the complement cascade upstream of C3 and also blocks the complement amplification loop. Danicopan has been shown to prevent deposition of C3 fragments on PNH erythrocytes *ex vivo* (Yuan, 2017). As a result, both intravascular hemolysis (mediated by the activation of the complement terminal pathway) and extravascular hemolysis (EVH, likely via C3 fragment opsonization) could be blocked or significantly attenuated by danicopan. In addition, although danicopan 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. Lastly, FD is among the lowest plasma concentrations of all complement plasma proteins, making it a more druggable target.

Currently approved treatments for PNH are the humanized monoclonal antibodies C5 inhibitors eculizumab (Soliris®) and ravulizumab (Ultomiris®). In countries where these products are authorized, eculizumab and ravulizumab will be used in this study as commercial background therapies. However, the ultimate intent and scope of this study is to evaluate the benefit/risk of danicopan as add-on therapy to C5 inhibitors in PNH patients.

2.2. Background

2.2.1. Complement Factor D

Factor D is one of nine serine proteases in the complement system. It 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 is the rate-limiting step of AP activation (Figueroa, 1991, Volanakis, 1996). It 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, Volanakis, 1996). 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 (PNH) is a rare disease that has a reported prevalence of approximately 16 per million people (Hill, 2007). PNH may occur at any age; it has been reported in children as young as 2 years to adults as old as 83 years, but it is most frequently diagnosed in adults, with a median age at diagnosis of approximately 40 years (Curran, 2012, Hillmen, 1995). Men and women are affected equally, and no familial tendencies exist.

PNH is caused by a somatic mutation in the phosphatidylinositol N-acetylglucosaminyl transferase subunit A (PIG-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 intravascular hemolysis mediated by the membrane attack complex of complement and to extravascular hemolysis, presumably mediated by C3 fragment opsonization, primarily due to constitutive activation of the complement AP via the tick over mechanism (Schubert, 2015). In addition to anemia that can require frequent RBC transfusions, PNH patients are at high risk for thrombotic events, which can be life-threatening and is the major cause of morbidity and mortality in untreated patients. PNH patients also experience smooth muscle dysfunction (e.g., dysphagia, erectile dysfunction, abdominal pain), presumably related to the liberation of intracellular hemoglobin (Hgb) and 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 morbidity and 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.

Currently approved treatments for PNH are the humanized monoclonal antibody C5 inhibitors eculizumab and ravulizumab and the C3 inhibitor pegcetacoplan. Although C5 inhibitors prevent intravascular hemolysis by inhibiting formation of the membrane attack complex, approximately 30% of patients on eculizumab continue to have ongoing extravascular hemolysis (Debureaux, 2019).

2.3. Benefit/Risk Assessment

2.3.1. Meningococcal Infection

Since a primary function of the complement system is to fight infections, pharmacologic inhibition of the complement system could theoretically result in an increased rate or severity of infections. As suggested by individual case reports with complement system deficiencies, including FD, inhibition of the complement system may result in a lifetime increased risk of infection, notably with *Neisseria meningitidis* (Biesma, 2001, Hiemstra, 1989, Sprong, 2006) .

Patients receiving complement inhibitor therapy such as C5 inhibitors, in general, may have increased susceptibility to increased risk of bacterial infections, particularly *Neisseria meningitidis* (Socié, 2019). However, this risk remains theoretical for FD inhibition as the classical pathway of complement is not inhibited by FD blockade and FD inhibition appears to have little impact on serum bactericidal activity in vaccinated or previously exposed patients (Konar, 2017).

To reduce the risk of meningococcal infection, all patients must be vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug. Patients who initiate study drug 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 (e.g., Advisory Committee on Immunization Practices ([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.

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. 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 and throughout the study as described in the Schedule of Assessments in Section 1.2.

2.3.2. Liver Enzyme Elevations

In human healthy volunteers, elevations in alanine aminotransferase (ALT) levels have been observed in the multiple ascending dose study (ACH471-002) with the high doses of 500 mg twice daily and 800 mg twice daily for 14 days (Investigators Brochure). These ALT elevations were not associated with signs or symptoms of hepatic failure, occurred after completion of dosing, and were self-limited.

Transient elevations in transaminases have occurred in the Phase 2 PNH studies, some in association with breakthrough hemolysis. These transient elevations were not associated with evidence of hepatic decompensation and resolved within a short time period. Liver function tests including, ALT, aspartate aminotransferase (AST), alkaline phosphatase (ALP), γ-glutamyl transferase (GGT), and total, direct, and indirect bilirubin are being closely monitored in all clinical studies to ensure early identification of any potential cases of drug-induced liver toxicity. Rigorous stopping criteria are included ensuring prompt discontinuation of any patient with evidence of liver injury (see Section 7).

2.3.3. 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 10.6. Risk assessment for COVID-19 vaccination is described in Section 10.7.

2.3.4. Benefits

PNH is a serious, life-threatening disease, and there are unmet needs in this population that are not addressed by an approved C5 inhibitor that could potentially be addressed by an effective oral FD inhibitor. Three groups of patients whose PNH is not adequately controlled have been identified:

- In patients who have a suboptimal response to eculizumab or ravulizumab, C5 inhibitors have been used to control intravascular hemolysis, leading to reduction of thrombo-embolic events and improved survival. However, 20%-50% of patients remain transfusion-dependent due to persistent extravascular hemolysis (EVH), and 20%-40% of patients exhibit different degrees of residual anemia (Risitano, 2020). Danicopan 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 or ravulizumab due to a genetic polymorphism in 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 danicopan.
- Rare patients (~1%) with no response to eculizumab or ravulizumab due to mutations in C5 (e.g., Arg885His) (Nishimura, 2014) could also benefit from danicopan because it acts at a different target in the complement cascade and should be unaffected by a mutation in C5.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of danicopan as compared to placebo as add-on therapy to a C5 inhibitor at 12 weeks	• Change in hemoglobin (Hgb) relative to baseline after 12 weeks of treatment with danicopan compared to placebo
Secondary	
Key Secondary	
• To evaluate the efficacy of danicopan on Hgb improvement in absence of transfusion as compared to placebo as add-on therapy to a C5 inhibitor at 12 weeks	• Proportion of patients with Hgb increase of ≥ 2 g/dL at Week 12 in the absence of transfusion
• To evaluate the efficacy of danicopan as compared to placebo as add-on therapy to a C5 inhibitor on transfusion avoidance at 12 weeks	• Proportion of patients with transfusion avoidance (TA), defined as patients who remain transfusion-free and do not require a transfusion as per protocol-specified guidelines through Week 12
• To evaluate the effect of danicopan as compared to placebo as add-on therapy to a C5 inhibitor on Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue scores for 12 weeks of treatment	• Change from baseline in FACIT Fatigue scores at Week 12
• To evaluate the effect of danicopan as compared to placebo as add-on therapy to a C5 inhibitor on absolute reticulocyte count	• Change from baseline in absolute reticulocyte count at Week 12
Other Secondary	
• To evaluate the efficacy of danicopan as add-on therapy to a C5 inhibitor on transfusion requirements at 24 weeks for those patients receiving 24 weeks of danicopan	• Change in the number of red blood cell (RBC) units transfused and transfusion instances during the 24 weeks of treatment with danicopan compared to the 24 weeks prior to initiation of treatment with danicopan • Percentage of patients who have transfusion avoidance through 24 weeks of treatment

Objectives	Endpoints
• To evaluate the efficacy of danicopan as compared to placebo as add-on therapy to a C5 inhibitor on transfusion requirements at 12 weeks	• Change in the number of RBC units transfused and transfusion instances during the 12 weeks of treatment with danicopan compared to the 12 weeks while receiving placebo
• To evaluate the effect of danicopan as add-on therapy to a C5 inhibitor on Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue scores for 24 weeks of treatment	• Change from baseline in FACIT Fatigue scores at Week 24 in all patients
• To assess the efficacy of danicopan as add-on therapy to a C5 inhibitor on Hgb stabilization	• Percentage of patients with Hgb stabilization during the last 12 weeks of treatment in patients receiving 24 weeks of danicopan
• To evaluate the efficacy of danicopan on Hgb improvement in absence of transfusion as add-on therapy to a C5 inhibitor at 24 weeks	• Proportion of patients with Hgb increase of ≥ 2 g/dL at Week 24 in the absence of transfusion
• To assess additional laboratory markers relevant in PNH patients	• Change from baseline of danicopan treated patients compared to placebo in total and direct bilirubin at 12 weeks • Changes in PNH RBC clone size and C3 fragment deposition on PNH RBCs at 12 weeks of treatment with danicopan compared to placebo • Changes in lactate dehydrogenase (LDH) at 12 weeks • Percentage of patients with Hgb normalization at 12 weeks and 24 weeks

Objectives	Endpoints
Exploratory	
• To assess Patient-Reported Outcomes (PRO) and other health-related quality of life (QoL) measures during 24 weeks of treatment	• Change from baseline relative to placebo in Three-level EuroQoL 5 dimensions (EQ-5D-3L) scores at Week 12 • Change from baseline in EQ-5D-3L scores at Week 24 • Change from baseline relative to placebo in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 Scale (QLQ-C30) at Week 12 • Change from baseline in EORTC-QLQ-C30 scale at Week 24 • Change from baseline relative to placebo in Work Productivity and Activity Impairment Questionnaire: Anemic Symptoms (WPAI: ANS) at Week 12 • Change from baseline in WPAI:ANS scores at Week 24 • Change from baseline relative to placebo in Healthcare Resource Utilization (HRU) at Week 12 • Change from baseline in HRU scores at Week 24
• To characterize PK and PD of danicopan	• Plasma concentrations of danicopan over time • Changes from baseline in PD biomarkers
Safety	
• To evaluate the safety and tolerability of 24 weeks of treatment with danicopan as add-on therapy to a C5 inhibitor	• Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), laboratory abnormalities, and events leading to discontinuation of study drug during Treatment Periods 1 and 2
• To evaluate the safety and tolerability of danicopan as add-on therapy to a C5 inhibitor during the LTE Period	• Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), laboratory abnormalities, and events leading to discontinuation of study drug

4. STUDY DESIGN

4.1. Overall Design

This is a multiple-region, randomized, double-blind, placebo-controlled, multiple-dose, Phase 3 study in patients with PNH who have clinically evident EVH on a C5 inhibitor (eculizumab or ravulizumab). This study will include approximately 84 patients who are receiving a background therapy with an C5 inhibitor according to the usual dose and schedule and continue to experience anemia with or without the need of transfusion. Randomization will be stratified by transfusion history (ie, > 2 or ≤ 2 transfusions within 6 months of Screening) and Hgb (ie, < 8.5 g/dL and ≥ 8.5 g/dL) at Screening, and Japanese patients (defined as patients enrolled from Japan)/non-Japanese patients.

Patients will be randomized to danicopan tid or placebo tid, in a 2:1 ratio for 12 weeks (Treatment Period 1) in addition to their background C5 inhibitor (eculizumab or ravulizumab). At Week 12, patients randomized to receive placebo will be switched to danicopan for an additional 12 weeks (Treatment Period 2) and patients randomized to danicopan will continue on danicopan for an additional 12 weeks while remaining on the ongoing C5 inhibitor therapy.

This is followed by a 2-year long-term extension (LTE Period), period in which patients will continue to receive danicopan + C5 inhibitor therapy.

In this study, patients will have been on an approved C5 inhibitor for a time period sufficient to receive the full benefit of the therapy but remain anemic. Prolonged therapy with a C5 inhibitor alone is not projected to have additional impact on their clinical response. Historical transfusion needs and pretransfusion Hgb levels will be captured for 52 weeks prior to the Screening visit. These historical data will be used to assess the efficacy and safety of combination therapy in this study.

The screening hematology assessments should occur no earlier than 4 weeks after a transfusion, if possible in order to minimize the effect of the transfusion on the screening Hgb level, which will be used for stratification purposes. If patient's transfusion needs do not allow for this 4-week interval, the patient may still be screened.

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 drug. Patients who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. (see Section 6.5.2).

The starting dose of danicopan or placebo is 150 mg tid. A minimum of 4 weeks of treatment will be required at each dose level before any subsequent escalation to the next dose level. Doses may be escalated to a maximum of 200 mg tid based on safety and clinical effect at protocol-specified time points (Week 6, Week 12, and Week 18) (See Section 6.6 dose escalation guidelines). All dose escalations will be made on a patient-by-patient basis at the discretion of the Principal Investigator to a maximum of 200 mg tid, in consultation with the Sponsor. The maximum dose is 200 mg tid. Patients may not switch from their Day 1 C5 inhibitor to any other approved C5 inhibitor during the first 24 weeks of the study but may do so during the LTE Period (see Section 6.5.1).

The C5 inhibitor + placebo Group will be dose escalated in the same manner as the C5 inhibitor + danicopan Group during the study to maintain the blind to the patient. After all patients have completed Week 12, the C5 inhibitor + placebo group will switch from placebo to danicopan, starting at the 150 mg tid dose with opportunity to be escalated to 200 mg tid during Treatment Period 2.

All patients will return to the clinic for safety and other protocol-specified assessments during Treatment Period 1, Treatment Period 2 and during the LTE Period as shown in Table 1,Table 2, and Table 3, respectively. Patients will have the option to have some designated visits performed either in-clinic or via the home healthcare service provided by the 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.

Upon completion of the Treatment Period 2 (Week 24), patients may enter the LTE Period at the same danicopan dose they were receiving at Week 24, in addition to their background C5 inhibitor therapy. During the LTE Period, patients may be dose escalated to a maximum of 200 mg tid, at the discretion of the Principal Investigator and in consultation with the sponsor.

The LTE period will consist of a first year of LTE (Year 1) and a second year of optional LTE (Year 2). All patients will complete 72 weeks of LTE (Year 1) assessments as shown in Table 3. After Week 72 (at the end of the first year of LTE), patients have the choice to complete participation in this study or continue to the optional second year of LTE. Once Study ALXN2040-PNH-303 opens for enrolment, all patients participating in the second optional year of LTE must transition without treatment interruption to Alexion Study ALXN2040-PNH-303, completing the End of Treatment Period Visit as soon as possible (no taper or follow up visits are required), or complete participation in the current study by completing the End of Treatment Period Visit, plus Taper and Follow Up Visits as soon as possible. See Section 4.4 for definition of study completion.

If a patient discontinues from the study, dosing of study drug should be tapered over 6 days (Taper Visit 1 and 2), and a Follow-up Visit will be conducted approximately 30 days after the last dose of study drug during the Tapering Period. Patients will continue to receive C5 inhibitor therapy at the same dose and interval that they were receiving during the taper and follow-up visits.

4.2. Scientific Rationale for Study Design

The purpose of this study is to evaluate whether patients with clinically evident EVH on a C5 inhibitor therapy (when administered a therapeutic dose), may benefit from the addition of danicopan.

A recent report showed that eculizumab failed to completely block terminal pathway activity in several clinically relevant situations ex vivo (Harder, 2017). Terminal pathway inhibition by eculizumab became less effective as more complement was activated. The degree of residual terminal pathway activity in the presence of eculizumab correlated with the number of surface-deposited C3b molecules. Addition of danicopan to reduce the density of C3b is expected to convert the incomplete terminal pathway inhibition by eculizumab into complete inhibition, leading to a synergistic effect. To test this, an *in vitro* study was conducted to assess the synergy of danicopan combined with eculizumab. The study was performed in an AP-

dependent hemolytic assay using RBCs from a PNH patient and 20% normal human serum in the presence of 10 mM Mg^{2+}+EGTA. A strong synergy in protection of PNH RBCs from hemolysis was observed, suggesting the potential for a similar synergistic effect in the clinical setting. This experiment indicates that danicopan doses of ≤ 200 mg tid could contribute meaningfully in a combination regimen with eculizumab.

Enrollment in the Phase 2 dose-finding, open-label study of danicopan in patients with PNH who have been treated with eculizumab has been completed. The study allowed for dose escalation at 4-week intervals through Week 12, with additional escalations permitted after Week 12, based on biochemical and clinical response. Results from this ongoing Phase 2 combination study continue to demonstrate clinically significant improvements in both the primary and secondary endpoints. In addition to the rise in Hgb that has been observed in patients receiving danicopan and improvements in reticulocyte counts and bilirubin levels, near elimination of RBC transfusion needs over the 24-week treatment/study period has also been demonstrated.

Both eculizumab and ravulizumab patients will be included as the C5 inhibitor therapy. Both agents are utilized in the real-world setting as a standard of care, those patients who have clinically evident EVH on either eculizumab or ravulizumab will be enrolled in this study. The study will enroll at least 35% of the patients with ravulizumab as the C5 inhibitor therapy.

4.3. Justification for Dose

Details regarding healthy volunteer dose-ranging studies can be found in the Investigator's Brochure. To date, doses up to 200 mg tid as monotherapy in the ACH471-100 study have demonstrated clinically significant improvements in Hgb, LDH, and patient reported well-being. Treatment has been generally well tolerated.

The dose range used in the proof of concept study (ACH471-101) was 100 to 200 mg tid. This range was clinically effective and generally well tolerated in patients with PNH on a C5 inhibitor. In this prior study, 150 mg tid was a reasonable effective starting dose in a subset of patients, with upward titration based on clinical response to 200 mg tid. Approximately 25% of patients in this study were escalated to the 200 mg dose during the 24-week treatment period. Patients with abnormalities of ALT and/or direct bilirubin at baseline received a starting dose of 100 mg tid and were cautiously escalated based on clinical response, up to the maximum of 200 mg tid. No hepatic safety signals have been identified at starting doses of either 100 or 150 mg in the danicopan clinical studies. Based on the safety data of all patients treated with danicopan in studies ACH471-101, ACH471-103, ACH471-204, and ACH471-205, along with the efficacy data observed in study ACH471-101 (danicopan + C5 inhibitor) and PK/PD modeling and simulation, the 150 mg dose is considered to be the adequate starting dose for PNH patients. Therefore, in study ALXN2040-PNH-301, the starting dose of danicopan will be 150 mg tid. Dose increase will be made based on safety monitoring and Hgb levels and will not exceed 200 mg tid. Patients will continue to receive C5 inhibitor according to their usual dose and schedule.

The etiology of clinically significant, persistent anemia in the setting of C5 inhibition is extravascular hemolysis, which is mechanism based. C5 inhibition with eculizumab, or ravulizumab still allows for C3 cleavage and these cleavage fragments are then deposited on PNH RBCs, marking them for extravascular destruction. This process occurs independent of the half-life of the C5 inhibitor.

4.4. End of Study Definition

A patient is considered to have completed this study if at the end of the first year of LTE, they decide not to participate in the optional second year of LTE and completed the Week 72 Visit, plus the taper and follow up visits.

For those who enter the optional second year of LTE, a patient is considered to have completed this study if they:

- transition to ALXN2040PNH-303, after completing the end of treatment period visit at any time during the second year of LTE; no taper or follow up visits are needed for the transition

OR

- decide not to transition to ALXN2040-PNH-303, and complete the end of treatment period visit at any time during the second year of LTE, plus the taper and follow up visits

OR

- complete Week 120 visit, plus the taper and follow up visits.

The end of the study is defined as the date of the last follow up visit of the last patient in the study.

4.5. Data Monitoring Committee

An independent DMC comprising experts in relevant biomedical fields and one external statistician who have no direct relationship with the study will be appointed by the sponsor. The DMC will review and evaluate the accumulated study data for patient safety and make recommendations on continuing study drug administration. The DMC will review study information on a regular basis as outlined in the DMC charter, which is maintained separately from the study protocol.

Final decisions regarding the conduct of the study will be made by the sponsor after consultation with the DMC. All appropriate regulatory authorities and IRBs/IECs will be notified of any significant action.

Each member of the DMC will be required to sign a contract agreement, which includes a confidentiality and financial disclosure statement, assuring no conflicts of interest as a condition for membership on the committee.

The specific responsibilities of the DMC are described in the DMC Charter, which is maintained as a separate document.

5. STUDY POPULATION

5.1. Inclusion Criteria

Patients are eligible to be included in the study only if all of the following criteria apply:

1. Diagnosis of PNH.
2. Clinically evident extravascular hemolysis (EVH) defined by:
   - Anemia (Hgb ≤ 9.5 g/dL) with absolute reticulocyte count ≥ 120×10^9/L.
3. Receiving an approved C5 inhibitor for at least 6 months prior to Day 1 in this study at an approved dose (or higher) and with no change in the prescribed dose or interval for at least 24 weeks preceding Day 1. For those patients who recently switched from eculizumab to ravulizumab, they must have received at least the loading dose and 3 maintenance doses (minimum of 24 weeks) of ravulizumab preceding Day 1. Infusions outside the prescribed interval due to a logistical reasons/patient convenience are not considered a change in the prescribed interval and should be discussed with the Medical Monitor prior to randomization.
4. Platelet count ≥ 30,000/μL without the need for platelet transfusions.
5. Absolute neutrophil counts (ANC) ≥ 500/μL.
6. 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 drug. Patients who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination.
7. Age 18 years or older (or greater than or equal to minimum adult age in accordance with local legal requirements).
8. Female patients of childbearing potential must agree to use a highly effective or acceptable method of contraception from the date of signing the informed consent until the specified duration after the last dose of their background C5 inhibitor as per the product labelling. Female patients of childbearing potential must also have a negative serum pregnancy test during Screening and negative urine pregnancy test on Day 1.
9. Female patients with documented evidence of non-childbearing potential need not employ a method of contraception.
10. Nonsterile 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 to 90 days after their last dose of study drug.
    - Males who are surgically sterile need not employ additional contraception.
    - Males must agree not to donate sperm while enrolled in this study and for 90 days after their last dose of study drug.

11. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
12. Must have access to emergency medical care.
13. Patients who are on iron, folic acid, and vitamin B_{12} supplementation are eligible for the study if on a stable dose for at least 30 days prior to Day 1. See Section 6.5.

5.2. Exclusion Criteria

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

1. History of a major organ transplant (e.g., heart, lung, kidney, liver) or HSCT.
2. Known aplastic anemia or other bone marrow failure that requires HSCT or other therapies including anti-thymocyte globulin and/or immunosuppressants, unless the dosage regimen of immunosuppressant has been stable for at least 12 weeks before Day 1 and patient is expected to remain on stable doses through Week 24 (see Section 6.5).
3. Received another investigational agent other than C5 inhibitors (eculizumab or ravulizumab) 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, etc.) or any conditions leading to anemia that are not primarily due to PNH.
6. Active bacterial or viral infection, a body temperature >38°C on two consecutive daily measures, evidence of other infection, or history of any febrile illness within 14 days prior to first study drug administration.
7. History or presence of any clinically relevant co-morbidities that would make the patient inappropriate for the study (eg, 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).
8. Laboratory abnormalities at screening, including:
    - ALT > 2 × ULN (> 3 × ULN in the case of patients with documented liver iron overload defined by serum ferritin values ≥ 500 ng/mL). The inclusion of patients with documented iron overload and ALT > 2 × ULN will be done in a case by case basis, with prior discussion with the Medical Monitor.
    - Direct bilirubin > 2 × ULN, with the exception of:
        - patients who, in the opinion of investigator, have direct bilirubin > 2 × ULN due to EVH and/or
        - patients with documented Gilbert's syndrome (if Gilbert's syndrome is suspected, the patient will be tested for this condition at screening). See Section 8.1 for details.

9. Any other clinically significant laboratory abnormality as judged by the Investigator that, in the opinion of the Principal Investigator, would make the patient inappropriate for the study or put the patient at undue risk.
10. Females who are pregnant, nursing, or planning to become pregnant during the study or within 90 days of study drug administration.
11. Current evidence of biliary cholestasis.
12. 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 (HCV antibody positive), except for patients with documented successful treatment and documented sustained virologic response (SVR) at Screening
13. Evidence of human immunodeficiency virus (HIV antibody positive) infection at Screening
14. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 and/or are on dialysis.
15. Hypersensitivity to the investigational drug (danicopan) or any of its excipients

5.3. 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.

Prospective patients should be screened within 45 days of first administration of study drug. All evaluations must be completed before the patient is accepted into the study. If the patient is unable to receive study drug within 45 days of screening, the patient may be rescreened once.

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

For patients screened more than 45 days prior to the first administration of study drug, all screening procedures must be reassessed to confirm eligibility. In this case, patients must sign a new ICF but should be assigned the same patient number as for the initial screening.

6. STUDY DRUG

"Study Drug" in this protocol refers to danicopan or matching placebo.

Patients should take all doses of study drug approximately 15 to 30 minutes after eating a meal or snack. Water intake is not restricted.

6.1. Study Intervention Administered

Table 5: Study Interventions Administered

Compound Name	Danicopan (ALXN2040)	Placebo
Type	Drug	Placebo
Dose Formulation	Tablet	Tablet
Unit Dose Strengths	50 mg; 100 mg	50 mg; 100 mg
Dosage Levels	150 mg; 200 mg	150 mg; 200 mg
Route of Administration	Oral	Oral
Sourcing	Provided by sponsor	Provided by sponsor

The container closure system used to package danicopan film coated tablet is white high-density polyethylene bottle with white child resistant polypropylene screw cap, fitted with induction-sealed aluminum-faced liner.

Most doses will be taken outside of the clinic. Patients will be provided with sufficient study drug to last until their next study visit. On visits when PK/PD sampling is scheduled, the patients will be instructed to take their dose at the clinic to enable predose sampling. At dose escalation decision visits, patients will return to the clinic to be dispensed study drug and receive new dosing instructions. See time points in Section 1.2.

6.2. Preparation/Handling/Storage

At the pharmacy, study drug must be stored as provided at controlled room temperature (20°C to 25°C), with allowed excursion of 15°C to 30°C. Patients should be instructed to keep their study drugs in the original container at room temperature.

The Principal Investigator or designee (e.g., 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 drug. This includes acknowledgment of receipt of each shipment of study drug (quantity and condition) and patient dispensing records and returned or destroyed drug. Dispensing records will document quantities received from the Sponsor. (or designee) 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.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a double-blind, placebo-controlled Study with 2:1 randomization. The randomization scheme will be stratified by transfusion history (ie, > 2 or ≤ 2 transfusions within 6 months of Screening), Hgb (ie, < 8.5 g/dL and ≥ 8.5 g/dL) at Screening, and Japanese patients (defined as patients enrolled from Japan)/non-Japanese patients. The stochastic dynamic allocation rules on

the stratification factor will be used to assign patients to either danicopan or placebo treatment group at a 2:1 ratio through an interactive response technology (IRT) system on Study Day 1.

Although all patients will receive active drug during Treatment Period 2 and LTE Period, the treatment arm assignment during Treatment Period 1 will not be unblinded until after database lock occurs.

The IRT will be programmed with blind-breaking instructions. In the event that emergency unblinding is necessary, the IRT will provide clear step-by-step instructions for the investigator to follow. Details are also provided in the IRT Site User Guide.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make efforts to contact Alexion prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. If a participant's intervention assignment is unblinded, Alexion must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

6.4. Assessments of Study Drug Compliance

Patients will be required to bring their supply of study drug to each scheduled in-clinic 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 in-clinic dispensing visit.

6.5. Background and Concomitant Therapies

Use of specific concomitant medications other than a C5 inhibitor will be considered on a case-by-case basis with decisions made jointly between the Principal Investigator and sponsor, based on available knowledge of danicopan as well as the characteristics of the potential concomitant medication.

Details of all concomitant medication use, including all medications administered for the treatment of AEs, must be recorded in the patient's electronic case report form (eCRF). 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 30 days prior to Day 1; patients should be maintained on stable doses (without any modifications of quantity or frequency) of these agents through Week 24.
- Concomitant administration of steroids or other immunosuppressants is permitted if the dosage regimen is stable for at least 12 weeks before Day 1 and remain on stable doses through Week 24.
- Oral, injectable, implantable, transdermal, or intravaginal hormonal therapies are allowed for either contraception or hormonal replacement therapy.

- 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.

The use of concomitant medications during the study will be assessed at the time points indicated in Table 1.

6.5.1. Background C5 Inhibitor Therapy: Eculizumab and Ravulizumab

All patients are to be treated with study drug in combination with a C5 inhibitor therapy (i.e., eculizumab or ravulizumab) at the approved dosages for the purpose of data collection and analysis. C5 inhibitor used in this manner will be considered a background therapy. If patients switch to a different approved C5 inhibitor after completion of the study at Week 24, the new medication used in this manner will be also considered a background therapy.

Approved C5 inhibitor dose may not be increased, nor interval shortened, during this study (with the exception of ravulizumab weight-based dosing based on changes in weight). The dose of the C5 inhibitor may be decreased, if indicated, with a dose re-escalation to the prior dose if the dose reduction was not tolerated.

Changes in frequency of C5 inhibitor administration that are due to patient convenience or logistical reasons, but do not result in a change of the prescribed dosage and frequency are considered stable and should be discussed with the Medical Monitor prior to randomization.

Patients may not switch from their Day 1 C5 inhibitor to any other C5 inhibitor during the first 24 weeks of the study but may do so during the LTE period. The only authorized switch is from eculizumab to ravulizumab (possible only in those countries where ravulizumab is commercially available).

C5 inhibitor therapy will be provided according to local regulations and approvals.

6.5.2. Vaccines

To reduce the risk of meningococcal infection, all patients must be vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug. Patients who initiate study drug 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, Advisory Committee on Immunization Practices ([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 on once study drug

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 eCRF.

6.6. Study Drug Dose Modification

Doses of study drug (danicopan or placebo) may be escalated to a maximum of 200 mg tid, based on safety and clinical effect, at specified time points during the initial treatment period and during the LTE Period using the criteria below. All dose escalations decisions will be made based on central laboratory data and at the discretion of the Principal Investigator, in consultation with the sponsor. This applies to both Treatment Periods 1 and 2. The C5 Inhibitor + Placebo Treatment Group will be escalated in the same manner as the C5 Inhibitor + Danicopan Treatment Group during the study to maintain the blind.

6.6.1. Dose Escalation During Treatment Period 1

If the starting dose is well tolerated and the available safety data are satisfactory, a patient may be escalated to the next highest dose at the following time points:

- At the Week 6 Visit, if the patient's Hgb level at Week 4 has not increased by ≥2 g/dL from their baseline value (Day 1), or the patient received a transfusion during the previous 4 weeks.
- At the Week 12 Visit, if the patient's Hgb level at Week 10 has not normalized to at least the midpoint of the normal range for gender from their baseline value or the patient received a transfusion during the previous 4 weeks.

6.6.2. Dose Escalation During Treatment Period 2

- At the Week 18 Visit, if the patient's Hgb level at Week 16 has not normalized to at least the midpoint of the normal range for gender from their baseline value (Day 1) or the patient received a transfusion during the previous 4 weeks.

6.6.3. Dose Escalation During the LTE Period

- Any patient who has not already been dose escalated up to 200 mg study drug may be escalated up to a maximum of 200 mg danicopan tid, if they have been on their previous dose for at least 4 weeks and the Investigator believes that additional efficacy can be achieved. Dose escalations after Week 24 visit will be discussed with the sponsor before being implemented.

6.6.4. Monitoring After Drug Escalation

- If a patient has been dose escalated, laboratory blood samples for measurement of standard laboratory safety assessments should be obtained at the next week visit

following the escalation, either in clinic or via the visiting healthcare service as per the schedule of assessments.

At any time-point after the dose escalation, if patient safety or tolerability warrants dose reduction to the previous dose this may occur in consultation with the Sponsor. This dose reduction will only occur, if both Principal Investigator and the Sponsor agree that the patient will benefit from the lower dose.

Any patient who is at a dose of 100 mg tid upon implementation of this amendment, should be escalated to 150 mg tid at the next clinic visit (an unscheduled visit may be used for this purpose) and subsequently should follow the dose escalation guidelines outlined above.

6.7. Dose Interruptions

If danicopan dose is interrupted for any reason, an assessment should be made if the stop is temporary or the patient is to be withdrawn based on the criteria described in Section 7. Discussion about the reasons for interruption and plans for potential re-initiation should occur between the Investigator and the Alexion Medical Monitor. Re-initiation of treatment with danicopan should be done under careful clinical monitoring, including laboratory monitoring and after consultation with the Alexion Medical Monitor. If upon resumption of treatment, the patient has a recurrence of the event, permanent discontinuation should be considered as described in Section 7.1.

Any temporary preplanned treatment interruption should be discussed between the Investigator and the Alexion Medical Monitor and tapering should be considered (refer to Section 7.2).

The patient should continue participation until the end of the study unless the prespecified events for treatment discontinuation have been met. Any interruption of study drug and the reason for the interruption should be fully documented in the source documents and eCRF.

6.8. Transfusion Guidelines Before and During the Study

It is recommended to administer pRBC transfusion when a subject 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. If further matching for Kell and JK antigens can be conducted without delaying making the blood available for emergent transfusion, this additional testing is recommended. 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 pRBCs to be transfused. In the event of a transfusion is required, a blood sample for central lab is to be collected as an assessment 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

If study drug (danicopan or placebo) is discontinued for any reason, the dose will be tapered over a 6-day period as described in Section 7.2 below. Study drug will not be provided to the patients after the last scheduled dosing. After the end of therapy visit or Early Termination visit, all patients will be followed for an additional 30 days after the last dose of study drug.

7. DISCONTINUATION OF STUDY DRUG AND PATIENT DISCONTINUATION OR WITHDRAWAL

In rare instances, it may be necessary for a patient to permanently discontinue study intervention. If study intervention is permanently discontinued, the patient will taper the dose as described in Section 7.2, and will remain in the study for 30 days after last dose of study drug 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 Principal Investigator (or designee) may decide, for reasons of medical prudence or patient noncompliance, to discontinue dosing of study drug for an individual patient. The Principal Investigator will discontinue dosing study drug in any patient who meets an any reasons listed below, and should notify the Medical Monitor immediately, and if possible, before dosing is terminated. Patients will continue to receive C5 inhibitor therapy, as per the Principal Investigator's judgment but the study drug will be permanently discontinued.

Reasons for patient withdrawal may include:

- Intercurrent illness that would, in the judgment of the Investigator, affect assessment of clinical status to a significant degree
- Development of any of the following liver function test abnormalities in the absence of hemolysis:
  - ALT > 8 × ULN
  - ALT > 5 × ULN for more than 2 weeks
  - Increase of ALT > 3 × ULN and > 3 × from baseline and total bilirubin > 2 × ULN or INR > 1.5, in the absence of warfarin anticoagulation
  - Increase of ALT > 3 × ULN and > 3 × from baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)
- Patient withdrawal from their background C5 inhibitor. Investigators should follow the instructions on discontinuation and monitoring of the patient as outlined in the approved corresponding Summary of Product Characteristics (SmPC)/Local Product Information for eculizumab or ravulizumab.
- Persistent Grade 3-4 toxicity (including a clinically significant laboratory abnormality) despite appropriate intervention 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 non-compliance
- Discontinuation of the study at the request of the Sponsor, regulatory agency, or Ethics Committee or IRB

- Any other condition or circumstance that would jeopardize the welfare of the patient if s/he were to continue in the study
- The reason for any patient's discontinuation and the date of withdrawal will be recorded in the patient's eCRF. The patient's eCRF, 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 2 for treatment Week 24 should be performed as an early termination visit.

Upon first observation of ALT 3 × baseline, a repeat test must be performed (ALT, AST, direct bilirubin, and INR) within 48 to 72 hours. The site should contact the patient and inquire about the presence of any symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash).

If necessary for safety reasons, local laboratories are permitted to identify patients that may need to be discontinued from the study and results need to be discussed with the Medical Monitor, however the final discontinuation from the study requires central laboratory determinations and discussion with the Medical Monitor

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.

7.1. Study Stopping Criteria

A consideration for the dosing to be terminated may be implemented based on DMC recommendation, if one or more of the following occurs (see Section 2.3.2 on risks of liver enzyme elevations):

- Two or more patients discontinue study therapy due to liver function test abnormalities as detailed below
  - ALT > 8 × ULN
  - ALT > 5 × ULN for more than 2 weeks
  - Increase of ALT > 3 × ULN and > 3 × from baseline and total bilirubin > 2 × ULN or INR > 1.5, in the absence of warfarin anticoagulation
  - Increase of ALT > 3 × ULN and > 3 × from baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

Because patients may experience hemolysis which may result in increased bilirubin AST and even ALT, increases in bilirubin AST and/or ALT during the study must be evaluated in the context of hemolysis. The Principal Investigator will evaluate LDH and Hgb levels, as well as baseline bilirubin AST and ALT levels, to determine if the increases observed are due to an effect on liver function or are secondary to hemolysis. Any liver function test elevation felt to be associated with hemolysis (and not caused by study drug) will not be included in study stopping decisions.

Anytime a patient has to discontinue the study drug, the dose tapering instructions and schedule (see Section 7.2 and Table 6) should be followed unless the patient cannot tolerate tapering of study drug or the discontinuation is due to an SAE.

7.2. Dose Taper

If the study drug is discontinued or the dose is interrupted (Section 6.7), the dose of danicopan or placebo will be tapered over a 6-day period. The dosing taper regimen is described in Table 6. In addition, the taper schedule may be adjusted to allow for slower taper in a patient who is not tolerating discontinuation of drug.

If the patient withdraws from the study at any time, the patient will complete the Early Termination visit as soon as possible prior to tapering. Patients should take the study drug per protocol until the tapering period begins.

Table 6: Study Drug Taper Schedule

Danicopan or Placebo Dose at Termination	Taper Period 1 (T1) (Taper Days 1-3)	Taper Period 2 (T2) (Taper Days 4-6)
150 mg tid	100 mg tid	50 mg tid
200 mg tid	100 mg tid	50 mg tid

Abbreviations: tid = three times per day; T = taper
T1 and T2 visits may be 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.

Patients will continue to receive their approved C5 inhibitor at the same dose and interval during the taper and follow-up period that they were receiving during the treatment period.

7.2.1. 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 (+ 7) days after the last dose of study drug (danicopan or placebo). During the Follow-up Period, physical examinations, assessment of vital signs, all required safety laboratory testing, and collection of blood and urine samples will be performed at various time points in the clinic as specified in Table 3.

7.3. 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 Appendix 1.

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 1.2.

8.1. Screening Period

The Principal Investigator or designee is responsible for administering and obtaining freely given informed consent before the patient enters the study and before any study-related procedures are performed. Each patient will sign (written or electronic) an ICF (see Section 10.1.3). This may include additional consent forms for human immunodeficiency virus testing or other procedures which may be performed prior to patients being accepted into the study.

A window of up to 45 days is permitted to allow screening and any required vaccinations. Screening procedures may be spread over more than one visit within the 45-day screening period. The screening clinic and laboratory procedures listed in Section 10.2 must be performed and documented prior to dosing. This will include a review of the inclusion and exclusion criteria. The patient's medical history will be reviewed, and a complete physical examination will be conducted. The medical history should include the patient's transfusion history of a minimum of 52 weeks prior to screening. 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 B_{12} supplementation are eligible for the study if on a stable dose for at least 30 days prior to Day 1.

For women of childbearing potential, a serum pregnancy test must be negative to be eligible for the study.

All laboratory assessments for eligibility are performed by the central laboratory. However, use of local laboratories to determine eligibility will be permitted if the central laboratory cannot initially provide results for the following assessments: platelets, ANC, direct Coombs, D-dimer, and INR. If local laboratories are used to determine eligibility for the assessments stated above, a central laboratory sample should be obtained pre-dose on Day 1 to establish the patient's baseline values. Use of local laboratory values for eligibility s will need to be discussed with the Medical Monitor.

If screening laboratory assessments show elevated indirect bilirubin levels in conjunction with normal liver function tests (AST and ALT), or if the patient has a history of unexplained jaundice, unexplained high bilirubin levels, or a history otherwise suggestive of Gilbert's syndrome, the patient will be tested for this condition. If the patient has a history of Gilbert's syndrome it should be documented as the patient's medical history. Refer to the Laboratory Manual for testing procedure.

If the patient is unable to receive study drug within 45 days of screening, the patient may be rescreened once. The repeating of individual screening laboratory results that fall outside the reported normal range may be permitted on a case-by-case basis with the written preapproval of the Medical Monitor (or designee).

As part of the screening process, patients will be evaluated for vaccination requirements as detailed in Section 6.5.2.

8.2. Efficacy Assessments

Blood will be collected according to the Schedule of Assessments (see Section 1.2) to assess the efficacy endpoints of change in hemoglobin, reticulocyte counts, bilirubin, and lactate dehydrogenase. PNH RBC clone size, C3 fragment deposition on PNH RBCs, AP and classical pathway activities, and Bb, C3, FD, and free C5 levels will also be assessed. Blood collection procedures are described in Section 8.4.1.1.

Transfusion data, including the number of RBC units transfused, the associated pre-transfusion hemoglobin value (with reticulocyte count, if available) and the reason for transfusion will be collected from the time of screening until follow-up (from study site records and any other location where the patient receives any transfusions) and recorded in each patient's eCRF.

Given that the primary endpoint of the study is change from baseline in Hgb after treatment with danicopan vs placebo, and PNH RBCs are more prone to hemolysis during sample collection, management, and/or shipment, a backup central hematology sample must be obtained at the Week 12 and Week 24 visits for all patients.

8.3. Patient-Reported Outcomes

All patients enrolled in the study will self-administer questionnaires for the FACIT-Fatigue (Version 4), European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 Scale (QLQ-C30), and EQ-5D-3L (Visual Analogue Scale and Time Trade Off scores) scales and Work Productivity and Activity Impairment Questionnaire: Anemic Symptoms V2.0 (WPAI: ANS) (see Section 1.2). Local language versions of each of the tools will be provided separately.

Health Resource Utilization data will be collected as per schedule shown in Section 1.2. For HRU, the Investigator or designee will record for each participant the number of clinic visits, emergency services utilized, hospitalization, missed work and also record the number of times the patient had darkened urine. Local language versions of each of the tools will be provided separately.

All PROs and QoL assessments (written or electronic) will be administered before the treatment dose on Day 1. On other clinic visits, PROs and QoLs should be administered as early as possible. If patient is to receive infusion of their C5 inhibitor agent on a clinic visit where PROs and QoLs will be obtained, it is recommended that patients fill out the PRO and QoL instruments before the C5 inhibitor infusion.

8.4. Safety Assessments and Procedures

Safety will be evaluated by monitoring and assessment of AEs, clinical laboratory tests, physical examination findings, and vital signs measurements. Planned time points for all safety assessments are provided in Section 1.2. All findings must be recorded in the patient's source documents and in the patient's eCRF.

8.4.1. Clinical Laboratory Tests

Blood and urine samples will be collected for efficacy, safety, and PD laboratory evaluation as listed in Table 7 in Appendix 2 at the times indicated in Section 1.2.

If measurement of a serum complement pathway indicator is considered necessary by the Investigator, it should be discussed with the Medical Monitor and the procedures described for unblinding (see Section 6.3) and discontinuation of the patient from the study (see Section 7) should be followed.

8.4.1.1. Blood Collection

Patients will be in a seated 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.

Unanticipated additional blood may be collected throughout the study for safety monitoring and additional PD assessments, if necessary.

8.4.2. Physical Examinations

A complete physical examination will be performed at Screening and on Day 1 and will include an assessment of general appearance and a review of systems. Height (at screening only) and weight will also be measured and recorded. Measurements of height and weight should be taken with the patients in light clothing or underwear and without shoes.

A brief physical examination will be conducted at all other in-clinic visits, as indicated in Section 1.2. Additional brief, complete, or symptom-driven physical examinations may be conducted at the discretion of the Investigator or designee and/or when patients present with AEs.

8.4.3. Vital Signs

The Principal Investigator or designee will obtain blood pressure, heart rate, and respiration rate at the visits indicated in Section 1.2. Vital signs will be measured following a 5-minute rest. Vital sign values will be recorded in the patient's source documents and in patient's eCRF.

8.4.4. Electrocardiograms

The Principal Investigator or designee will obtain electrocardiogram (ECG) measurements at the times indicated in Section 1.2. 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: HR, RR, PR, 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 as contributing to the 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 Principal Investigator or designee. All ECG parameters and assessments must be recorded or stored in the patient's source documents and in patient's eCRF. Any clinically significant finding must be reported as an adverse event.

8.5. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE are in Appendix 3. Adverse events will be reported 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 on all AEs including those that are serious, considered related to the study intervention or study procedures, or that caused the patient to discontinue the study intervention.

8.5.1. 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 drug, at the time points specified in Section 1.2.

Medical occurrences, including pregnancies, that begin before the start of study intervention but after obtaining informed consent will be recorded as AEs. This does not include pre- or post-treatment complications that occur as a result of protocol-mandated procedures (e.g., invasive procedures, such as venipuncture or biopsy), which should be reported as AEs. Pregnancy is not considered an AE. A pregnancy occurring after the start of study intervention should be reported on the pregnancy forms, as described in Section 10.3.8.

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

Investigators are not obligated to actively seek AEs or SAEs 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 intervention or study participation, the Investigator must promptly notify the sponsor, (i.e., within 24 hours of the Investigator becoming aware of the event); such events are not entered into the eCRF).

8.5.2. Method of Detecting AEs and SAEs

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

8.5.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs will be followed 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 given in Appendix 3.

8.5.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study intervention 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 intervention under clinical investigation. The sponsor will ensure compliance with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Suspected unexpected serious adverse reactions (SUSARs) will 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 a SAE or other specific safety information (e.g., 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.

8.5.5. Pregnancy

Details of any pregnancy in female patients and/or female partners of male patients that occurs or is confirmed within the timelines listed in Section 8.5.1 will be collected. If a pregnancy is reported, the investigator should inform the sponsor within one business day of learning of the pregnancy and should follow the procedures outlined in Appendix 3 and Appendix 4.

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

8.6. Treatment of Overdose

For this study, any dose of study drug greater than the prescribed dose within a 24-hour period will be considered an overdose.

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

In the event of an overdose, the Investigator/treating physician should:

1. Based on the Investigator's judgement, contact the Sponsor's Medical Monitor
2. 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
3. Closely monitor the patient for any untoward effects of the overdose
4. Any overdose reported by the patient (purposeful or accidental) should be recorded as an AE at minimum and assessed for seriousness as appropriate
5. If necessary, based on consultation with the Sponsor's Medical Monitor, obtain a plasma sample for PK analysis or safety labs

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Sponsor's Medical Monitor.

8.7. Pharmacokinetics

Pharmacokinetics (PK) will be evaluated using plasma from whole blood collected during the study as outlined in Section 1.2. Study drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded. Additional information on sample collection and shipping instructions will be provided in a separate laboratory manual.

8.8. Pharmacodynamics

Pharmacodynamics will be evaluated using serum (for AP activity, C3, CP activity, and free C5) and plasma (for Bb and FD) from whole blood collected during the study as outlined in Section 1.2. PD assessments that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded. Additional information on sample collection and shipping instructions will be provided in a separate laboratory manual. The Sponsor may store samples for other biomarker tests for future research subject to local and regional regulatory approval.

8.9. Genetic Samples

Subject to patient consent, a sample will be collected at baseline (Day 1) for potential genetic analysis Appendix 5: Genetics. Genetic analyses may be conducted: 1) if a patient does not respond to the investigative drug; 2) if a patient experiences drug-related toxicity; or 3) to further characterize the underlying disease.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The null statistical hypothesis is the improvement in hemoglobin level from baseline at Week 12 for danicopan being similar to the improvement for placebo; defined as the difference in mean change from baseline between danicopan and placebo at Week 12 is zero.

9.2. Sample Size Determination

The PNH literature indicates that patients with PNH who have received an approved C5 inhibitor but are still anemic have hemoglobin levels, on the average, of 10.5 g/dL (McKinley, 2017). All patients entering this study will have a hemoglobin level of ≤ 9.5 g/dL. A minimum of 2 g/dL in difference between danicopan and placebo treatments in terms of mean improvement from baseline after 12 weeks of treatment is, considered clinically meaningful.

A total of approximately 84 patients will be enrolled into this study and randomized in a 2:1 ratio to danicopan and placebo study arms. It is anticipated that approximately 10% of patients will discontinue prior to the primary endpoint. For the primary endpoint of change from baseline to Week 12 in hemoglobin level, the statistical power using a two-sample t-test is 99% to detect the difference in mean change from baseline of 2 g/dL (alternative hypothesis), assuming the statistical significance level of 0.05 (two-sided) and the standard deviation of 1.6 g/dL, which is estimated from study ACH471-101. For the key secondary endpoint of patients with Hgb increase of ≥ 2 g/dL at Week 12 in the absence of transfusions, the study has >95% power assuming at least 35% of patients in the danicopan arm and 5% of patients in the placebo arm can meet the criterion. For the key secondary endpoint of patients with TA, the study has 70% power for the TA endpoint assuming 90% of patients in the danicopan arm and 64% of patients in the placebo arm will have TA. For the key secondary endpoint of change from baseline to Week 12 in FACIT-Fatigue score, the study has 91% power with a two-sample t-test to detect a 9-point difference between treatment arms in mean change from baseline, which is considered clinically meaningful. The power calculation is based on the assumption of a standard deviation of 11 for FACIT-Fatigue change, which was observed in Study ALXN1210-PNH-301 in PNH patients. The power is 80% based on the standard deviation assumption of 13, which was observed in Study ACH471-101.

9.3. Populations for Analyses

The analysis populations are as follows:

- Intent-to-treat (ITT) population: All randomized patients; data will be analyzed by the treatment groups to which patients are randomly assigned, even if the patient does not take the assigned treatment, does not receive the correct treatment, or does not comply with the protocol.
- Per Protocol population: Intent-to-treat (ITT) patients who do not have protocol deviations expected to affect the primary efficacy endpoint (Week 12). Such protocol deviations will be prespecified in the statistical analysis plan prior to database lock.
- Safety population: All patients who take at least one dose of danicopan or placebo.

If the ITT population and Per Protocol population have a similar number of patients (<5% difference), analyses will not be performed using the Per Protocol population.

9.4. Statistical Analyses

Categorical variables will be summarized with counts and percentages. Continuous variables will be summarized with univariate statistics (e.g., mean, median, standard error).

Longitudinal summaries of efficacy and safety parameters will use pre-defined visit weeks. Visit windows around planned measurement times will be constructed, if appropriate, based on the midpoint between planned study visits.

Efficacy and safety analysis results will be presented for both Treatment Periods of the study and by treatment group (danicopan and placebo).

9.4.1. Patient Disposition and Demographic/Baseline Characteristics

The number and percentages of patients will be provided for patient disposition for each study population. For enrolled patients who are not randomized, reasons for not being randomized will be listed and summarized. For patients who are randomized but do not receive study therapy, reasons for not receiving study therapy will be listed and summarized. For patients who are excluded from Per Protocol population, primary reasons of being excluded will be listed and summarized.

Frequency distribution and summary statistics for demographic and baseline variables will be summarized. Key demographic and baseline variables to be summarized include geographic region, age, gender, race, height, weight, body mass index, RBC transfusion history 52 weeks prior to screening, approved C5 inhibitor prior to screening, hemoglobin level, reticulocyte count, platelet count, and neutrophil count.

The summaries will be tabulated for the safety population and also for the Per Protocol population if the analysis is performed on the Per Protocol population.

9.4.2. Study Drug Exposure, Compliance, and Concomitant and Background Therapies

Overall percent compliance to danicopan and placebo dosage regimen, calculated as the percentage of doses taken relative to doses scheduled to be taken, will be summarized. Extent of exposure in days will be evaluated and summarized from the first dose date to the last dose date of danicopan or placebo during both treatment periods.

Concomitant medication/therapy and background therapy verbatim terms will be coded using the latest version of the World Health Organization Drug Dictionary. The numbers and percentages of patients in each treatment group taking concomitant/background medications will be summarized by anatomic and therapeutic chemical classification and preferred term.

Note that an approved C5 inhibitor taken regularly with danicopan or placebo during double-blind and open-label treatment periods is considered background therapy. The extent of exposure of approved C5 inhibitors taken during treatment periods will be presented separately from concomitant therapies.

9.4.3. Efficacy Analyses

Summary statistics for the baseline and post-baseline measurements, and changes from baseline will be presented by pre-defined visit for all continuous efficacy variables to be analyzed.

9.4.3.1. Primary Efficacy Analysis

The primary efficacy endpoint is change in hemoglobin at Week 12 relative to baseline (defined as the lowest Hgb value, between and including screening and Day 1) between danicopan and placebo. The longitudinal changes from baseline in hemoglobin will be analyzed using a mixed model for repeated measures (MMRM) (Mallinckrodt, 2001, Mallinckrodt, 2004) which includes the fixed, categorical effects of treatment, study visit, and study visit by treatment group interaction as well as the continuous, fixed covariate of baseline hemoglobin value and the stratification randomization indicator of transfusion history in the model. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

The primary objective is to evaluate the efficacy of danicopan as compared to placebo on change in hemoglobin after a 12-week of treatment. To address the impact of transfusion on hemoglobin values, for patients who are transfused on or after Week 8, the hemoglobin value collected at Week 12 will not be included in the primary efficacy analysis. This rule will also apply to longitudinal observations collected at earlier visits, ie, hemoglobin values collected within 4 weeks after transfusion will not be included in the primary efficacy analysis.

The primary test for statistical significance of the treatment group difference between danicopan and placebo in Hgb change from baseline to Week 12 will be conducted via a re-randomization test method at the 2-sided 0.05 significance level. Iterations of re-randomized treatment assignments will be simulated for all randomized patients using the same original randomization algorithm, while keeping patient stratification factors values and entry order as observed and used in the actual randomization. For each set of the re-randomized treatment assignments, an estimate of treatment group difference will be obtained by using the same MMRM model as specified above. The p-value for the re-randomization test will be calculated as the number of re-randomized treatment group differences that are more extreme than the treatment group difference calculated under the actual randomization (ie, absolute value of re-randomized group difference larger than the absolute value of group difference under the actual randomization) divided by the total number of simulated re-randomizations.

With the relatively small sample size and short duration of blinded treatment (12 weeks), all efforts will be made to minimize missing Week 12 measurements. Longitudinal graphic presentations will also be provided to examine the hemoglobin profile throughout 12 weeks of treatment with danicopan or placebo, plus an approved C5 inhibitor.

The primary efficacy analysis will be based on the ITT population. The re-randomization test for treatment group differences will be considered as the primary analysis. The test for treatment group differences directly from the MMRM model using the actual treatment assignments will also be reported as a sensitivity analysis. A supportive analysis will be carried out for the primary efficacy endpoint, changes in Hgb measurement, based on the Per Protocol population to examine the impact of major protocol deviations. Additional sensitivity analyses will be performed to assess the treatment effect under alternative missing data mechanism assumptions. The details of such analyses will be specified in the statistical analysis plan.

9.4.3.2. Secondary Efficacy Analysis

The secondary efficacy endpoints are listed in Section 3. The secondary efficacy analysis will be conducted on the ITT population.

Key secondary efficacy endpoints, in order of importance, are described below. Hierarchical fixed sequence test procedure is utilized to determine the statistical significance at two-sided level of 0.05 for each endpoint sequentially.

1. Difference in proportion of patients with Hgb increase of ≥ 2 g/dL at Week 12 in the absence of transfusions
2. Difference in proportion of patients with RBC transfusion avoidance between danicopan and placebo groups during the 12 weeks of treatment
3. Difference in changes from baseline in FACIT-Fatigue scores between danicopan and placebo groups at Week 12.
4. Difference in changes from baseline in absolute reticulocyte counts between danicopan and placebo groups at Week 12.

For the parameter of proportions such as patients with Hgb increase of ≥ 2 g/dL at Week 12 in the absence of transfusions (defined as achieving ≥ 2 g/dL increase in Hgb from baseline to Week 12 and remaining transfusion free during 12-week Treatment Period 1), patients achieving transfusion avoidance and Hgb normalization at Week 12, the Cochrane-Mantel-Haenszel test will be used to compare between danicopan and placebo arms.

For the changes in RBC transfusion units/instances from 12 weeks prior to initiation of treatment to 12-week Treatment Period 1, an analysis of covariance (ANCOVA) model including treatment arms and transfusion units/instances from 12 weeks prior to treatment initiation will be used to compare between danicopan and placebo arms.

For change from baseline in numeric endpoints such as FACIT-Fatigue scores, EQ-5D-3L scores, EORTC QLQ-C30 scores, absolute reticulocyte count, total and direct bilirubin, or other PNH-related biomarkers at Week 12 the MMRM model as specified in the primary efficacy analysis will be employed to compare the mean difference between danicopan and placebo.

The hierarchical fixed sequence test procedure calls for the current hypothesis to be rejected; that is, if the p-value for test statistic is < 0.05, then proceed to test the significance of the next hypothesis from the key secondary endpoints listed above by clinical importance. The sequential testing process will be stopped when the hypothesis cannot be rejected.

Results based on various statistical procedures used to analyze data for the remaining secondary efficacy and exploratory endpoints will be descriptive as follows:

- Number and proportion of patients with hemoglobin stabilization during the last 12 weeks of treatment, for patients receiving 24 weeks of danicopan treatment. Hemoglobin stabilization is defined as avoidance of no more than a 1.0 g/dL decrease in Hgb levels at Week 24 from Week 12.
- Change in RBC transfusion units/instances from 24 weeks prior to initiation of treatment to the 24-week treatment period for patients receiving 24 weeks of danicopan treatment.

- Proportion of patients with Hgb increase of ≥ 2 g/dL at Week 24 in the absence of transfusions, proportion of patients with transfusion avoidance through 24 weeks treatment period and proportion of patients with hemoglobin normalization at Week 24
- Change in FACIT-Fatigue, absolute reticulocyte count, total and direct bilirubin, LDH and other PNH-related biomarkers relative to baseline (Day 1) for patients receiving 24 weeks of danicopan treatment.
- Change from baseline in PNH RBC clone size, C3 fragment deposition on PNH RBCs, measures of alternate pathway and classical pathway activity, Bb, C3, and FD levels at Week 12 and Week 24.
- Change from baseline in exploratory PRO and QoL endpoints at Week 12 and Week 24.

9.4.4. Analyses of Safety

All safety analyses will be conducted on the safety population. The evaluation of safety will be performed separately for the 12-week blinded Treatment Period 1, subsequent 12-week Treatment Period 2, and the LTE for all patients exposed to danicopan, from the first dose to the end of the LTE. The safety analysis will be based primarily on the frequency of adverse events, clinical laboratory assessments, vital signs, and 12-lead ECG. Other safety data will be summarized if deemed clinically meaningful.

Descriptive statistics using summary statistics will be calculated for quantitative safety data as well as for the difference to baseline by visit. Frequency tables will be provided for categorical variables. No inferential statistical analysis of safety data is planned.

Adverse events will be coded using latest version of the *Medical Dictionary for Regulatory Activities* (MedDRA). Reports will be provided to the medical monitor for approval of the coded terms after the database is clean, prior to database lock. Treatment-emergent adverse events (i.e., those adverse events that newly occur or worsen in severity after the first dose of the study drug will be summarized by system organ class and preferred term. Tabulated listing of patients with SAEs and those who discontinue from the study due to an adverse event will be provided.

Incidence of clinical laboratory abnormalities Grade 3 and above (based on version 5.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE]) will be summarized. For laboratory tests with CTCAE toxicity grades available, laboratory abnormalities will be summarized by worst treatment emergent grade. Any laboratory adverse event will also be classified by the site based on clinical adverse event severity in addition to CTCAE and will be reported with the clinical adverse events.

Shift tables will be provided for liver function test results and other selected laboratory test results based on CTCAE grades. In addition, shift tables based on multiple of ULN will also be produced for liver function test measurements.

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

Other exploratory techniques (eg, graphic presentations), may also be used to facilitate clinical interpretations of the safety results.

9.4.5. Analyses of Pharmacokinetics (PK) and Pharmacodynamics (PD)

Individual plasma concentration data for all patients who receive at least 1 dose of study drug (ie, danicopan) and who have evaluable PK data will be included in the PK analysis for danicopan. Descriptive statistics will be calculated for plasma concentration data at each sampling time, as appropriate. Population-PK modeling will be conducted using data from this study and/or in combination with data from other studies.

PD analyses will be performed for all patients who receive at least 1 dose of danicopan and who have evaluable baseline and post dose PD data. Descriptive statistics will be presented for all danicopan PD endpoints at each sampling time. The PD effects of ALXN2040 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 danicopan PK-PD relationships may be explored using data from this study or in combination with data from other studies.

9.5. Interim Analyses

An interim analysis may be conducted at the discretion of the study sponsor (based on enrollment progression) when approximately 75% of patients have been randomly assigned to study treatment and have had the opportunity to complete the 12-week Treatment Period 1 (information fraction = 0.75). The purpose of the interim analysis is to evaluate the study for stopping early for efficacy. If conducted, the primary endpoint of change in Hgb levels at Week 12, as well as the key secondary endpoints will be evaluated using the alpha-spending methods specified below to control family-wise error rate.

- The evaluation of primary endpoint at interim analysis will be using the gamma family alpha-spending function (Hwang, 1990) with parameter -4.
- The evaluation of key secondary endpoints at interim analysis will be using the gamma family alpha-spending function with parameter 1.

Due to the hierarchical nature of primary and key secondary endpoints, and proper alpha-spending function used to control error rate at one-sided 0.025 level for each endpoint, the overall family-wise error rate is controlled at one-sided 0.025 level across primary and key secondary endpoints among interim and final analyses (Glimm, 2010, Tamhane, 2010).

The recommendation of stopping study enrollment and placebo-controlled Treatment Period 1 for efficacy can be made only if, at a minimum, the primary endpoint of change in Hgb levels at Week 12 and the key secondary endpoints of proportion of patients with Hgb increase ≥ 2g/dL in the absence of transfusion and proportion of patients with transfusion avoidance through 12week Treatment Period 1 meet the prespecified significance level. If the interim analysis is conducted with the timing and alpha-spending methods specified above, there is minimal change to the overall power for the primary endpoint, about 2-4% overall power decrease for the transfusion avoidance endpoint, and about 2-4% overall power decrease for the FACIT-Fatigue endpoint.

The sponsor will decide whether to perform the interim analysis based on enrollment progression. If full enrollment is already completed or close to completion by the time of the interim analysis specified above, the study will go directly to full analysis without an interim analysis.

The interim analysis will be conducted under the auspices of an independent DMC. The final decision to stop the study enrollment and placebo-controlled Treatment Period 1 for efficacy will be at the recommendation of the DMC. If such decision is made, the study may be modified to allow patients in the placebo arm to receive danicopan. The DMC review of the data will be independent of the Sponsor as the Sponsor will remain blinded. Details of the DMC's responsibilities and logistics will be outlined in the DMC charter before the dosing of the first patient.

9.6. Staged Population PK/PD Analysis

The staged population PK/PD analysis is planned prior to interim analysis, as well as prior to database lock. Pharmacodynamics will include AP activity, Bb, FD, C3, CP activity, and free C5.

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:

- 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 Brochure, and other relevant documents (e.g., 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

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 (written or electronic) 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 or electronic informed consent was obtained before the patient was enrolled in the study and the date the consent was obtained. The authorized person obtaining the informed consent must also sign (written or electronic) the ICF.

If the ICF is revised, patients must be re-consented (written or electronic) to the most current version of the ICF during their active participation in the study.

A hard or digital 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.

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

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.

10.1.5. Dissemination of Clinical Study Data

Company-sponsored study information and tabular study data will be posted on the US National Institutes of Health's website (www.ClinicalTrials.gov) and/or other publicly-accessible sites as required by the laws and regulations of the countries in which the study is conducted.

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 FDA, other government agencies, or foreign drug regulatory authorities, or to the public. No publication of study design or results is permitted without specific approval of the Sponsor. 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 (e.g., 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 (e.g., Contract Research Organizations).

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 2 years after study completion 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 entered in 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.

Definition of what constitutes source data can be found in the Medical Monitoring and Clinical Monitoring Plans.

10.1.8. Study and Site Closure

The sponsor or designee 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 intervention development

10.1.9. Publication Policy

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 FDA, other government agencies, or foreign drug regulatory authorities, or to the public. No publication of study design or results is permitted without specific approval by the Sponsor. To gain approval, a copy of the manuscript for review must, therefore, be sent to the Sponsor 60 days before submission for publication.

It is the intent of the Sponsor. to present the results of this study at future scientific meetings. Additionally, it is the intent of the Sponsor to publish the results of this study in leading scientific journals. The Investigator of each investigative site will be invited to be an author in conjunction with the Investigator(s) from the Sponsor. The Sponsor will determine additional authors. Presentations and manuscripts will be provided and agreed to by the authors and by the Sponsor

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 7 will be performed by the central 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 7: Protocol-Required Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other Assessments[1]
Complete blood count (CBC), including: Red blood cell (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 (HCO_3) Bilirubin (fractionated)[2] Blood urea nitrogen (BUN) Calcium Calculated eGFR[3] Chloride C-reactive protein (CRP) Creatine kinase[4] Creatinine Gamma-glutamyl transferase (GGT) Glucose[5] Lactate dehydrogenase Lipid profile including: Cholesterol/HDL ratio High-density lipoprotein cholesterol (HDL-C) Low-density lipoprotein cholesterol (LDL-C) Non-HDL-C Total cholesterol Triglycerides Very low-density lipoprotein cholesterol (VLDL-C) Potassium Sodium Total protein Uric acid	Analysis including: Bilirubin Color Glucose Ketones Leukocytes Nitrite Occult blood pH Protein Specific gravity Urobilinogen Microscopic examination of sediment	Alternative pathway (AP) activity Bb C3 C3 fragment deposition Classical pathway (CP) activity Free C5 D-dimer Direct Coombs Factor D Free hemoglobin Haptoglobin PNH clone size PT/PTT/INR Urine pregnancy test[6] Iron studies: -Serum ferritin -Serum iron -Transferrin saturation -TIBC -Total Iron Binding Capacity (TIBC) Serology: -HCV and HBV antibodies -HIV-1 and HIV-2 antibodies -UGT1A1 (Gilbert's)

[1] Check the Schedule of Assessments for specific times when these tests should be done.
[2] Fractionate and obtain measurements of direct and indirect bilirubin for all patients. If indirect bilirubin levels are > ULN at Screening but ALT and AST are normal, test for Gilbert's syndrome.
[3] Provide estimated glomerular filtration rate (eGFR) based on 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 Day 1, 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.

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

10.3.1. Definitions

Adverse events (AEs) 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 considered drug related. An AE can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

Medical occurrences, including pregnancies, that begin before the start of study intervention but after obtaining informed consent will be recorded as a pre-treatment AE. While pregnancy itself is not considered an AE, for the purposes of safety monitoring, a pregnancy occurring after signing the ICF should be reported on the pregnancy forms and sent to Alexion Global Drug Safety ([redacted] or fax [redacted]).

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during treatment, having been absent prior to treatment, or worsens relative to the pretreatment state. In this study, any AE first assessed after receipt of the first dose of danicopan until 30 days after the last dose of study drug 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 (e.g., 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 (e.g., headache) not present at baseline.
- Any case of abuse of alcohol, illicit drugs, or prescription drugs; abuse of study drug(s) or protocol-specified drug(s); addiction.
- A pregnancy that occurs or becomes confirmed during a clinical study (see Section 1.2).
- Laboratory test or other clinical test (e.g., ECG or X-ray) with a clinically significant abnormality (as defined below).
- An effect of the study drug, including comparator.
- Any dose of medication (study drug or other concomitant medication) that is taken at a dose higher than the prescribed dose (i.e., an overdose). Overdose should be reported as an AE whether or not it is associated with any symptoms or signs.

The following are not considered to be AEs:

- Medical or surgical procedures (e.g., surgery, endoscopies, tooth extraction, transfusion, etc.) - 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 (e.g., hospitalization for elective surgery, social and/or convenience admissions, etc.)

Clinically significant changes in objective findings (e.g., 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 drug 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 AE, 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 participant's medical record. In the latter case, the condition should be reported as medical history.

All participants 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 i.e., the participant 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 participant who was exposed to the study drug)
- Is an important medical event or reaction

10.3.3. Documentation and Reporting of Adverse Events

AEs, including TEAEs, may be reported by a participant or his/her representative, or to the Investigator elicited by the Investigator during questioning and examination of a participant. 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 should 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 should be reported as a single AE (e.g., fever, elevated WBC, cough, abnormal chest X-ray, etc. can all be reported as “pneumonia”).

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

10.3.4. Treatment and Follow-Up of Adverse Events

All AEs should 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 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

AEs include events that have 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 (e.g., invasive procedures, such as venipuncture, biopsy, etc.).

Any AE (i.e., a new event or an exacerbation of a preexisting condition) with an onset date after the participant provides informed consent through the 30 days following the participant's last study drug 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 drug dose must 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 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 drug (s), the PI (or designee) should promptly document and report the event to Alexion Global Drug Safety ([redacted] or fax [redacted]).

10.3.6. Severity and Grading of Adverse Events

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 participant. If a lab abnormality is deemed to be clinically significant, it should be reported as an AE and the AE grade reported should correspond to the grade of the lab abnormality on the CTCAE grading scale.

10.3.7. Assessment of Causality

The Investigator must assess the likelihood that the study drug caused or contributed to each AE, and document this assessment assigning one of the binary criteria to each AE:

- **Not related: There is no reasonable possibility the study intervention caused the adverse event.**
  - The adverse event 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 adverse event.**

- The adverse event 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

For the purposes of determining expedited reporting status to Health Authorities, Sponsor considers the assessments of 'unrelated' and 'unlikely' as unrelated to study drug and 'possible', 'probable', and 'definite' as related to study drug.

In addition, for any analyses of AE data in which only two categories of 'related' and 'unrelated' are used, the assessments of 'unrelated' and 'unlikely' will be combined into the category of 'unrelated', and the assessments of 'possible' and 'probable' and 'definite' will be combined into the category of 'related'.

10.3.8. Pregnancy

Any pregnancy, including in a female partner of a male participant, that occurs or becomes confirmed during a clinical study (time frames outlined in Section 1.2) must be reported to Alexion Global Drug Safety (GDS) within 24 hours of first knowledge of the pregnancy. The report should be provided on the Pregnancy/Breastfeeding Outcome form. While pregnancy itself is not considered an AE, for the purposes of safety monitoring, it should be reported to Alexion GDS on the pregnancy forms.

All pregnancies temporally related to study drug should be followed and discussed with the medical monitor as follows:

- The Investigator will follow up with the participant or the participant's female partner approximately every 3 months throughout the pregnancy and report to Alexion GDS using the Pregnancy/Breastfeeding Outcome form. A follow up on the status of the baby will be collected at 3 months of age of the baby.
- The Investigator will report any information on the status of the pregnancy including outcome to Alexion GDS ([redacted] or fax [redacted]
- Any termination of pregnancy will be reported, regardless of fetal status (i.e., presence or absence of anomalies) or indication for the procedure.

Any SAEs related to the pregnancy (see below), or occurring during the participant's pregnancy, or after delivery, must be documented and reported to Alexion GDS both electronically via the Rave Safety Gateway and via the Pregnancy/Breastfeeding Outcome form. SAEs occurring in the child (e.g., congenital anomalies or other conditions present at birth, whether genetically inherited or occurring in utero) must also be reported to Alexion GDS both electronically via the Rave Safety Gateway and via the Pregnancy/Breastfeeding Outcome form.

- Reportable SAEs associated with pregnancy include, but are not limited to:
- Pregnancy losses (e.g., spontaneous abortion, late fetal death, elective termination)
- Life-threatening developments (e.g., placental abruption, fetal distress)

- Congenital anomalies
- Neonatal or maternal death, or
- Any event resulting in maternal or neonatal hospitalization/prolonged hospitalization.

10.3.9. Reporting Serious Adverse Events and Pregnancies

The Sponsor has requirements for the expedited reporting of safety events meeting specific requirements to worldwide regulatory authorities, and therefore, must be notified immediately regarding the occurrence of any SAE and/or pregnancy that occurs during the study (time frames outlined in Section 1.2).

For SAEs and/or pregnancies occurring during the study, the Investigator or delegate will enter all relevant information in the eCRF.

All SAEs that occur during the course of the study, whether or not causally related to the investigational product, must be entered into the eCRF immediately (within 24 hours of the investigator becoming aware of the event) and electronically transmitted to Alexion GDS via the Rave Safety Gateway.

In addition, the Investigator must:

- Report all site-specific SAEs to the relevant Institutional Review Board (IRB) / Independent Ethics Committee (IEC) within the timeframe specified by the IRB / IEC as per local procedures/policies.
- If the subject is an active participant in the study:
- Enter follow-up information in the eCRF until the SAE has resolved, or, in the case of permanent impairment, until stabilized.
- Ensure that the causality assessment for all SAEs is entered in the eCRF.
- If the patient is no longer participating in the study, report the follow-up information to the sponsor.

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

10.3.10. Investigator Reporting Requirements for SUSARs

The Sponsor is responsible for ensuring that Investigators and central ECs/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 ECs or IRBs as per EC 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 EC or IRB procedures for reporting any other safety information.

10.3.11. Concomitant/Background Medication Assessments

Details of all concomitant/background medication use, including all medications administered for the treatment of AEs, will be recorded in the participant's CRF at each study visit.

10.3.12. Monitoring Participant Safety

The safety of participants will be monitored by Investigators and by Sponsor's medical monitor (or designee) on an ongoing basis while participants are receiving the study drug.

10.3.13. Removal of Participants from the Study or Study Drug

A participant 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 participant noncompliance, to discontinue dosing in a participant. The PI should also stop dosing in any participant who meets an individual stopping rule. In either case, whenever possible, the 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 protocol, whichever is considered to be in the best interest of the participant. When dosing is terminated, study participation is not necessarily immediately terminated. Instead, whenever possible, the participant 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 Appendix 1.

Reasons for participant withdrawal include (but are not limited to):

- One or more of the stopping criteria described in the protocol is met
- Intercurrent illness that would, in the judgment of the Investigator, affect assessments of clinical status to a significant degree
- Unacceptable toxicity (including a clinically significant laboratory abnormality) necessitating discontinuation of study 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 participant's best interest to continue the study
- Participant request to discontinue for any reason
- A female participant becomes pregnant or wishes to become pregnant
- Participant noncompliance
- Discontinuation of the study at the request of the Sponsor, regulatory agency, or Ethics Committee or IRB
- Any other condition or circumstance that would jeopardize the welfare of the participant if s/he were to continue in the study

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

10.4. Appendix 4: Contraception Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following at least 6 months prior to dosing:
    - Documented hysterectomy
    - Documented bilateral salpingo-oophorectomy
    - Documented bilateral oophorectomy

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

Note: Documentation must come from the site personnel's: review of the patient's medical records.

Postmenopausal female meeting both of the criteria below:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- A high follicle stimulating hormone (FSH) level in the postmenopausal range must be used to confirm a postmenopausal state.

Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal 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.

Contraception Guidance: Patients on C5 inhibitor therapy should adhere to the contraception guidelines as per local country label requirements

Contraception for Male Patients

All non-sterile male patients must use highly effective or acceptable methods of contraception with their partner(s) of childbearing potential from the first day of dosing (Day 1) through 90 days (a spermatogenesis cycle) after their last dose of study drug.

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 refraining from heterosexual intercourse during the entire period from the first day of dosing (Day 1) through 90 days after their last dose of study drug. Periodic abstinence (e.g., calendar, symptothermal, post-ovulation 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.

Acceptable contraceptive methods include:

- A combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods)

Male patients must agree to refrain from sperm donation while enrolled in this study and for 90 days (a spermatogenesis cycle) after their last dose of study drug.

Contraception for Female Patients

Female patients of childbearing potential must use a highly effective or acceptable method of contraception from the date of signing the informed consent until the specified duration after the last dose of their background C5 inhibitor as per the product labelling.

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
- IUD or 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. Periodic abstinence (e.g., calendar, symptothermal, post-ovulation 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.

Acceptable contraceptive methods include:

- A combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods)

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

Female patients of non-childbearing potential need not employ a method of contraception.

Collection of Pregnancy Information

Any pregnancy, including female partner pregnancies of male patients, that occurs or becomes confirmed during a clinical study must be reported to the Sponsor (or designee) within one business day of first knowledge of the pregnancy, as described in Section 8.5.5. The report should be provided on the pregnancy form. While pregnancy itself is not considered an AE, for the purposes of tracking, it should be captured as an AE as well as reported on the pregnancy forms.

All pregnancies temporally related to taking study drug 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 6-8 weeks 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 (i.e., 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. SAEs occurring in the child (e.g., 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 (e.g., spontaneous abortion, late fetal death, elective termination)
- Life-threatening developments (e.g., placental abruption, fetal distress)
- Congenital anomalies
- Neonatal or maternal death

- Any event resulting in maternal or neonatal hospitalization/prolonged hospitalization.

10.5. Appendix 5: Genetics

Subject to patient consent, a sample will also be collected at screening for potential genetic analysis. 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 (MCP/CD46)
- Thrombomodulin (THBD)
- CR1

All genetic samples will be stored for a maximum of 3 years after completion of the clinical study report. During that time, samples may be retested if other mutations are discovered that may be associated with PNH. 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 3-year storage period defined above, or once the sponsor is informed of withdrawal of consent for further analysis, the sample will be destroyed consistent with accepted laboratory standards and no further testing or analysis will be completed. Any data already generated from the sample may continue to be used for the purposes of this study and future research.

10.6. Appendix 6: 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 participant 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 participants 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 participant 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 8.

Table 8: Potential Risks and Mitigation Measures due to COVID-19

Risks Category	Summary of Data/ Rationale for Risk	Mitigation Strategy
Potential risks		
Potentially higher risk population for SARS-CoV-2 infection	Participants in this study have to be vaccinated against meningococcal infections prior to treatment with a C5 inhibitor. It is unknown how this may impact their risk for SARS-CoV-2 infection.	During the time that the COVID-19 pandemic is active, Alexion will recommend that sites in a position to start the study and enroll participants follow the national and institutional guidances regarding prevention of SARS-CoV-2 infection. Additionally, during that time period, it is expected that Investigators and their staff will take all possible precautions in order to minimize a participant's potential exposure to SARS-CoV-2 infection. Depending on the site, this will consist of measures such as social distancing, temperature screening, enhanced cleaning, and use of personal protective equipment for participants, staff, and caregivers as necessary.
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 participants at sites unless the sites have the resourcing and capabilities to implement the study per protocol.

Table 8: Potential Risks and Mitigation Measures due to COVID-19

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

Abbreviations: C5 = complement protein 5; COVID-19 = coronavirus disease 2019; eCRF = electronic case report form; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

10.7. Appendix 7: 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 danicopan administration, based on danicopan's mechanism of action. There is currently no information available evaluating the safety and efficacy of COVID-19 vaccines in participants treated with danicopan. Same precautions should be taken as described in Section 6.5.2.

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 9: .

Table 9: Potential Risk and Mitigation Measures due to COVID-19 Vaccination

Risk Category	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential risk		
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 participant 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.

10.8. Appendix 8: Abbreviations

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
AP	Alternative pathway (of complement)
AST	Aspartate aminotransferase
Bb	Bb fragment of complement factor B
C3	C3 complement protein
C5	C5 complement protein
C3G	C3 glomerulopathy
CIOMS	Council for International Organizations of Medical Sciences
CP	Complement classical pathway
CRF	Case report form
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	electronic case report form
eGFR	Estimated glomerular filtration rate
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-3L	Three-level version of EuroQoL 5 Dimensions questionnaire
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
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
Hct	Hematocrit
HCV	Hepatitis C virus
Hgb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	Human immunodeficiency virus
HR	Heart rate
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
INR	International normalized ratio
IRB	Institutional review board
IRT	Interactive response technology
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
LDH	Lactate dehydrogenase
LTE	Long-Term extension
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measures
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)

Abbreviation	Definition
PNH	Paroxysmal nocturnal hemoglobinuria
pRBC	Packed red blood cells
PRO	Patient-reported outcome
PT	Prothrombin time
PTT	Partial thromboplastin time
QLQ-C30	Quality of Life Questionnaire-Core 30 Scale
QoL	Quality of life
QRS	Group of electrocardiogram waves comprising the Q, R, and S waves
QT	Period (in milliseconds) from the beginning of the QRS complex until the end of the T wave
QTcF	QT interval Fridericia Correction Formula
RBC	Red blood cells
RR	Respiration rate
SAE	Serious adverse event
SUSAR	Suspected unexpected serious adverse reaction
TA	Transfusion avoidance
TEAE	Treatment-emergent adverse event
tid	Three times per day
ULN	Upper limit of normal
WBC	White blood cell
Wk	Week
VHA	Visit Healthcare Assessment

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