Alexion Pharmaceuticals, Inc.

STATISTICAL ANALYSIS PLAN

PROTOCOL NUMBER: ALXN2040-PNH-301

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)

Product Name: Danicopan (ALXN2040, previously ACH-0144471)

Protocol Version: Amendments 6.0 (25 Feb 2022), 6.2 (30 Mar 2022) and 6.3 (08 Aug 2022)

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Date: 10 Aug 2022

Version: 2.0

1. APPROVAL SIGNATURES

[redacted]

11-Aug-2022 | 11:56:28 EDT

[redacted]

Date dd Mmm yyyy

[redacted]

11-Aug-2022 | 12:12:02 EDT

[redacted]

Date dd Mmm yyyy

[redacted]

11-Aug-2022 | 12:57:40 EDT

[redacted]

Date dd Mmm yyyy

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and acronyms are used in this statistical analysis plan (SAP).

Table 1: Abbreviations and Acronyms

Abbreviation or Acronym	Explanation
ADA	antidrug antibodies
AE	adverse event
ALT	alanine aminotransferase
APH	alternate pathway activity
ANCOVA	Analysis of Covariance
AST	aspartate aminotransferase
Bb	Bb fragment of complement factor B
BP	blood pressure
C3	complement C3
CH50	classical pathway activity
CI	confidence interval
CMH	Cochrane-Mantel-Haenszel
COVID-19	Coronavirus Disease 2019
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV%	coefficient of variation percentage
DBL	database lock
DMC	Data Monitoring Committee
ECG	electrocardiogram
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-3L	Three-level EuroQoL 5-dimension
EQ VAS	EuroQoL visual analog scale
EVH	extravascular hemolysis
FAS	full analysis set
FACIT	Functional Assessment of Chronic Illness Therapy
FD	factor D
Hgb	hemoglobin
HR	heart rate
HRU	healthcare resource utilization
IMP	investigational medicinal product
ITT	intent-to-treat
LDH	lactate dehydrogenase
LTE	long-term extension
MAR	missing-at-random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measures
MI	multiple imputation
MNAR	missing not at random
PD	pharmacodynamics
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PNH	paroxysmal nocturnal hemoglobinuria
PP	per protocol
pRBC	packed red blood cells
PT	preferred term
PTAE	pretreatment adverse event

Table 1: Abbreviations and Acronyms

Abbreviation or Acronym	Explanation
QLQ-C30	Quality of Life Questionnaire-Core 30 Scale
QoL	quality of life
QTcF	corrected QT interval by Fridericia formula
RBC	red blood cell
RR	respiratory rate
SAE	serious adverse event
SAS®	Statistical Analysis Software®
SAP	statistical analysis plan
SMQ	standardized MedDRA query
SoA	schedule of assessments
SOC	system organ class
SS	safety set
TA	transfusion avoidance
TEAE	treatment-emergent adverse event
tid	thrice daily
TTH	table-top hemolysis
ULN	upper limit of normal
WHO-DRUG	World Health Organization Drug
WPAI:ANS	Work Productivity and Activity Impairment Questionnaire: Anemic Symptoms

4. DESCRIPTION OF THE PROTOCOL

ALXN2040-PNH-301 is a multiple-region, randomized, double-blind, placebo controlled, multiple-dose, Phase 3 study to evaluate the efficacy and safety of danicopan versus placebo in patients with paroxysmal nocturnal hemoglobinuria (PNH) who have clinically evident extravascular hemolysis (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 who continue to experience anemia with or without the need of transfusion support. Randomization will be stratified by transfusion history (ie, > 2 or ≤ 2 transfusions within 6 months of Screening) and hemoglobin (Hgb) level (ie, < 8.5 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 thrice daily (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 in addition to their C5 inhibitor 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 their ongoing C5 inhibitor therapy. At the end of the Treatment Period 2 (Week 24), patients may enter the Long-Term Extension (LTE) Period and continue to receive danicopan and their C5 inhibitor therapy.

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 effects at any of the protocol-specified time points (Weeks 6, 12, and 18 and after Week 24). If a patient discontinues from the study, dosing of danicopan or placebo should be tapered over 6 days (Taper Visits 1 and 2), and a Follow-up Visit will be conducted approximately 30 days after the last dose of study drug. Refer to Protocol Section 6.6 for more details on dose escalation.

The primary objective of this study is to evaluate the efficacy of danicopan as compared to placebo as add-on therapy to a C5 inhibitor on change in Hgb after 12 weeks of treatment. The key secondary objectives are to evaluate the treatment effect of danicopan as compared to placebo as add-on therapy to a C5 inhibitor on an Hgb increase of ≥ 2 g/dL in the absence of transfusion, transfusion avoidance (TA), Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue score, and absolute reticulocyte count after 12 weeks of treatment.

An interim analysis, performed under the auspices of the independent Data Monitoring Committee (DMC), may be conducted when approximately 75% of patients (planned as N = 63) have been randomly assigned to study treatment and have had the opportunity to complete the 12-week placebo-controlled Treatment Period 1. The purpose of the interim analysis is to evaluate the study for efficacy. The alpha-spending method and success criteria for the interim analysis are specified in Section 8. If the decision is made to stop the study enrollment early for efficacy per DMC recommendation based on this interim analysis, enrollment will be stopped, the study will be unblinded, and all study endpoints (efficacy, safety, pharmacokinetics [PK], and pharmacodynamics [PD]) analyses will be conducted based on interim data available as of the database lock (DBL) and an interim clinical study report (CSR) will be produced. For additional details on the interim analysis, please refer to Section 8.

If the interim analysis does not meet the prespecified success criteria defined in Section 8, the study will continue as planned with no modifications. A study DBL is planned to occur after full enrollment is achieved and all patients (planned as N = 84) have reached the end of the 12-week randomized placebo-controlled period (Treatment Period 1). A CSR will be produced and will include efficacy, safety, PK, and PD analyses based on full enrollment and data collected up to the database cut-off date (including available data for patients already in Treatment Period 2 and LTE Period).

4.1. Changes From Analyses Specified in the Protocol

Not applicable.

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

Refer to Section 10.2.

5. DEFINITIONS

5.1. Efficacy

5.1.1. Primary Endpoint

The primary efficacy endpoint of the study is the change in Hgb relative to Baseline after 12 weeks of treatment with danicopan compared to placebo.

5.1.2. Key Secondary Endpoints

The key secondary efficacy endpoints of the study (to be tested in a hierarchical manner) are as follows:

1. Proportion of patients with an Hgb increase of ≥ 2 g/dL at Week 12 in the absence of transfusion
2. Proportion of patients with TA, defined as patients who remain transfusion free and do not require a transfusion as per protocol-specified guidelines through Week 12

   For the purpose of this analysis, patients who meet the protocol-specified guidelines for a transfusion will be counted as having received a transfusion, regardless of whether a transfusion was administered. The following are the protocol-specified transfusion guidelines:

   It is recommended to administer packed red blood cell (pRBC) transfusion when a subject has any of the following:

   - An Hgb value of < 7 g/dL regardless of the presence of clinical signs or symptoms
   - An Hgb value of < 9 g/dL with signs or symptoms of sufficient severity to warrant a transfusion
3. Change from Baseline in FACIT Fatigue scores at Week 12
4. Change from Baseline in absolute reticulocyte counts at Week 12

5.1.3. Other Secondary Endpoints

Other secondary efficacy endpoints of the study are as follows:

- 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 the initiation of treatment in patients randomized to the danicopan arm
- Percentage of patients who have TA through 24 weeks of treatment in patients randomized to danicopan arm
- 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
- Change from Baseline in FACIT Fatigue scores at Week 24 in all patients

- Percentage of patients with Hgb stabilization during the last 12 weeks of treatment in patients receiving 24 weeks of danicopan
- Proportion of patients with an Hgb increase of ≥ 2 g/dL at Week 24 in the absence of transfusion
- 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 complement C3 (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 and 24 weeks

5.1.4. Exploratory Endpoints

The exploratory endpoints of the study are as follows:

- Change from Baseline relative to placebo in 3-level EuroQoL 5-dimension (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) scores at Week 12
- Change from Baseline in EORTC QLQ-C30 scores at Week 24
- Change from Baseline relative to placebo in Work Productivity and Activity Impairment Questionnaire: Anemic Symptoms (WPAI:ANS) scores 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

5.2. Pharmacokinetic and Pharmacodynamic Endpoints

The PK and PD endpoints of the study are as follows:

- Plasma concentrations of danicopan over time
- Changes from Baseline in PD biomarkers (Bb fragment of complement factor B [Bb], factor D [FD], C3, free C5, hemolytic alternate pathway activity [APH], hemolytic classical pathway activity [CH50])

5.3. Safety

The safety and tolerability of danicopan compared with placebo will be evaluated by physical examination, vital signs, electrocardiograms (ECGs), laboratory assessments, and incidence of

adverse events (AEs) and serious adverse events (SAEs). Incidence of antidrug antibodies (ADAs) to ravulizumab will be reported as specified in Section 5.3.6.

5.3.1. Adverse Events

An AE is defined as any unfavorable and unintended sign (eg, including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Situations in which an untoward medical occurrence did not occur (eg, hospitalization for elective surgery if planned before the start of the study and admissions for social reasons or for convenience) and anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen are not AEs.

The severity of AEs will be graded using Common Terminology Criteria for Adverse Events (CTCAE) v4.03 or higher.

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Grade 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting selfcare activities of daily living
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

AEs are further defined in Protocol Section 10.3.

5.3.2. Vital Signs

Vital signs will include assessments of systolic and diastolic blood pressures (BPs), temperature, respiratory rate (RR), and heart rate (HR). Systolic and diastolic BPs will be documented in millimeters of mercury. Temperature will be obtained in degrees Celsius or Fahrenheit. HR will be documented in beats per minute. RR will be documented in breaths per minute.

5.3.3. Laboratory Assessments

Samples for the analysis of serum pregnancy, hematology, chemistry, coagulation, and urinalysis will be collected (see Protocol Section 10.2 for a listing of all clinical laboratory parameters). A central laboratory will be used to evaluate all laboratory assessments.

5.3.4. Electrocardiograms

A single 12-lead ECG will be conducted as per the schedule of assessments (SoA) in the study protocol. HR, PR interval, QRS duration, and QT interval will be measured, and corrected QT interval by Fridericia formula (QTcF) and RR interval will be calculated.

5.3.5. Physical Examination

A physical examination will be performed assessing general appearance; skin; head, eyes, ears, nose, and throat; neck; lymph nodes; chest; heart; abdominal cavity; limbs; central nervous system; and musculoskeletal system. An abbreviated physical examination will be performed consisting of a body system-relevant examination based on Investigator judgment and patient symptoms.

5.3.6. Immunogenicity

For patients enrolled under local protocol amendment 4.1 and receiving background therapy ravulizumab as investigational medicinal product (IMP) in the study, blood samples will be collected to test for the presence and titer of ADAs to ravulizumab. Incidence of ADAs will be reported. Further characterization of antibody responses may be conducted as appropriate, including binding and neutralizing antibodies, PK/PD, safety, and activity of ravulizumab.

6. DATASETS ANALYZED (STUDY POPULATIONS)

6.1. Full Analysis Set

The full analysis set (FAS) or all randomized population will consist of all enrolled patients that are randomized to either the danicopan or placebo treatment group.

The primary population for assessment of efficacy is the FAS, and the analyses will follow intent-to-treat (ITT) principle (ie, 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.

6.2. Per Protocol Set

The per protocol (PP) set will consist of all randomized patients in the FAS that meet all the following criteria:

- Took ≥ 80% of total danicopan dose amount assigned per protocol during the 12-week randomized Treatment Period 1
- Met all inclusion and did not meet any exclusion criteria of the study
- Never received the wrong randomized treatment during the 12-week randomized Treatment Period 1 (ie, all patients who received assigned treatment)
- Had no inadvertent unblinding of treatment assignment
- Had no other important protocol deviations that may impact the assessment of the primary and key secondary endpoints

The primary efficacy endpoint analysis, as well as key secondary endpoint analyses, will be performed on both the FAS and PP set. If the FAS, based on ITT principle, and the PP set have a similar number of patients (< 5% difference), analyses will not be performed using the PP set.

6.3. Safety Set

The safety set (SS) will consist of all patients that received at least 1 dose of study drug (danicopan or placebo). Safety analysis will be performed on the SS and will be based on the treatment patients actually received.

6.4. Other Sets

The PK analysis set will consist of all patients who received at least 1 dose of danicopan and who have evaluable PK data.

7. STATISTICAL ANALYSIS

All data collected in this study will be presented using summary tables, figures, and data listings. For categorical variables, frequencies and percentages will be presented by treatment group and overall. For continuous variables, descriptive statistics (n, mean, median, SD, minimum, and maximum) will be presented by treatment group and overall.

7.1. Study Patients

7.1.1. Disposition of Patients

A summary of the number of the screened patients (patients who signed informed consent of the study), screen failures, randomized patients, and treated patients (received at least 1 dose of study drug) will be tabulated. For all randomized patients, a summary of patient disposition will be presented by treatment group and overall. The number and percentage of patients that completed the study through the end of the randomized Treatment Period 1 or discontinued/withdrew early before the end of the randomized Treatment Period 1, along with reason for discontinuation/withdrawal will be presented. Similar patient disposition summary will be provided for Treatment Period 2, LTE Period, and the entire study.

A table summarizing the number of patients screened, randomized, treated, and completed treatment by region will be provided. Region will be defined based on study sites at which patients receive study drug and will include North America, Europe, Japan, the rest of Asia Pacific, and Latin America. A similar summary by country will also be produced.

The number and percentage of patients in each analysis set will be tabulated. For patients that are excluded from the PP set, the primary reasons for exclusion will be listed and summarized.

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

7.1.2. Protocol Deviations

Protocol deviations from monitoring reports and other relevant sources will be reviewed. All important protocol deviations will be summarized by category and listed for all patients in the FAS.

7.1.3. Demographics, Disease Characteristics, and History

All demographic and baseline characteristic information will be summarized using the FAS and SS. Summary statistics will be presented by treatment group and overall. Demographic and baseline characteristics will also be summarized by treatment group and stratification groups for the FAS, SS, and PP set. By-patient listings of demographic information, disease characteristics, PNH medical history, and medical/surgical history will be produced.

7.1.3.1. Demographics and Baseline Characteristics

The following demographic and baseline characteristic variables will be summarized:

- Sex
- Race

- Ethnicity
- Age (years) at informed consent and frequency of patients in the following categories: < 65 and ≥ 65 years (65 to 74, 75 to 84, and 85 years and older)
- Baseline weight
- Baseline height
- Baseline body mass index
- Transfusion history stratification (> 2 or ≤ 2 transfusions within 6 months of Screening)
- Screening Hgb level stratification (< 8.5 and ≥ 8.5 g/dL)
- Japanese patients (patients enrolled from Japan [Yes/No])

7.1.3.2. Disease Characteristics

The following PNH disease characteristics will be summarized:

- Age (years) at PNH diagnosis
- Method of PNH diagnosis
- Years from PNH diagnosis to informed consent
- Age (years) at the first C5 inhibitor infusion
- Duration (years) from the initial C5 inhibitor treatment to the first dose of study drug
- Current C5 inhibitor background therapy (including dose level and frequency)
- Duration (years) from the start of current C5 inhibitor to the first dose of study drug
- PNH clone sizes (RBC Types II and III and granulocyte) at Baseline
- Hgb at Baseline
- Absolute reticulocyte counts at Baseline
- LDH at Baseline
- FACIT-fatigue scores at Baseline
- pRBC transfusion requirements during the year and 24-week period prior to receiving study drug including number of transfusion instances and units transfused
- All PNH symptoms experienced at any time prior to informed consent
- All PNH associated conditions that were diagnosed at any time prior to informed consent

7.1.3.3. Medical/Surgical History and Baseline Physical Examination

Medical history will be summarized by system organ class (SOC) and preferred term (PT) using the latest available version of standardized Medical Dictionary for Regulatory Activities (MedDRA; version 23.1 or above) and will be reported by treatment group and overall.

Likewise, baseline physical examination information will be summarized by treatment group and overall.

7.1.4. Prior and Concomitant Medications/Therapies

Prior and concomitant medications will be summarized. Prior medications are defined as medications taken prior to the first dose of study drug and include all medications taken within 28 days prior to informed consent as well as all *Neisseria meningitidis* vaccinations administered within 3 years of dosing with danicopan. Concomitant medications are defined as medications received by the patients during the study on/after the date of the first dose of the study drug. No concomitant medications are specifically prohibited by the protocol.

Medications will be coded using the World Health Organization Drug (WHO-DRUG) Dictionary version in use by Alexion at the time of the analysis. Medication summaries by treatment group, (ie, number [%] of patients using prior and concomitant medications) will be presented by WHO-DRUG Anatomical Therapeutic Chemical Level 3 and by WHO-DRUG generic name. Concomitant medication summary will be produced for the 12-week randomized Treatment Period 1, Treatment Period 2, LTE Period, and throughout the entire study treatment.

Listings of prior and concomitant medications will be produced. A by-patient listing of *N meningitidis* vaccination will be produced showing the date(s) of vaccinations for each patient. A by-patient listing of nondrug therapies and procedures will be produced by treatment group.

7.1.4.1. C5 Inhibitor

Summary statistics (mean, SD, median, minimum, and maximum) will be produced for each C5 inhibitor (eculizumab and ravulizumab) in the randomized Treatment Period 1, Treatment Period 2, and LTE Period by treatment group for the following using the FAS and SS:

- Number of infusions
- Total dose administered (milligrams)
- Total infusion volume administered (milliliters)
- Total time on C5 inhibitor (days) calculated as the time in days from the first C5 inhibitor infusion date until the last infusion date

For patients who are receiving C5 inhibitor as an IMP, the total number of patients with an infusion interruption as well as the total number of infusions interrupted will be summarized. In addition, the frequency and percentage of patients that had a percentage of drug compliance range by increments of 10% (ie, $\geq$ 90% to $\leq$ 100%; $\geq$ 80% to < 90%, etc) will also be summarized. This will be calculated as follows:

Percent compliance = Total number of infusions taken / Total number of expected infusions

By-patient listings will be produced for C5 inhibitor exposure.

7.2. Efficacy Analyses

The FAS is the primary population for all efficacy analyses. The primary efficacy endpoint analysis, as well as key secondary endpoint analyses, will also be conducted using the PP set as supportive analysis for those endpoints. Unless otherwise specified, Baseline is defined as the last available assessment prior to the initiation of study treatment (the first dose of study drug). In general, the baseline assessment will be the Day 1 assessment. If the Day 1 assessment is missing, the latest observation during the Screening Period, where available, will be used as the baseline assessment. In general, when evaluating mean change from Baseline in numeric laboratory parameters, only values reported by the central laboratory will be included in the analysis.

Unless otherwise specified, statistical tests for treatment comparisons will be conducted at a 2-sided 0.05 significance level.

In addition to the analyses described below, the observed values and changes from Baseline of efficacy endpoints at each study visit will also be summarized by treatment group using descriptive statistics (n, mean, median, SD, minimum, and maximum for continuous variables and frequencies and percentages for categorical variables).

7.2.1. Primary Endpoint Analysis

The primary efficacy endpoint of the study is the change in Hgb relative to Baseline after 12 weeks of treatment with danicopan compared to placebo in patients who are receiving background C5 inhibition treatment. The estimand attributes for the primary endpoint are described in Table 2 below. For this analysis, Baseline is defined as the lowest Hgb value observed between and including Screening and Day 1. The longitudinal changes from Baseline in Hgb collected at postbaseline visits during the 12-week randomized Treatment Period 1 will be analyzed using an MMRM method (Mallinckrodt, 2001; Mallinckrodt, 2004). The model includes the fixed, categorical effects of treatment group, study visit, and study visit-by-treatment group interaction, as well as the fixed, continuous covariate of a baseline Hgb value and the randomization stratification factor of transfusion history. An unstructured covariance matrix will be used to model the within-patient errors. If this analysis model fails to converge, the covariance matrix structures will be evaluated in the following order until model convergence is met: Toeplitz, first-order autoregressive, and compound symmetry. The order is specified according to decreasing number of covariance parameters in the structure.

The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The treatment comparison for the primary efficacy analysis will be based on the difference between danicopan and placebo groups at Week 12. The difference between treatment groups in least-square mean estimates and its associated SE will be calculated along with a 2-sided 95% confidence interval (CI). The test will be conducted at a 2-sided 0.05 significance level.

Under the US local protocol amendment, the primary test for statistical significance of the treatment group difference between danicopan and placebo will be conducted via a re-randomization test method at the 2-sided 0.05 significance level. Re-randomized treatment assignments will be simulated for all randomized patients for 1500 iterations 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.

The primary objective of this study is to evaluate the efficacy of danicopan as compared to placebo as add-on therapy to a C5 inhibitor on change in Hgb after 12 weeks of treatment in patients with PNH who have clinically evident EVH on a C5 inhibitor. Transfusion is an intercurrent event that can occur during the treatment period and impact patient Hgb values. To address the impact of transfusion, Hgb values collected within 4 weeks after transfusion will not be included in the MMRM model for the primary efficacy analysis.

With the relatively small sample size and 12-week placebo-controlled treatment period, all efforts will be made to minimize missing Week 12 measurements. Longitudinal graphic presentations will also be provided to examine the Hgb profile throughout 12 weeks of treatment with danicopan or placebo, plus a C5 inhibitor.

The primary efficacy analysis will be based on the FAS with ITT principle. For the US local protocol amendment, 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. For ex-US countries, the test for treatment group differences directly from the MMRM model using the actual treatment assignments will be considered as the primary analysis, while the re-randomization test for treatment group differences will be reported as a sensitivity analysis. A supportive analysis will be carried out for the primary efficacy endpoint of change in Hgb based on the PP set, using the same method described above.

7.2.1.1. Handling of Dropouts or Missing Data

For the primary endpoint of change in Hgb from Baseline to Week 12, missing Hgb assessments for a particular patient at a particular visit will not be imputed. The specified MMRM analysis can produce valid statistical inference under the missing-at-random (MAR) missing data mechanism assumption. Sensitivity analyses to assess treatment effects under alternative missing data mechanism assumptions are specified in Section 7.2.1.5.

Missing data for QoL instruments will be handled as specified in the instructions for each instrument (see also Section 10.5).

Missing data for secondary endpoints will be handled as specified in Section 7.2.2.

7.2.1.2. Subgroup Analysis

Subgroup analysis of efficacy endpoints will be performed on the FAS. Summaries of observed Hgb values and change from Baseline at each study visit will be produced for the subgroups defined by the randomization stratification factors of transfusion history (> 2 or ≤ 2 transfusions within 6 months of Screening), screening Hgb level (< 8.5 and ≥ 8.5 g/dL), and Japanese patients (patients enrolled from Japan [Yes/No]). Similar summaries of the primary endpoint and the key

secondary endpoints will also be produced for subgroups based on sex, race, region, age at informed consent (< 65 and ≥ 65 years), and background C5 inhibitor therapy (eculizumab or ravulizumab).

7.2.1.3. Multicenter Studies

While this is a multicenter study, a very small number of patients are anticipated to be enrolled at each study site. Therefore, center will not be used as an explanatory factor in the efficacy analyses.

7.2.1.4. Hypothesis Testing and Significance Level

The treatment comparison test for the primary efficacy endpoint will be conducted based on a 2-sided Type I error rate of 0.05. If statistical significance is achieved for the primary endpoint, the 4 key secondary endpoints described in the study protocol will be tested for treatment comparison (danicopan versus placebo) at a 2-sided 0.05 level. To control the overall Type I error across study endpoints, the tests will be conducted using a closed-testing procedure in the order as specified in Section 7.2.2.1 so that the lack of significance of a test precludes statistical significance of subsequent tests.

If the interim analysis for efficacy is conducted, the significance level for the primary and key secondary endpoints will be adjusted using the alpha-spending method specified in Section 8.

7.2.1.5. Sensitivity Analyses

The MMRM analysis specified for the primary endpoint analysis assumes MAR for the missing data mechanism. A tipping point sensitivity analysis will be performed to evaluate the robustness of the primary efficacy analysis by assessing the treatment effect under alternative missing data assumptions. The analysis will be performed based on the delta-adjusted stress testing method, and the missing data mechanism assumption will be missing not at random (MNAR). This approach assumes that patients that discontinue from danicopan treatment experience worsening, defined by a prespecified adjustment (delta) in the primary efficacy endpoint compared with the observed values from patients that continue the study to next visit (Ratitch, 2014; Ratitch, 2013). Since a reduction in Hgb indicates worsening, the prespecified value of delta will be a negative quantity. A fixed set of delta values (from less conservative to more conservative) will be used to encapsulate the change in Hgb associated with missing values for the active treatment group, and the tipping point multiple imputation analysis as described by Ratitch et al will be applied (Ratitch, 2013). For each value of delta, imputed values for missing Hgb at each time point will be obtained by first sampling from an MAR-based multiple imputation (MI) model including the variables of treatment, baseline values, and values observed at all scheduled visits during the 12-week randomized Treatment Period 1 and then subtracting the value of delta from all imputed values in the danicopan arm. The mean change from Baseline in Hgb will then be analyzed using the same MMRM model specified above based on data observed, as well as data imputed. The treatment effect will be determined, and the value of delta for which the result is no longer statistically significant will be considered as the “tipping point” in the sense that the positive conclusion drawn from the primary analysis is reversed when patients who drop out are assumed to experience this fixed worsening after the discontinuation visit. After such a tipping point is determined, clinical judgment will be applied as to the plausibility of the assumptions underlying this tipping point. This methodology is expected to inform what it would take to overturn study

conclusions based on varying assumptions about missing data. A 0 value of delta will be considered equivalent to the primary analysis. For this analysis, a series of delta values for Hgb decreasing in increments of -0.5 g/dL will be applied (ie, -0.5, -1, -1.5, …). Refer to Appendix Section 10.5.5 for further illustration of the tipping point sensitivity analysis.

Individual patient profiles of Hgb values over time during the randomized controlled Treatment Period 1 will be plotted to examine the pattern of missingness.

In addition, as a supplemental analysis, the MMRM analysis for the primary efficacy endpoint will be performed by including all longitudinal Hgb values collected at scheduled visits during the randomized Treatment Period 1 (ie, including values collected within 4 weeks after transfusion).

Table 2: Estimand Attributes for the Primary and Key Secondary Endpoints

Endpoint	Treatment Regimens	Targeted Patient Populations	Patient-Level Outcome Measure	Handling of Intercurrent Events	Population-Level Summary Measure
Primary: Hgb	Danicopan vs. placebo as add-on therapy to a C5 inhibitor	All randomized PNH patients with CE-EVH while on C5 inhibitor treatment	Change from Baseline to Week 12 in Hgb	Analysis includes all values collected at scheduled visits while patients remain on the study treatment during the randomized Treatment Period 1. Hgb values collected within 4 weeks after transfusion will be excluded.	Treatment group difference in the mean change from Baseline to Week 12 in Hgb
Key secondary: An Hgb increase of ≥ 2 g/dL at Week 12 in the absence of transfusion	Danicopan vs. placebo as add-on therapy to C5 inhibitor	All randomized PNH patients with CE-EVH while on C5 inhibitor treatment	Binary indicator (Yes/No) of patient achieving an Hgb increase of ≥ 2 g/dL at Week 12 in the absence of transfusion	The criterion is defined as achieving an increase of ≥ 2 g/dL in Hgb from Baseline to Week 12 and remaining transfusion free during the 12-week randomized Treatment Period 1. Patients that withdraw from the study early during the 12-week	Treatment group difference in the proportion of patients achieving the criterion

Table 2: Estimand Attributes for the Primary and Key Secondary Endpoints

Endpoint	Treatment Regimens	Targeted Patient Populations	Patient-Level Outcome Measure	Handling of Intercurrent Events	Population-Level Summary Measure
				randomized Treatment Period 1 will be considered as not achieving the criterion.	
Key secondary: TA	Danicopan vs. placebo as add-on therapy to C5 inhibitor	All randomized PNH patients with CE-EVH while on C5 inhibitor treatment	Binary indicator (Yes/No) of achieving TA through the randomized Treatment Period 1, defined as remaining transfusion free and not requiring a transfusion as per protocol-specified guidelines	TA is defined as remaining transfusion free and not requiring a transfusion as per protocol-specified guidelines while remaining on the study treatment during the randomized Treatment Period 1. Patients that withdraw from the study early during the 12-week randomized Treatment Period 1 will be considered as not achieving TA.	Treatment group difference in the proportion of patients achieving TA
Key secondary: FACIT-Fatigue scores	Danicopan vs. placebo as add-on therapy to C5 inhibitor	All randomized PNH patients with CE-EVH while on C5 inhibitor treatment	Change from Baseline to Week 12 in FACIT-fatigue scores	The analysis includes all values collected at scheduled visits while patients remain on the study treatment during the randomized Treatment Period 1. Values collected after transfusion will be included.	Treatment group difference in the mean change from Baseline to Week 12 in FACIT-fatigue scores
Key secondary: absolute	Danicopan vs. placebo as add-	All randomized PNH patients	Change from Baseline to	The analysis includes all	Treatment group difference in the

Table 2: Estimand Attributes for the Primary and Key Secondary Endpoints

Endpoint	Treatment Regimens	Targeted Patient Populations	Patient-Level Outcome Measure	Handling of Intercurrent Events	Population-Level Summary Measure
reticulocyte counts	on therapy to C5 inhibitor	with CE-EVH while on C5 inhibitor treatment	Week 12 in absolute reticulocyte counts	values collected at scheduled visits while patients remain on the study treatment during the randomized Treatment Period 1. Values collected after transfusion will be included.	mean change from Baseline to Week 12 in absolute reticulocyte counts

Abbreviations: CE-EVH = clinically evident extravascular hemolysis; FACIT = Functional Assessment of Chronic Illness Therapy; Hgb = hemoglobin; PNH = paroxysmal nocturnal hemoglobinuria; TA = transfusion avoidance; vs. = versus

7.2.2. Secondary Endpoint Analyses

7.2.2.1. Key Secondary Endpoint Analyses

The 4 key secondary efficacy endpoints of the study are as follows:

- Difference in proportion of patients with an Hgb increase of ≥ 2 g/dL at Week 12 in the absence of transfusion
- Difference in proportion of patients with RBC TA between danicopan and placebo groups during 12 weeks of treatment
- Difference in changes from Baseline in FACIT-Fatigue scores between danicopan and placebo groups at Week 12
- Difference in changes from Baseline in absolute reticulocyte counts between danicopan and placebo groups at Week 12

The estimand attributes for the key secondary endpoints are described in Table 2. The key secondary endpoints will be tested in a hierarchical manner provided that statistical significance was declared for the primary endpoint. The tests will be conducted using a closed-testing procedure in the rank order specified above so that the lack of significance of a test precludes statistical significance of subsequent tests.

The proportion of patients achieving TA throughout the 12-week randomized Treatment Period 1 will be compared between treatment groups using the Cochrane-Mantel-Haenszel (CMH) test stratified by randomization stratification factors of transfusion history (> 2 or ≤ 2 transfusions within 6 months of Screening) and screening Hgb level (< 8.5 or ≥ 8.5 g/dL). The 95% CI for the difference in the proportions between the treatment arms will be calculated using the Miettinen and Nurminen method (Miettinen, 1985). Patients who withdraw from the study treatment early or have missing transfusion occurrence assessment during the 12-week randomized Treatment

Period 1 will be considered as not achieving TA for Treatment Period 1. In addition, a supportive analysis will be conducted using alternative handling of early discontinuation in TA definition: Patients who withdraw from the study due to lack of efficacy during the 12-week randomized Treatment Period 1will be considered as not achieving TA for Treatment Period 1. For patients who withdraw from the study for any other reason during Treatment Period 1, their data up to the time of withdrawal will be used to assess TA.

The proportion of patients with an Hgb increase of ≥ 2 g/dL at Week 12 in the absence of transfusion (defined as achieving an increase of ≥ 2 g/dL in Hgb from Baseline to Week 12 and remaining transfusion free during the 12-week randomized Treatment Period 1) will be compared between treatment groups via the CMH test, and the 95% CI for difference between treatment arms will be produced using the Miettinen and Nurminen method as described above. Patients that withdraw from the study treatment early during the 12-week randomized Treatment Period 1 or have a missing Hgb value at Week 12 will be considered as not achieving the criterion.

For the endpoints of change from Baseline in FACIT fatigue scores and change from Baseline in absolute reticulocyte counts, the longitudinal postbaseline changes collected during 12-week randomized Treatment Period 1 will be analyzed using the same MMRM method used for the primary endpoint analysis. The model includes the fixed, categorical effects of treatment group, study visit, and study visit-by-treatment group interaction, as well as the fixed, continuous covariate of baseline value and the randomization stratification factors of transfusion history and screening Hgb level. An unstructured covariance matrix will be used to model the within-patient errors. If this analysis fails to converge, the following covariance matrix structures will be evaluated in the following order until model convergence is met: Toeplitz, first-order autoregressive, and compound symmetry. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The difference between treatment groups in least-square mean estimates at Week 12 and its associated SE will be calculated along with the test p-value and 2-sided 95% CI.

7.2.2.2. Other Secondary Endpoint Analyses

Other secondary endpoints are listed in Section 5.1.3.

7.2.2.2.1. Other Secondary Endpoints at Week 12

Patients' transfusion burden characterized by the number of transfusion instances and the number of RBC units transfused during the 12 weeks after the start of study treatment (ie, Treatment Period 1) and 12 weeks prior to the initiation of study treatment will be summarized by treatment group. Change in the number of transfusion units/instances from 12 weeks prior to 12 weeks after the initiation of study treatment will be compared between treatment groups via an ANCOVA model. The model will include treatment group and transfusion units/instances from 12 weeks prior.

For the endpoints of change from Baseline to Week 12 in total bilirubin, direct bilirubin, PNH RBC clone sizes (Types II and III), C3 fragment deposition on PNH RBCs, and LDH, the longitudinal changes collected during 12-week randomized Treatment Period 1 will be analyzed using the same MMRM method specified in Section 7.2.2.1. Baseline for LDH is defined as the average of all available assessments prior to the first dose of study drug.

The proportion of patients with Hgb normalization (defined as an Hgb value above lower limit of normal reference range) at Week 12 will be summarized and compared between treatment groups via the CMH test described in Section 7.2.2.1. Patients with transfusions within 4 weeks prior to Week 12 will be considered as not meeting Hgb normalization regardless of the actual value observed at Week 12.

In addition, the proportion of patients who showed an improvement of at least 3 points and the proportion of patients who showed an improvement of at least 5 points on the FACIT Fatigue scores during the 12-week randomized Treatment Period 1 will be summarized by study visit and treatment group.

7.2.2.2.2. Other Secondary Endpoints at Week 24

For patients randomized to the danicopan group and entered in Treatment Period 2, the proportion of patients with TA during the 12-week Treatment Period 2, the proportion of patients with TA through the 24-week Treatment Period 1 and Treatment Period 2, the proportion of patients with Hgb stabilization from Week 12 to Week 24, the proportion of patients with an Hgb increase of $\geq$ 2 g/dL at Week 24 in the absence of transfusion, and the proportion of patients with Hgb normalization at Week 24 will be summarized, and 95% CI will be provided based on exact confidence limits using the Clopper-Pearson method. Hgb stabilization is defined as avoidance of more than a 1 g/dL decrease in Hgb levels at Week 24 from Week 12. Patients with transfusions within 4 weeks prior to Week 24 will be considered as not meeting Hgb stabilization or Hgb normalization regardless of the actual value observed at Week 24.

For patients randomized to the danicopan group, change in transfusion burden (the number of transfusion instances and the number of RBC units transfused) from 24 weeks prior to 24 weeks after the initiation of study treatment and change in FACIT Fatigue scores from Baseline to Week 24 will be summarized. The mean change estimate and its associated 95% CI will be provided.

For patients randomized to the placebo group and switched to active danicopan during Treatment Period 2, the proportion of patients with TA during the 12-week Treatment Period 2, as well as the change in transfusion burden from the 12-week randomized Treatment Period 1 to 12-week Treatment Period 2, will be summarized.

For numeric endpoints with longitudinal values collected during Treatment Period 2 (Hgb, reticulocyte count, FACIT Fatigue scores, total bilirubin, direct bilirubin, RBC clone sizes (Types II and III), C3 fragment deposition on PNH RBCs, and LDH), the longitudinal changes from Baseline during the 12-week Treatment Period 2 will be analyzed using MMRM method within each treatment arm. The model includes the randomization stratification factors of transfusion history and screening Hgb level, study visit, and baseline value. The least-square mean estimate for the change from Baseline to Week 24 will be provided with 95% CI.

For numeric endpoints, the longitudinal least-square mean change profiles throughout the 24-week Treatment Period 1 and Treatment Period 2 from the MMRM analyses will be graphed in spaghetti plots.

At the time of DBL for the placebo-controlled Treatment Period 1, it is anticipated that some patients may still be ongoing during Treatment Period 2 (between Week 12 and Week 24). In this scenario, the analysis described above for efficacy endpoints at Week 24 will be conducted

on a subset of patients who already reached the end of Treatment Period 2 (either completed or discontinued from Treatment Period 2), that is, excluding patients still ongoing during Treatment Period 2.

7.2.3. Exploratory Endpoint Analyses

Exploratory endpoints are listed in Section 5.1.4.

For EQ-5D-3L scores (visual analog scale and US and UK health state index), EORTC-QLQ-C30 scores, WPAI:ANS scores, and HRU scores, the observed values and changes from Baseline will be summarized descriptively by study visit and treatment group for both Treatment Period 1 and Treatment Period 2.

The longitudinal changes collected during 12-week randomized Treatment Period 1 in EQ-5D-3L scores and EORTC-QLQ-C30 scores will also be analyzed using the same MMRM method specified in Section 7.2.2.1.

The proportion of patients who showed an improvement of at least 10 points for the following 3 subscales from the EORTC-QLQ-C30 will be summarized by study visit and treatment group: global health status, physical functioning, and EORTC-Fatigue.

Refer to Section 10.5 for a more detailed description of the scales and the scoring methods.

7.2.4. Other Efficacy Analyses

For patients randomized to the placebo group and switched to active danicopan during Treatment Period 2, the proportion of patients who had an increase of ≥ 2 g/dL in Hgb from Week 12 to Week 24 in the absence of transfusion during the 12-week Treatment Period 2 will be summarized.

All primary, secondary, and exploratory efficacy endpoints will be descriptively summarized for the LTE Period, as well as for Treatment Period 1 and Treatment Period 2.

7.2.5. Pharmacokinetic and Pharmacodynamic Analyses

Predose and postdose PK samples will be taken at the time points as listed in the SoA in the study protocol. Individual plasma concentration data for all patients who received at least 1 dose of study drug (ie, danicopan) and who have evaluable PK data will be included in the PK analysis for danicopan. All individual predose trough concentrations (C_{trough}) will be listed, and descriptive statistics (number of nonmissing observations [N], arithmetic mean, SD, median, coefficient of variation percentage [CV%], minimum, maximum, geometric mean, and geometric CV%) will be used to summarize the predose concentrations at each visit. Similarly, all individual postdose (2-hour) concentrations will be listed and summarized for each visit using descriptive statistics. 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 received at least 1 dose of study drug and who have evaluable baseline and postdose PD data. Predose and postdose PD samples will be taken at the time points as listed in the SoA in the study protocol and Protocol Table 4. Concentrations of the biomarkers (Bb, FD, C3, and free C5) at Baseline and over time, activities of APH and CH50 relative to positive control and relative to Baseline, and percentage changes in

APH, CH50, and Bb from Baseline will be listed for all individuals and mean ± SD for each treatment group will be presented in figures. Descriptive statistics (number of nonmissing observations [N], arithmetic mean, SD, median, CV%, minimum, maximum, geometric mean, and geometric CV%) will be summarized by study visit and treatment group.

Assessments of danicopan PK-PD relationships may be explored using data from this study or in combination with data from other studies.

Analyses for population-PK and PK-PD relationships are out of scope of the current SAP and will be specified in a separate document.

7.2.6. Handling of Samples With Table-top Hemolysis

It is possible that a small proportion of central laboratory chemistry samples can undergo in vitro erythrocyte lysis or table-top hemolysis (TTH) caused by sample mishandling. This is unrelated to hemolysis due to PNH. The reasons for TTH vary and include delayed or improper centrifugation and traumatic blood draws. In addition, PIGA-deficient erythrocytes from patients with PNH are more susceptible to mechanical lysis than non-PNH erythrocytes (Smith, 1985). If such TTH occurs, it results in release of RBC contents including LDH, potassium, and aspartate aminotransferase (AST). In contrast to hemolysis in patients with PNH, in which serum potassium is normal, for samples affected by TTH, both potassium and LDH are markedly and proportionally increased (Goyal, 2015; Oostendorp, 2012). Marked hyperkalemia (defined as ≥ 6 mmol/L) seen in TTH, but not PNH hemolysis, differentiates TTH (in vitro) from PNH hemolysis (in vivo) and is not clinically significant (Hollander-Rodriguez, 2006; Kovesdy, 2014).

For analysis purposes, samples from the central laboratory with serum potassium ≥ 6 mmol/L and LDH ≥ 2× upper limit of normal (ULN) will be defined as having TTH. Due to the artefactual increase in certain chemistry laboratory values in samples affected by TTH, potassium, alanine aminotransferase (ALT), AST, magnesium, phosphorous, and LDH values in samples affected by TTH will not be used in the analysis of any efficacy or safety endpoints.

7.3. Safety Analyses

All safety analyses will be conducted on the SS. For the 12-week randomized Treatment Period 1 DBL, all safety data available at the time of data cut-off will be provided in patient listings. AEs will be coded in MedDRA (version 23.1 or above) and presented by MedDRA SOC and PT. No formal hypothesis testing is planned. Unless otherwise specified, Baseline is defined as the last available assessment prior to the first dose of study drug.

7.3.1. Study Duration, Treatment Compliance, and Exposure

Treatment exposure duration (days for a specific period) is calculated as date of the last dose for the period − date of the first dose for the period + 1. Treatment exposure duration will be summarized by treatment group with descriptive statistics for Treatment Period 1, Treatment Period 2, LTE Period, and throughout the entire study treatment. In addition, treatment exposure duration will also be summarized by dose level for all patients treated with danicopan.

Treatment compliance percentage based on actual danicopan dosage is defined as the total dose amount of danicopan received divided by the total dose amount of danicopan expected to be

received by a patient during a specific period, such as a visit period or a treatment period. Specifically,

Expected total dose amount = assigned dose level × daily frequency × period duration in number of days

Received total dose amount = tablet dosage level × number of tablets received

where the number of tablets received is calculated as number of tablets dispensed - number of tablets returned for a specific period.

In addition, treatment compliance percentage based on tablet counts only is defined as the total number of tablets received divided by the total number of tablets expected to be received by a patient during a specific period, such as a visit period or a treatment period.

Treatment compliance percentage will be calculated for each visit interval with study drug accountability assessment and for Treatment Period 1, Treatment Period 2, and LTE Period for each patient and will be summarized by treatment group. In addition, the number and proportion of patients who had treatment compliance percentage in range by increments of 10% (ie, ≥ 90% to ≤ 100%; ≥ 80% to < 90%; ≥ 70% to < 80%, etc) during Treatment Period 1 and Treatment Period 2 will also be summarized by treatment group.

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

7.3.2. Adverse Events

AEs will be classified by SOC and PT using the latest available version of MedDRA (version 23.1 or above) and will be reported by treatment group and overall. AEs determined to have occurred before the first dose of the study drug will be classified as pretreatment adverse events (PTAEs). AEs that occur on or after the first dose of study drug or placebo will be considered treatment-emergent adverse events (TEAEs) as described in Section 10.4.7. Analyses of PTAEs and TEAEs will be tabulated and presented separately. Patients having multiple AEs within a category (eg, overall, SOC, and PT) will be counted once in that category. For severity/relationship tables, the patient's highest grade/most related event within a category will be counted. Percentages will be based on the number of treated patients in the SS within a cohort and overall. Tables will be sorted by alphabetical order of SOC and by descending frequency of PT within SOC. PTs with the same frequency will be sorted in alphabetical order. Listings will be provided for all TEAEs and PTAEs for the SS. TEAE summaries will be produced for the 12-week randomized Treatment Period 1, Treatment Period 2, and LTE Period. Any TEAEs spanning across treatment periods will be only counted once in the treatment period the event started.

AEs will include the displays described in the following subsections.

7.3.2.1. Overall Summary of AEs

An overall summary table of TEAEs will be presented using summary statistics (n, %). The number of events (n) and the number of patients with events (n, %) will be displayed for the following event subcategories:

- Total number of TEAEs and patients with TEAEs

- Related TEAEs
- Not related TEAEs
- Grade 1 TEAEs
- Grade 2 TEAEs
- Grade 3 TEAEs
- Grade 4 TEAEs
- Grade 5 TEAEs

The number and percentage of patients who withdraw from the study due to an AE, who have any TEAE leading to study treatment discontinuation, who have any TEAE leading to study drug dose reduction, or who died on the study will be presented. The overall summary described above will also be produced separately for SAEs, with the exception of severity grading.

7.3.2.2. AEs and SAEs by SOC and PT

The number of TEAEs and the number and percentage of patients with events will be presented by SOC and PT. Patients are counted once in each SOC and PT. Percentages will be based on the total number of patients who received at least 1 dose of study drug (danicopan or placebo) in the treatment group. SAEs will be summarized similarly.

In addition, the summary described above will also be produced for nonserious TEAEs for clinicaltrials.gov results posting purpose.

Additional summary tables stratifying AEs by age, sex, and race will also be provided. For all patients received danicopan treatment during the study, TEAEs will also be summarized by the dose levels the patients were on when AE started.

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

The number of TEAEs and the number and percentage of patients with events will be presented by SOC and PT as described above by relationship to study treatment (related or not related). If a patient has > 1 occurrence of an AE, the strongest relationship to study treatment will be used in the summary table. SAEs will be summarized similarly.

7.3.2.4. AEs by SOC, PT, and Severity

The number of TEAEs and the number and percentage of patients with events will be presented by SOC and PT as described above by severity (Grade 1, 2, 3, 4, or 5). If a patient has > 1 occurrence of an AE, the highest grade will be used in the summary table.

7.3.2.5. Deaths, Other SAEs, and Other Significant AEs

A listing of patient deaths will be produced.

Events of interest in this study include TEAEs of meningococcal infections and liver enzyme elevations. These events of interest will be summarized by treatment group in tabular form. See Section 10.4.7 for a list of AE MedDRA terms that will be considered for these summaries.

7.3.3. Other Safety

7.3.3.1. Analyses for Laboratory Tests

Observed values and changes from Baseline in numeric central laboratory parameters will be summarized descriptively at each visit by treatment group. Baseline is defined as the last nonmissing assessment value prior to the first dose of study drug. All laboratory values will be classified as normal, below normal, or above normal based on normal ranges supplied by the central laboratory. Shift tables over time will be presented for all central laboratory values, where applicable, using normal, low, or high based on normal range values. For purposes of analyses, laboratory results based on standardized units will be used.

Incidence of clinical laboratory abnormalities Grade 3 and above (based on version 5.0 of the National Cancer Institute CTCAE) will be summarized. For laboratory tests with CTCAE toxicity grades available, laboratory abnormalities will be summarized by worst treatment emergent grade.

Box plots will be presented for the following central laboratory parameters by visit: Hgb, LDH, bilirubin (total and direct), creatinine, estimated glomerular filtration rate, AST, ALT, gamma-glutamyl transferase, absolute neutrophil count, platelets, D-dimer, and prothrombin time/partial thromboplastin time/international normalized ratio. Additionally, scatter plots of the worst value after the first study drug versus Baseline will be provided for the aforementioned parameters.

The number and percentage of patients who had postbaseline laboratory values meeting any of the following criteria will be summarized by treatment group:

- ALT > 3× ULN, 5× ULN, and 8× ULN
- AST > 3× ULN, 5× ULN, and 8× ULN
- ALT > 3× ULN and total bilirubin > 2× ULN
- ALT > 3× ULN and total bilirubin > 2× ULN and alkaline phosphatase < 2× ULN

In addition, the liver enzyme elevation summary described above will also be produced by the subgroups of patients who had and did not have ALT > 2× ULN at Baseline.

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

7.3.3.2. Vital Signs

Absolute values and changes from Baseline in vital signs (BP, HR, RR, and temperature) at each visit will be summarized descriptively by treatment group. Baseline is defined as the last nonmissing assessment value prior to the first dose of study drug.

A listing of vital signs will be presented.

Absolute values and changes from Baseline in weight will be summarized by visit and treatment group. A listing of weight will be produced.

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

7.3.3.3. Electrocardiograms

Descriptive statistics by visit and treatment group will be presented for each ECG parameter (including PR interval, QRS duration, RR interval, QT interval, and QTcF interval) value and for change from baseline values.

The number and percentage of patients who had postbaseline abnormal ECG values meeting any of the following criteria will be summarized by treatment group:

- QT and QTcF intervals > 450 milliseconds
- QT and QTcF intervals > 480 milliseconds
- QT and QTcF intervals > 500 milliseconds
- QT and QTcF interval increases from Baseline > 30 milliseconds
- QT and QTcF interval increases from Baseline > 60 milliseconds

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

7.3.3.4. Nondrug Therapies and Procedures

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

7.3.3.5. Patients Enrolled Under Local Amendment

For patients enrolled under local protocol amendments and receiving background therapy ravulizumab as IMP in the study, the number and percentage of patients developing ADA and antidrug-neutralizing antibodies, where applicable, will be summarized by treatment group and overall. A by-patient listing of ADA laboratory results will be produced.

The number of TEAEs and the number and percentage of patients with events will be presented by SOC and PT and by relationship to ravulizumab background therapy (related or not related).

7.4. COVID-19-Related Data Analysis

The following Coronavirus Disease 2019 (COVID-19)-related data will be collected in this study:

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

The number of subjects with modified study visits and the reasons for modified study visits (COVID-19 related or other) will be summarized by treatment group and overall. Similarly, the number of subjects with missed study visits and the reasons for missed study visits (COVID-19 related or other) will be summarized by treatment group and overall.

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

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

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

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

8. INTERIM ANALYSIS

An interim analysis may be conducted when approximately 75% of patients (planned as N = 63) have been randomly assigned to study treatment and have had the opportunity to complete the 12-week, placebo-controlled, randomized 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 4 key secondary endpoints, will be evaluated using the alpha-spending methods specified below to control family-wise error rate.

- The evaluation of the primary endpoint at the interim analysis will use the gamma family alpha-spending function (Hwang, 1990) with parameter -4. Specifically, the alpha level assigned for the primary endpoint at interim is 2-sided 0.018. Correspondingly, if the interim analysis is conducted, the nominal significance level for the primary endpoint at the final analysis is 2-sided 0.046.
- The evaluation of key secondary endpoints at the interim analysis will use the gamma family alpha-spending function with parameter 1. Specifically, the alpha level assigned for key secondary endpoint at interim is 2-sided 0.042. Correspondingly, if the interim analysis is conducted, the nominal significance level for key secondary endpoints at the final analysis is 2-sided 0.024.

Due to the hierarchical nature and closed-testing procedure of the primary and key secondary endpoints described in Section 7.2.1 and Section 7.2.2 and proper alpha-spending function used to control the error rate at a 2-sided 0.05 level for each endpoint, the overall family-wise error rate is controlled at a 2-sided 0.05 level across the primary and key secondary endpoints among the interim and final full enrollment analyses (Glimm, 2010; Tamhane, 2010).

The interim analysis DBL will include all data collected up to the data cut-off date mentioned above. For the interim analysis on efficacy, 75% of patients (planned as N = 63) who have been randomly assigned to study treatment and have had the opportunity to complete the 12-week, placebo-controlled, randomized Treatment Period 1 will form the interim efficacy analysis set. The efficacy analyses on the primary and key secondary endpoints will be conducted on the interim analysis set using the same methods specified in Section 7.2.1 and Section 7.2.2. The interim analysis for efficacy is considered successful if the tests of the primary endpoint of change in Hgb levels at Week 12 (as assessed by both the re-randomization test and the test directly from the MMRM model using the actual treatment assignments) and the key secondary endpoints of patients with an Hgb increase of ≥ 2 g/dL at Week 12 in the absence of transfusion and patients with TA through the 12-week randomized Treatment Period 1 are all statistically significant based on the significance levels specified above.

If there are more than 63 patients reaching the end of Treatment Period 1 by the interim analysis data cut-off described above (e.g., due to multiple patients randomized or completed randomized Treatment Period 1 on the same day), the actual number of patients included will be used to calculate the actual information fraction and the alpha spending thresholds for interim analysis based on the same gamma functions specified above. For example, if N=64 (64/84=76%) patients are included in the interim analysis for efficacy, the interim alpha level will be 2-sided 0.019 for primary endpoint and 0.042 for key secondary endpoints. If interim analysis is

conducted, the nominal alpha level for full enrollment analysis will be 0.044 for primary endpoint and 0.024 for key secondary endpoints.

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 made by Alexion after reviewing the recommendation from the DMC. If such decision is made, the study will be unblinded and all efficacy, PK, and PD endpoint analyses will be conducted using the interim analysis set based on available data collected up to interim DBL cut-off date. All patients dosed by the interim database cut-off date will form the interim safety analysis set. Safety analyses will be conducted based on available data collected up to the cut-off date. A CSR will be produced based on the interim analysis results.

If the interim analysis did not meet the success criteria specified above, the study will continue as planned to full enrollment with no modifications.

The decision on whether to perform the efficacy interim analysis will be based on enrollment progression. If full enrollment is already completed or close to complete by the time of the interim analysis specified above, the study will go directly to the final full analysis without an interim analysis. If the interim analysis for efficacy is not conducted, a full alpha level of 2-sided 0.05 will be used for the final analysis with full enrollment.

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10. APPENDICES

10.1. Protocol Schedule of Assessments

Refer to the protocol for a schedule of assessments.

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

- Re-randomization test is specified as the primary method for treatment comparison for primary endpoint analysis in Section 7.2.1 and the treatment comparison test directly from the MMRM model is specified as sensitivity analysis according to the US local protocol amendment. It is also clarified that the treatment comparison test directly from the MMRM model is the primary analysis while the re-randomization test is sensitivity analysis for ex-US countries.
- The efficacy interim analysis success criterion in Section 8 is updated to require significance from both the re-randomization test and the test directly from the MMRM model for the primary endpoint.
- Patient profile plots of Hgb values over time are added in Section 7.2.1.5.
- The definition of TEAE of Interest – Liver Enzyme Elevation is updated in Section 10.4.7.
- A summary of TEAEs by dose level for all patients treated with danicopan is added in Section 7.3.2.2.
- An analysis of patients with an improvement of at least 5 points on the FACIT Fatigue scores during the 12-week randomized Treatment Period 1 is added in Section 7.2.2.2.1.
- Section 10.6 is added to specify additional summary outputs to be produced for Japanese subgroup to support PMDA submission.

10.3. Sample Size, Power, and Randomization

The PNH literature indicates that patients with PNH who have received an approved C5 inhibitor but are still anemic have Hgb levels, on the average, of 10.5 g/dL (McKinley, 2017). All patients entering this study will have an Hgb level of ≤ 9.5 g/dL. A minimum difference of 2 g/dL 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 receive danicopan or placebo. It is anticipated that approximately 10% of patients will discontinue prior to the primary endpoint at Week 12. For the primary endpoint of change from Baseline to Week 12 in Hgb level, the statistical power using 2-sample t-test is 99% to detect the difference in mean change from Baseline of 2 g/dL (alternative hypothesis), assuming the 2-sided statistical significance level of 0.05 and the SD of 1.6 g/dL, which was estimated from results of Study ACH471-101. For the key secondary endpoint of patients with an Hgb increase of ≥ 2 g/dL at Week 12 in the absence of transfusion, the study has > 95% power for significant difference between treatment groups under a 2-sided 0.05 level, 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 significant difference between treatment groups, 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 scores, the study has 91% power with 2-sample t-test to detect 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 an SD of 11 for FACIT-Fatigue change, which was observed in Study ALXN1210-PNH-301 in PNH patients. The power is 80% based on the SD assumption of 13, which was observed in Study ACH471-101.

The randomization for treatment group assignment will be stratified by transfusion history (ie, > 2 or ≤ 2 transfusions within 6 months of Screening), screening Hgb level (ie, < 8.5 and ≥ 8.5 g/dL) at Screening, and Japanese patients (defined as patients enrolled from Japan)/non-Japanese patients. The stochastic dynamic allocation rules (ie, minimization) 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 system on Study Day 1.

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

10.4. Technical Specifications for Derived Variables

The following derived data will be calculated prior to analysis.

10.4.1. Age

Age will be presented as the number of years between date of birth and the reference date. The following ages (in years) may be computed using the formula (reference date − date of birth + 1) / 365.25, with reference dates indicated as follows in Table 3:

Table 3: Age and Reference Date

Age	Reference Date
Age at informed consent	Date of signing ICF
Age at randomization	Date of randomization
Age at PNH diagnosis	Date of PNH diagnosis
Age at the first dose of study drug	Date of the first dose of study drug

Abbreviations: ICF = informed consent form; PNH = paroxysmal nocturnal hemoglobinuria

For all dates, in cases where only the month and year are provided for a date, the day for the date will be imputed as 15. Missing month will be imputed as June. In cases where the day is observed but the month is missing, the date will be imputed as June 15.

10.4.2. Disease Duration

PNH disease duration will be presented as the number of years between the date of the first infusion and the date of PNH diagnosis (ie, INT [(date of the first infusion − date of PNH

diagnosis + 1) / 365.25] or a similar formula using months and years or years only in the event of partial dates for PNH diagnosis).

10.4.3. Definition of Baseline Values

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

10.4.4. Change From Baseline

Change in values from Baseline will be calculated as follows.

Change in value = (subsequent value − baseline value), given that both the baseline value and subsequent value are nonmissing.

10.4.5. Percent Change From Baseline

Percent change in values from Baseline will be calculated as follows.

% Change in value = (change in value) / (baseline value) × 100

where change in value = (subsequent value − baseline value), given that the baseline value is nonmissing and nonzero and the subsequent value is nonmissing.

10.4.6. Analysis Visits

Summaries over postbaseline time points or analyses at specific postbaseline time points will be performed based on the list of visits described in the SoA in the study protocol. For all assessments, the number of days from Baseline will be calculated using the following formula: (date of assessment) - (date of first study treatment) + 1. This number of days will be used to assign analysis visit. This may not always correspond to the electronic case report form visit.

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

For all visits, the lower bound and the upper bound for the analysis visit windows are defined as the midpoints of the target date of scheduled visits. If the date of assessment falls between the lower bound and the upper bound for a visit as defined in the SoA in the study protocol, then it will be assigned to that visit. If the interval separating 2 scheduled visits is an even number of days, that middle day will be included in the lower bound of the next visit window.

For example, for an assessment with a scheduled visit Day 127, a prior scheduled visit Day 113, and a subsequent scheduled visit Day 141, the window will start at 120 days from Baseline and will go to 133 days from Baseline.

If only 1 record is within an analysis visit window, the data from that record will be used in the analysis. If > 1 record is within the same analysis visit window, the record closest to the

midpoint of the interval will be used in the analysis. If 2 records are "tied" before and after the middle of the interval, the earlier record will be used in the analysis.

10.4.7. Adverse Events

The analysis of AEs is described in detail in Section 7.3.2.

Treatment-emergent AEs (TEAEs) are events with start dates and start times on or after the date and time of the first study drug dose. If the start date of an AE is partially or completely missing and the end (stop) date and time of the AE does not indicate that it occurred prior to first dose, then the determination of treatment-emergent status will be based on the following:

- If the start year is after the year of the first study drug dose, then the AE is treatment emergent; else,
- If the start year is the same as the year of the first study drug dose and
    - The start month is missing, then the AE is treatment emergent; else if
    - The start month is present and is the same or after the month of the first study drug dose, then the AE is treatment emergent; else,
- If the start date is completely missing, then the AE is treatment emergent.

All other AEs are considered PTAEs.

Patient percentages are based on the total number of treated patients in the particular treatment group. The rate of AEs adjusted by patient exposure is defined as number of events per 100 patient-years (i.e., number of events x 100/Total patient-years). Total patient-years is summed across all individual patient exposure duration.

The following provides a list of AESIs. In addition, a medical review will be done to ensure that no relevant events were missed:

Meningococcal infections: MedDRA PTs of Meningococcal bacteraemia, Meningitis meningococcal, Meningococcal infection, Meningococcal sepsis, Meningococcal carditis, Encephalitis meningococcal, Endocarditis meningococcal, Myocarditis meningococcal, Optic neuritis meningococcal, and Pericarditis meningococcal.

Liver enzymes elevation: MedDRA PTs fall under the following two SMQs

- SMQ Drug related hepatic disorders - severe events only [narrow] [20000007]
- SMQ Liver related investigations, signs and symptoms [narrow] [20000008]

10.4.8. Concomitant Medications/Therapies

The analysis of concomitant medications and therapies is described in detail in Section 7.1.4.

Concomitant medications or therapies are defined as any nonstudy medications or therapies that were taken or given while the patient also received study medication. A medication or therapy will be considered concomitant if the start date is on or after the date of the first study drug infusion, or if the start date is before the first infusion date and the end (stop) date is after the first infusion date. If the start date of a medication/therapy is partially or completely missing and

the end (stop) date of the medication/therapy does not indicate that it ended prior to first infusion, then the determination of the concomitant status will be based on the following:

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

All other medications/therapies are considered Prior Medications/Therapies.

10.5. Additional Details on Statistical Methods

10.5.1. FACIT-Fatigue Calculations

The FACIT-Fatigue questionnaire consists of 13 items scored on a 5-point Likert scale (0 = not at all, 4 = very much). The FACIT-Fatigue subscale scoring guideline (version 4) will be used as follows:

All negatively stated items (ie, all items except An5 and An7 from the CRF) are to be reversed by subtracting the response from 4. After reversing the proper items, all items are summed to obtain a score. The fatigue subscale score is then calculated by multiplying the sum of the item scores by 13, then dividing by the number of items answered. When there are missing data, prorating by subscale in this way is acceptable as long as > 50% of the items were answered. The score has a range of 0 through 52 and the higher the score, the better the QoL.

10.5.2. EORTC QLQ-C30 Scoring Calculations

The EORTC QLQ-C30 (version 3.0) consists of a total of 30 questions related to QoL, scored on a 4-point Likert scale for the first 28 questions (1 = not at all, 4 = very much) and scored on a scale of 1 (very poor) to 7 (excellent) for the final 2 questions that probe the patient's overall health and QoL. It is composed of both multi-item scales and single-item measures. These include 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea and vomiting), a global health status and a number of single items assessing additional symptoms (dyspnea, loss of appetite, insomnia, constipation, and diarrhea), and financial difficulties. The following Table 4 explains the scoring procedure.

Table 4: Scoring the EORTC QLQ-C30

EORTC QLQ-C30 Scales	Scale	Item Range[a]	Item Numbers	Raw Score[b]
Global health status/QoL	QL2	6	29 and 30	(Q29 + Q30) / 2
Functional scales				
Physical functioning	PF2	3	1 to 5	(Q1 + Q2 + Q3 + Q4 + Q5) / 5

Table 4: Scoring the EORTC QLQ-C30

EORTC QLQ-C30 Scales	Scale	Item Range[a]	Item Numbers	Raw Score[b]
Role functioning	RF2	3	6 and 7	(Q6 + Q7) / 2
Emotional functioning	EF	3	21 to 24	(Q21 + Q22 + Q23 + Q24) / 4
Cognitive functioning	CF	3	20 and 25	(Q20 + Q25) / 2
Social functioning	SF	3	26 and 27	(Q26 + Q27) / 2
Symptom scales				
Fatigue	FA	3	10, 12, and 18	(Q10 + Q12 + Q18) / 3
Nausea and vomiting	NV	3	14 and 15	(Q14 + Q15) / 2
Pain	PA	3	9 and 19	(Q9 + Q19) / 2
Dyspnea	DY	3	8	Q8
Insomnia	SL	3	11	Q11
Appetite loss	AP	3	13	Q13
Constipation	CO	3	16	Q16
Diarrhea	DI	3	17	Q17
Financial difficulties	FI	3	28	Q28

[a] Item range is the difference between the possible maximum and the minimum response to individual items.
[b] Raw score is the mean of the component items.
Abbreviations: EORTC = European Organization for Research and Treatment of Cancer; QLQ-C30 = Quality of Life Questionnaire-Core 30 Scale; QoL = Quality of Life

Once the raw scores are calculated, a linear transformation from 0 through 100 is applied to obtain the particular score as follows:

For functional scales: Score = {1 − (raw score − 1) / range} × 100

For all other scales/items: Score = {(raw score − 1) / range} × 100

Each scale has a range of 0% through 100%. A high scale score represents a higher response level. Thus, a high score for a functional scale represents a high level of functioning but a high score for a symptom scale represents a high level of symptomatology/problem.

Missing data: In the case of multi-item scales missing one of the items, raw scores can still be calculated using the completed items so long as > 50% of the items were answered. Thus, for example, if the fatigue scale is missing Q10, the average of Q12 and Q18 would be used to calculate the raw score. For single-item measures, the score will be set to missing.

10.5.3. EQ-5D-3L Scoring Calculations

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

10.5.3.1. Health State Index

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

For health state index, scoring algorithms derived for the US general population will be applied using individual health profiles. This scoring algorithm was derived from time tradeoff

assessments of EQ-5D health states made by a population sample of some 4000 US adults in face-to-face household interviews (Shaw, 2005). Health state index is to be calculated using the below equation with the US population-based sample estimates (Shaw, 2005). Variable definition is provided in Table 5.

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

Table 5: Definition for Variables Used in Calculating Health State Index Using US Population Estimates

Variable	Definition
M2	1 if mobility is Level 2; 0 otherwise
M3	1 if mobility is Level 3; 0 otherwise
S2	1 if self-care is Level 2; 0 otherwise
S3	1 if self-care is level 3; 0 otherwise
U2	1 if usual activities is Level 2; 0 otherwise
U3	1 if usual activities is Level 3; 0 otherwise
P2	1 if pain/discomfort is Level 2; 0 otherwise
P3	1 if pain/discomfort is Level 3; 0 otherwise
A2	1 if anxiety/depression is Level 2; 0 otherwise
A3	1 if anxiety/depression is Level 3; 0 otherwise
D1	The number of dimensions at Level 2 or 3 beyond the first
I2	The number of dimensions at Level 2 beyond the first
I3	The number of dimensions at Level 3 beyond the first

In addition, the scoring algorithms derived from the UK population will also be applied to obtain the health state index, using the equation below (Dolan, 1997). Variable definition is provided in Table 6.

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

Table 6: Definition for Variables Used in Calculating Health State Index Using UK Population Estimates

Variable	Definition
a	Constant: associated with any move away from full health. a=1 if any of the responses to the 5 domains is Level 2 or 3; a=0 if responses to all the 5 domains are Level 1.
MO	1 if mobility is Level 2; 2 if mobility is Level 3; 0 otherwise
SC	1 if self-care is Level 2; 2 if self-care is Level 3; 0 otherwise
UA	1 if usual activities are Level 2; 2 if usual activities are Level 3; 0 otherwise
PD	1 if pain/discomfort is Level 2; 2 if pain/discomfort is Level 3; 0 otherwise
AD	1 if anxiety/depression is Level 2; 2 if anxiety/depression is Level 3; 0 otherwise
M2	1 if mobility is Level 3; 0 otherwise
S2	1 if self-care is Level 3; 0 otherwise
U2	1 if usual activities are Level 3; 0 otherwise
P2	1 if pain/discomfort is Level 3; 0 otherwise

Table 6: Definition for Variables Used in Calculating Health State Index Using UK Population Estimates

Variable	Definition
A2	1 if anxiety/depression is Level 3; 0 otherwise
N3	1 if any dimension is Level 3; 0 otherwise

10.5.3.2. EuroQoL Visual Analog Scale

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

10.5.4. SAS Code for MMRM Analysis

The main analysis method for the primary endpoint of change from Baseline to Week 12 in Hgb and several numeric secondary endpoints is the MMRM analysis. The basic Statistical Analysis Software® (SAS®) code for the MMRM analysis of change in Hgb is given by:

```
proc mixed data = ADEFF method = reml;
class subjid trt01pn avisitn;
model chg = trt01pn avisitn trt01pn * avisitn base txstrata / ddfm = kr solution;
repeated avisitn / type = un subject = subjid;
lsmeans trt01pn * avisitn / cl diff;
run;
```

where subjid is the patient identifier, trt01pn is the randomized treatment group, avisitn is the visit variable, base is the value at Baseline, txstrata is the randomization stratification factor of transfusion history, and chg is the visit-wise change from Baseline in Hgb.

10.5.5. SAS Code for Tipping Point Sensitivity Analysis

The following illustrates the tipping point sensitivity analysis for the primary endpoint of change from Baseline to Week 12 in Hgb where a search is conducted for a tipping point that reverses the study conclusion from being favorable to active danicopan to being unfavorable. For the tipping point sensitivity analysis, the missing data mechanism for the missing change from baseline values at Week 12 will be MNAR.

Markov Chain Monte Carlo imputation method will first be used to fill in the intermittent missing values under the assumption of MAR and generate a monotone missing data pattern (eg, 100 datasets will be generated). Below is sample code:

```
proc mi data = ADEFF out = mono seed = 123 nimpute = 100;
by trt01pn;
```

```
mcmc impute = monotone;
var base Week1 - Week12;
run;
```

where trt01pn is the randomized treatment group, base is the Hgb value at Baseline, and Week 1 − Week 12 are the changes from Baseline in Hgb at the scheduled postbaseline visits from Week 1 to Week 12.

Subsequently, for a specific shift parameter value of delta, imputations are performed for missing change observations at all visits sequentially for all patients by sampling from an MAR-based MI model including the variables of randomized treatment group, baseline value, and values observed at all scheduled visits during the 12-week randomized Treatment Period 1, then applying delta adjustments at each visit for patients treated in the danicopan arm. The following is a partial SAS code for the multiple imputation analysis for a specified shift parameter value of delta at Weeks X and Y:

```
proc mi data = mono out = outmi seed = 123 nimpute = 1;
by _imputation_;
class trt01pn;
monotone method = reg;
var trt01pn base Week 1 – Week12;
mnar adjust (Week X / shift = delta adjustobs = (trt01pn = 'danicopan'));
mnar adjust (Week Y / shift = delta adjustobs = (trt01pn = 'danicopan'));
run;
```

Once completed datasets are generated, each of the 100 imputed datasets will then be analyzed separately using the MMRM model specified for the primary endpoint analysis (refer to Section 10.5.4 for SAS code), and inferences from each complete dataset will be combined via PROC MIANALYZE procedure to obtain an overall test statistic for the specified shift parameter value of delta.

```
proc mianalyze data = diff2;
by avisitn;
modeleffects estimate;
stderr;
run;
```

Multiple shift parameter values will be tested until the inference concludes that statistical significance disappears. In the tipping point analysis for the primary endpoint, a series of delta values for Hgb decreasing in increments of -0.5 g/dL will be applied (ie, -0.5, -1, -1.5, …).

10.6. Additional Analyses for Japanese Subgroup

In addition to the subgroup analysis described in Section 7.2.1.2, the following summary outputs will be produced for the subgroup of Japanese patients. Unless otherwise specified, the endpoints and variables definitions and methods used for these outputs will be the same as described in Section 7. These outputs may be used to support PMDA submission but will not be required to be included in study CSR.

- Summaries of study disposition, protocol deviations, demographics and baseline characteristics, disease characteristics, medical history, prior and concomitant medications, and C5 inhibitor background therapy as described in Section 7.1.
- Summaries of danicopan PK concentration and PD biomarkers over time as described in Section 7.2.5 for the subgroup of Japanese patients and the subgroup of non-Japanese patients.
- Summary of study drug exposure as described in Section 7.3.1 .
- Summaries of AE overview; TEAEs and SAEs by SoC and preferred term; TEAEs by severity; TEAEs by relationship to study treatment; TEAEs leading to study drug discontinuation; TEAEs leading to study drug dose reduction; TEAEs of Interest (meningococcal infections and liver enzyme elevations) as described in Section 7.3.2.
- Summary of patients with postbaseline laboratory values meeting the liver enzyme elevation criteria as described in Section 7.3.3.1.