Alexion Pharmaceuticals, Inc.

# STATISTICAL ANALYSIS PLAN

ACH471-103

| | |
|---|---|
| **Study Title:** | An Open-Label Study to Evaluate Efficacy and Safety of Long-Term Treatment With ACH-0144471 in Patients with PNH Who Completed Clinical Study ACH471-100 |
| **Study Number:** | ACH471-103 |
| **Study Phase:** | 2 |
| **Product Name:** | Danicopan (ALXN2040, previously ACH-0144471) |
| **Protocol Version:** | Amendment 4 (Version 5.0), dated 13 March 2018 |
| **Author:** | PPD |
| **Version Number:** | V 1.0 |
| **Effective Date:** | 23 February 2021 |

# 1. APPROVAL SIGNATURES

PPD

01-Mar-2021 | 15:01:21 EST

Date dd Mmm yyyy

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01-Mar-2021 | 15:27:09 EST

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01-Mar-2021 | 15:20:21 EST

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

## TABLE OF CONTENTS

# 3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

**Table 1. Abbreviations and acronyms**

| Abbreviation or acronym | Explanation |
|---|---|
| AE | Adverse event |
| ALT | Alanine aminotransferase (SGPT) |
| AST | Aspartate aminotransferase (SGOT) |
| ATC | Anatomical Therapeutic Chemical |
| BMI | Body mass index |
| BP | Blood pressure |
| BUN | Blood urea nitrogen |
| CBC | Complete blood count |
| cm | Centimeters |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ECG | Electrocardiogram |
| eGFR | Estimated Glomerular Filtration Rate |
| FA | Full Analysis |
| GGT | Gamma-glutamyl transferase |
| HCO3 | Bicarbonate |
| Hct | Hematocrit |
| HDL-C | High-density lipoprotein cholesterol |
| Hgb | Hemoglobin |
| HR | Heart rate |
| kg | Kilogram |
| LDH | Lactate dehydrogenase |
| LDL-C | Low-density lipoprotein cholesterol |
| MCH | Mean corpuscular hemoglobin |
| MCHC | Mean corpuscular hemoglobin concentration |
| MCV | Mean corpuscular volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MPV | Mean platelet volume |
| NCI | National Cancer Institute |
| PD | Pharmacodynamic(s) |
| PK | Pharmacokinetic(s) |
| PNH | Paroxysmal nocturnal hemoglobinuria |
| PR interval | Period that extends from the beginning of the P wave until the beginning of the QRS complex |
| PRO | Patient-reported outcome |
| PT | Preferred term (MedDRA) |
| QoL | Quality of life |
| QRS | Group of electrocardiogram waves comprising the Q, R, and S waves |
| QT interval | Period from deflection of QRS complex to end of T wave |
| QTcF | QT interval Fridericia Correction Formula |

| Abbreviation or acronym | Explanation |
|---|---|
| RDW | Red cell distribution width |
| RBC | Red blood cells |
| RR interval | period between QRS complexes |
| SAE | Serious adverse event |
| SAS® | Statistical Analysis Software® |
| SoA | Schedule of Assessments |
| SOC | System Organ Class (MedDRA) |
| TEAEs | Treatment-emergent adverse events |
| TID | Three times daily |
| VLDL-C | Very low-density lipoprotein cholesterol |
| WBC | White blood cell |
| WHO | World Health Organization |

# 4. DESCRIPTION OF THE PROTOCOL

This is a Phase 2 open-label extension study designed to evaluate long term safety and efficacy of danicopan (ALXN2040, formerly ACH-0144471) in monotherapy in patients with paroxysmal nocturnal hemoglobinuria (PNH) who demonstrated clinical benefit from danicopan in the primary study ACH471-100 and did not develop any safety concerns related to danicopan treatment. Clinical benefit in Study ACH471-100 was assessed by the Principal Investigator (PI), based on an improvement in hemoglobin (Hgb) and/or lactate dehydrogenase (LDH). The PI may escalate or reduce dosing during this study to manage clinical benefit or for safety or tolerability reasons. It is anticipated that no more than 12 patients will be entered into this study. Patients will be allowed to continue therapy until 1) danicopan is commercially available in their country; 2) the development of danicopan as a potential therapy for PNH is terminated; or 3) the therapy is no longer tolerated or effective. In addition, the sponsor reserves the right to close any study site or terminate the study at any time for any reason at the sole discretion of the sponsor.

Each patient will retain the same subject identification as in Study ACH471-100, but the study identification part is to be replaced by ACH471-103. Patients entered this study at the dose they were receiving at the completion of ACH471-100. Patients are to be dosed 3 times daily (tid) approximately 8 hours apart between dosing. Dosing may be increased in increments of 25 mg to a maximum of 250 mg tid if necessary and may be reduced for safety or tolerability reasons.

The primary objective of this study is to evaluate the safety and efficacy of long-term therapy with danicopan in patients with PNH.

The secondary objective of this study is to evaluate health-related quality of life measures in patients with PNH based on patient-reported outcome (PRO) instruments and its evolution over the course of long-term therapy with danicopan.

Safety assessments include adverse events, clinical laboratory tests, physical examinations, vital signs and electrocardiogram (ECG) measurements at specified study visits.

Efficacy will be evaluated by measuring LDH levels, Hgb levels, and reticulocyte counts at specified study visits. The number and frequency of red blood cell transfusions during the study will also be examined.

Blood samples will be collected prior to dosing at specified clinic visits for determination of trough plasma concentrations of danicopan.

Pharmacodynamics will be evaluated using serum, plasma, and whole blood samples collected at specified timepoints during the study.

Quality of Life (QoL) assessments will be conducted at specified study visits. The FACIT Fatigue scale questionnaire and the EORTC-QLQ-C30 scale will be administered to patients to collect health-related QoL during long-term treatment with danicopan. In addition, patients will be interviewed by independent outcomes researchers after approximately 3 and 9 months of treatment in this study to collect their experience of PNH, experience of danicopan treatment and perception of the evolution of their condition (these interviews were discontinued in 2019).

Additional details are described in the protocol, protocol administrative letters, and the Schedule of Assessment (SoA) is included in Appendix 9.1.

## 4.1. Changes from Analyses Specified in the Protocol

Finalization of the SAP before enrollment of the last patient in the study as planned in the protocol was not done. This SAP was finalized prior to database lock.

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

Not applicable.

# 5. DEFINITIONS

## 5.1. Efficacy

### 5.1.1. Efficacy Endpoints

The efficacy endpoints include the following:

- Change from baseline in LDH level
- Change from baseline in Hgb level in the absence of red blood cell transfusion
- Change from baseline in reticulocyte counts
- Number of red blood cell (RBC) units transfused and transfusion instances

### 5.1.2. Quality of Life Endpoints

The QoL endpoints include the patient-reported outcome assessments including:

- Change from baseline in FACIT Fatigue scale
- Change from baseline in EORTC-QLQ-C30 domain scales

The FACIT Fatigue scale and the EORTC-QLQ-C30 will be administered to patients at the protocol specified visit schedule to collect patients' health-related quality of life during continued treatment with danicopan. These tools are provided in Appendix 2 of the protocol.

### 5.1.3. Other Efficacy Endpoints

Other efficacy endpoints include change from baseline for the following biomarkers:

- Free Hgb
- Haptoglobin
- Complete blood count (CBC) components
- PNH clone size
- factor D level
- AP Wieslab
- D-dimer
- Direct Coombs

## 5.2. Safety

The safety and tolerability of danicopan will be evaluated by physical examinations, vital signs, electrocardiograms (ECGs), laboratory assessments, and incidence of adverse events (AEs) and serious adverse events (SAEs). Details of analysis is specified below.

### 5.2.1. Adverse Events (AEs)

AEs with an onset date after the patient provides informed consent will be recorded. A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during treatment, having been absent prior to treatment, or worsens relative to the pretreatment state. In this study, any AE first assessed after receipt of the first dose of danicopan until the final follow-up visit will be considered

treatment-emergent. An AE with onset before the completion of the primary study and ongoing at ACH471-103 enrollment will be followed up until resolution or stabilization.

Each AE will be assessed regarding its seriousness, severity and causal relationship with the study drug. The severity of an adverse event will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (published 14 Jun 2010). Causal relationship assessment will follow the categories of "unrelated", "unlikely", "possible", "probable" and "definite". For summary tables, assessments of "unrelated" and "unlikely" will be combined into the category of unrelated, and "possible", "probable" and "definite" will be combined into the category of related.

Further details are provided in the protocol Section 6.15.

### 5.2.2. Laboratory Assessments

Blood and urine samples will be collected at protocol-specified visits for safety evaluation. The laboratory tests performed as hematology, chemistry, urinalysis, and other assessments are listed in Table 2 in the protocol Section 6.7.

### 5.2.3. Vital Signs

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

### 5.2.4. Electrocardiogram

12-lead ECG recordings will be performed at protocol-specified visits in a supine position and before blood is drawn (whenever possible) following a 5-minute rest. Measurements of the following parameters will be obtained: HR, RR interval, PR interval, QRS duration, QT interval, and Fridericia's formula corrected QT interval (QTcF). The occurrence of depolarization or repolarization disorders, arrhythmic disorders or other abnormalities and the clinical significance of the occurrence will be noted. An abnormal ECG may be repeated to rule out improper lead placement as contributing to the ECG abnormality.

### 5.2.5. Physical Examination

Brief physical examinations including general appearance, cardiovascular and respiratory systems, abdomen, extremities/skin, and additional organs or systems targeted to any new signs or symptoms will be performed at times specified in the SoA or as necessary. All clinically significant physical examination findings that are new or worsened since the last physical examination must be recorded.

# 6. DATA SETS ANALYZED (STUDY POPULATIONS)

## 6.1. Full Analysis (FA) Set

All patients who receive at least one dose of danicopan in this study will be included in the full analysis set. Efficacy analyses will be performed using the full analysis set.

## 6.2. Safety Set

All patients who receive at least one dose of danicopan in this study will be included in the safety set. Safety analyses will be performed using the safety set.

# 7. STATISTICAL ANALYSIS

Descriptive and exploratory statistical methods will be utilized for data analysis. Descriptive statistics for continuous variables will minimally include the number of participants, mean, standard deviation, minimum, median, and maximum. For categorical variables, frequencies and percentages will be presented. Graphical displays will be provided as appropriate. All data collected in this study will be presented in listings. Assessments from unscheduled visits will not be included in table summaries but will be included in listings.

Only data from ACH471-103 will be included in analysis. The baseline data from the primary Study ACH471-100 will be carried over to this study for continuity in data presentation and clinical interpretation of long-term safety and efficacy, including patient demographics, baseline disease characteristics, medical/surgical history data, and first dose date. Baseline values of laboratory tests, vital signs, electrocardiogram data, FACIT fatigue scale and EORTC-QLQ-C30 questionnaire data from the primary study ACH471-100 will also be carried over for the calculation of change from baseline. Carried-over data will be included in data listings if they are presented in summary tables.

For evaluating long-term safety and efficacy of danicopan, unless specified otherwise, Baseline is defined as the Baseline in the primary study and Day 1 (Week 1) visit in this study is Day 84 visit in the primary study.

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

## 7.1. Study Patients

### 7.1.1. Disposition of Patients

The number of patients who completed the primary study will be presented. The number and percent of patients who enrolled in the extension study, completed the study, and discontinued the study will be summarized. For patients who discontinued the study, the reason for discontinuation will be summarized. Patients who discontinued study treatment will also be summarized by reason for treatment discontinuation. Data will be reported using all FA Set.

### 7.1.2. Protocol Deviations

All protocol deviations will be appropriately categorized, and the severity determined (major or minor) prior to database lock. The number and percentage of patients with protocol deviations will be summarized by protocol deviation category and major/minor designations. A listing will also be provided.

### 7.1.3. Demographics, Disease Characteristics, and Medical History

All demographic, baseline characteristics and medical history data will be carried over from the primary study and will be summarized using descriptive statistics for the FA Set. Listings will also be provided.

#### 7.1.3.1. Demographics

The following demographic variables will be summarized:

- Age (in years)
- Gender (n, %)
- Race (n, %)
- Ethnicity (n, %)
- Weight (kg)
- Height (cm)
- Body mass index (BMI, $kg/m^2$)

#### 7.1.3.2. Disease Characteristics

Baseline disease characteristics are to be carried from the primary Study ACH471-100, and will be summarized using descriptive statistics for the following parameters:

- Duration of PNH (months)
- Transfusion history
- Packed RBCs transfused within 3 years prior to first dose of study drug (units)
- PNH type III RBC clone size (%)
- PNH types II & III RBC clone size (%)
- Hemoglobin (g/dL)
- RBC counts ($10^6$/uL)
- Reticulocyte counts ($10^3$/uL)
- Free Hgb (mg%)
- Haptoglobin (g/L) platelet counts ($10^3$/uL)
- Absolute neutrophil counts ($10^3$/uL)
- ALT (IU/L)
- AST (IU/L)
- ALP (IU/L)
- GGT (IU/L)
- Total bilirubin (mg/dL)
- Indirect bilirubin (mg/dL)
- Direct bilirubin (mg/dL)

#### 7.1.3.3. Medical / Surgical History

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

### 7.1.4. Concomitant Medications / Therapies

Concomitant medication is defined as medications that either started prior to first dose of study drug and were continuing at the time of first dose of the study drug or started on or after the date of the first dose of the study drug. As patients in this study already received study drug treatment

in the primary study, all medications collected in this study are considered concomitant medications.

The latest version of World Health Organization (WHO) Drug Dictionary available will be used to code the medications. Medications will be summarized by Anatomical Therapeutic Chemical (ATC) level 2 class and generic drug name.

Concomitant medications in ACH471-103 will be summarized for the Safety Set. The number and percentage of patients receiving any medication will be summarized, as well as the number and percentage receiving any medication by ATC drug class and generic drug name. Patients reporting use of more than one medication at each level of summarization (any medication received, ATC class, and generic drug name) will be counted only once. ATC class will be presented alphabetically followed by decreasing frequency of generic name. Concomitant medications will be presented in listings.

A separate by-patient listing of vaccinations will be produced showing the date(s) and brand of vaccinations for each patient.

## 7.2. Efficacy Analyses

All efficacy analyses will be performed on the FA set.

In general, descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be provided for continuous variables, and counts and percentages will be provided for categorical variables. Analysis will be performed at each study visit. A "Last visit" will be defined as the last assessment on treatment.

All endpoints will be presented in listings. Specific listings will be noted only when the outcome will not be summarized in tabular form or further clarification is required.

### 7.2.1. Primary Analysis

The primary efficacy endpoints to assess the long-term efficacy of danicopan in PNH patients are:

- Change from baseline in LDH level
- Change from baseline in Hgb level in the absence of red blood cell transfusion
- Change from baseline in reticulocyte counts
- Number of red blood cell (RBC) units transfused and transfusion instances

For primary endpoints except number of RBC units transfused or transfusion instances, observed values and change from Baseline will be summarized by study visits. Analyses will be performed on the FA set. Longitudinal plots will be provided to display mean and median over time - for observed values as well as change from baseline. Occurrence of RBC transfusions during this study will be counted for each patient and the number of RBC transfusions will be summarized using descriptive statistics for continuous variables.

Data will also be presented in a listing sorted by patient, visit and endpoint.

#### 7.2.1.1. Handling of Dropouts or Missing Data

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

#### 7.2.1.2. Subgroup Analysis

No subgroup analysis is planned.

#### 7.2.1.3. Multicenter Studies

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

#### 7.2.1.4. Hypothesis Testing and Significance Level

None

#### 7.2.1.5. Sensitivity Analyses

None.

### 7.2.2. Secondary Analyses

Secondary endpoints include the patient-reported outcome assessments including FACIT Fatigue scale questionnaire and EORTC-QLQ-C30 questionnaire.

#### 7.2.2.1. FACIT Fatigue Scale (Version 4)

There are 13 items in the FACIT Fatigue scale questionnaire (Appendix 2 in the protocol). Each item includes 5 possible responses, 0-4, with 0 being "Not at all" and 4 being "Very much". Total score from these 13 items will be provided for each patient at each assessment. Negatively stated items must be reversed before being added to obtain the total score by subtracting the response from "4". All items except items #7 and #8 are negatively stated. The total score ranges from 0 to 52, with higher total scores indicating better quality of life.

FACIT total score and change from baseline will be summarized by study visit. FACIT total score and change from baseline in total score will be presented in a listing.

#### 7.2.2.2. EORTC-QLQ-C30 (Version 3)

There are 30 items in the EORTC-QLQ-C30 questionnaire (Fayers, 2001). The 2 global health status items have 7 possible responses, with 1 being poor and 7 being excellent. All the other 28 items have 4 possible responses, with 1 being "Not at All" and 4 being "Very Much". These 30 items are composed of both multi-item scales and single-item measures, which include five functional scales, nine symptom scales/items, and one global health status/QoL scale as the following (Appendix 9.2):

- Functional scales:
    - Physical functioning
    - Role functioning
    - Emotional functioning
    - Cognitive functioning
    - Social functioning
- Symptom scales/items:
    - Fatigue
    - Nausea and vomiting

  - Pain
  - Dyspnoea
  - Insomnia
  - Appetite loss
  - Constipation
  - Diarrhoea
  - Financial difficulties
- Global health status/QoL

All scales and single-item measures will be transformed into scores from 0 to 100. Details for transforming raw scores into scale scores for the scales and single-item measures are provided in Appendix 9.2.

A high scale score represents a higher response level. A high score for a functional scale represents a high/healthy level of functioning, and a high score for the global health status/QoL represents a high QoL, while a high score for a symptom scale/item represents a high level of symptomatology/problems.

Scale scores and change from baseline for each QLQ-C30 scale/single-item measures will be summarized by study visit. Scale scores and change from baseline will be presented in a listing.

### 7.2.3. Other Efficacy Analyses

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

- Free Hgb
- Haptoglobin
- CBC components
- PNH clone size
- Factor D
- AP Wieslab
- D-dimer
- Direct Coombs

Similar analyses as described for the primary endpoints will be performed for the above endpoints. Observed values and change from baseline will be summarized by protocol specified visits on the FA set.

### 7.2.4. Pharmacokinetic and Pharmacodynamic Analyses

Blood samples will be collected prior to dosing at each clinic visit for determination of trough plasma concentrations of danicopan. All individual trough concentrations will be listed and will be summarized using descriptive statistics (number of non-missing observations (N), arithmetic mean, SD, median, coefficient of variation (CV%), minimum, maximum, geometric mean and geometric CV%).

Analysis for PD biomarkers of interest are described in the efficacy analyses.

## 7.3. Safety Analyses

All safety analyses will be conducted on the Safety set. AEs will be coded in MedDRA (Version 23.1 or above) and presented by MedDRA SOC and preferred term. No formal hypothesis testing is planned. Unless otherwise specified, baseline is defined as the Baseline in the primary study.

### 7.3.1. Treatment Duration and Treatment Compliance

Treatment duration (days from the first dose to the last dose before taper) will be summarized with descriptive statistics. Both the date of the first dose from the primary study and the date of first dose of this study will be used to calculate treatment duration. Dosing regimen and duration will be listed by patient.

Treatment compliance percentage is defined as the actual total dose over the expected total dose for a patient for each dosing regimen or for overall. Specifically,

Expected total dose = Assigned dose × Daily frequency × Duration in days
Actual total dose = Dosage strength × Number of tablets consumed

Where number of tablets consumed is calculated as the difference between the number of tablets dispensed and the number of tablets returned. Overall treatment compliance is the sum of actual total doses of all dosing regimens over the sum of the expected total doses of all dosing regimens.

For each subject, average actual daily dose for each dosing regimen is calculated as actual total dose over the duration of days when the subject is on that dosing regimen. Similarly, the overall average actual daily dose is calculated as the actual total dose over the total treatment duration days.

Overall treatment compliance and average actual daily dose will be summarized and is only based on dosing during this extension study.

### 7.3.2. Adverse Events (AEs)

TEAEs are AEs that have their onset on or after the first dose of study drug in ACH471-103. Patients enrolled in this study have already received their first dose of study drug treatment in the primary study (ACH471-100). Therefore, these AEs are all TEAEs. All AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) available.

AE onset day = AE onset date - first dose date + 1

All treatment emergent adverse events (TEAE) will be summarized with counts and percentages for number of adverse events and patients with adverse events.

#### 7.3.2.1. Overall Summary of Adverse Events

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

- Any TEAEs

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

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

For AEs with onset before the completion of the primary study and ongoing at ACH471-103 enrollment, a separate listing will be presented.

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

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

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

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

#### 7.3.2.4. AEs and SAEs by SOC, PT, and Severity

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

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

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. The AE MedDRA terms that will be considered for these summaries is listed below.:

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

Liver enzymes elevation: Grade 3 events within the high level term (HLT) of Liver function analyses and events within the HLT of Hepatocellular damage and hepatitis NEC.

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

### 7.3.3. Other Safety

#### 7.3.3.1. Analyses for Laboratory Tests

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

Where applicable, laboratory results will be classified as "low," "normal," or "high" with respect to the parameter-specific reference ranges (i.e., below the lower limit of the normal range, within the normal range, or above the upper limit of the normal range).

For laboratory tests with CTCAE toxicity grades available, laboratory abnormalities are summarized by worst treatment-emergent grade [treatment emergent (TE) lab abnormalities]. For tests that have CTCAE toxicity grades in both high and low directions, e.g. serum glucose, etc., the summary table should specify separately for the TE abnormalities as being high or being low in toxicity grades. Note that the post-baseline laboratory value with the highest treatment-emergent toxicity grade is reported for each test.

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

Number and percentage of patients who had post-baseline laboratory values meeting any of the following criteria will be summarized:

- Alanine aminotransferase (ALT) >3 × ULN, 5 × ULN, 8 × ULN
- Aspartate aminotransferase (AST) >3 × ULN, 5 × ULN, 8 × ULN
- ALT >3 × ULN and total bilirubin >2 × ULN
- ALT >3 × ULN and total bilirubin >2 × ULN and ALP < 2 × ULN

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

#### 7.3.3.2. Vital Signs

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

#### 7.3.3.3. Electrocardiogram

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

At each time point, the number and percentage of patients falling into the following treatment emergent ECG abnormality categories will be presented:

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

All ECG data will be presented in a listing.

#### 7.3.3.4. Physical Examination

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

## 7.4. COVID-19 Related Analyses

The following COVID-19 related data will be collected for subjects who were ongoing in this study after December 31, 2019:

1. Modified and missed study visits (and COVID-19 related reasons)
2. Discontinuation (impacted by COVID-19)
3. COVID-19 Exposure
4. Protocol deviations related to COVID-19

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

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

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

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

# 8. REFERENCES

1. Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group; The EORTC QLQ-C30 Scoring Manual (3rd Edition); European Organisation for Research and Treatment of Cancer, Brussels 2001.

# 9. APPENDICES

## 9.1. Protocol Schedule of Assessments

**Table 3. Schedule of Assessments**

| | Months 1-6 (Weeks 1-25)[1] | | | | | | | >6 Months[2] | | Taper and Follow-up | | | Dose Esc[3] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1[4] | 5 | 9 | 13 | 17 | 21 | 25 | Clinic Visits | Local Labs | T3 | T6 | F/U[5] | 3-4 Day | 2 Wk |
| **Enrollment Assessments** | | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | |
| Inclusion/ Exclusion Criteria | X | | | | | | | | | | | | | |
| Vaccination Boosters | See Section 6.2 | | | | | | | | | | | | | |
| Urine Pregnancy Test | X | X | X | X | X | X | X | X | X | | | X | | |
| **Patient-Reported Outcomes Assessment Interviews** | Interviews will be conducted after approximately 3 and 9 months, as described in Section 7.1.4 | | | | | | | | | | | | | |
| **Dosing and Drug Distribution** | | | | | | | | | | | | | | |
| ACH-0144471 Dosing | X | | | | | | | | | X | X | | | |
| Study Drug Dispensing | X | X | X | X | X | X | X | X | | X | X | | | |
| **Clinical Assessments** | | | | | | | | | | | | | | |
| Physical Exam | X | X | X | X | X | X | X | X | | X | X | X | | |
| Vital Signs | X | X | X | X | X | X | X | X | | X | X | X | | X |
| Body Temperature | X | X | X | X | X | X | X | X | | X | X | X | | X |
| Weight | X | X | X | X | X | X | X | X | | X | X | X | | |
| Patient-Reported Outcome Measures Assessments (QoL Questionnaires) | X | | | X | | X | | X[6] | | | | X | | |
| 12-Lead ECGs (single) | X | | | X | | | X | X[7] | | | | | | |
| **AEs/SAEs** | X | | | | | | | | | | | | | |
| **Concomitant Medications, including transfusions** | X | X | X | X | X | X | X | X | | X | X | X | | X |
| **Laboratory Assessments** | | | | | | | | | | | | | | |
| Hematology, Chemistry, and Urinalysis[8] | X | X | X | X | X | X | X | X | | X | X | X | X[9] | X |
| Free Hemoglobin, Haptoglobin, D-dimer, Direct Coombs | X | | X | | X | | X | X | | | | | | X |
| Local Labs: Hgb, Free Hgb, LDH[10] | | | | | | | | | X | | | | X | |
| PK samples[11] | X | X | X | X | X | X | X | X | | X | X | X | | X |
| PNH Clone Size[12] | X | | | | | | X | X[12] | | | | X | | |
| Factor D, AP Wieslab[12] | X | | | | | | X | X[12] | | | | | | |
| Plasma/Serum Samples for Non-genetic Biomarker Testing[11] | X | X | X | X | X | X | X | X | | X | X | X | | |

AE = Adverse Event; ECG = Electrocardiogram; F/U = Follow-up Visit; Hgb = Hemoglobin; PK = Pharmacokinetic; QoL = Quality of Life; SAE = Serious Adverse Event; T3 = Day 3 of the taper; T6 = Day 6 of the taper; Wk = Weeks

1 Visits may take place within a window of ±3 days relative to the specified day.

2 Clinic visits should take place every 8 weeks, starting with Week 25 visit. Local Labs should be drawn 4 weeks after clinic visits. Both clinic visits and local lab draws may take place within a window of ±7 days relative to the specified day.

3 Measurement of LDH and liver function tests (ALT, AST, GGT, ALP), to be drawn locally or at the clinic 72-84 hours after escalation, and at a clinic visit 2 weeks after escalation, as described in Section 7.1.3.

4 Day 84 of the study ACH471-100 will be Day 1 (Week 1) of this study. Data collected as part of the final visit for ACH471-100 may be used for the Week 1 data as appropriate.

5 The follow-up visit should be 14 days after the last dose of study drug (including taper).

6 PRO assessments should be conducted after approximately 9 months, to align with the PRO Assessment Interview, and then every 6 months for the duration of the study.

| | Months 1-6 (Weeks 1-25)[1] | | | | | | | >6 Months[2] | | Taper and Follow-up | | | Dose Esc[3] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1[4] | 5 | 9 | 13 | 17 | 21 | 25 | Clinic Visits | Local Labs | T3 | T6 | F/U[5] | 3-4 Day | 2 Wk |

7 Every other visit (weeks 41, 57, 73, etc).

8 Hematology, chemistry, and urinalysis, as described in Table 2.

9 Liver function tests (ALT, AST, GGT, ALP) and LDH only (Section 7.1.2).

10 Only for Hgb, Free Hgb, LDH (Section 7.1.3).

11 Samples will be collected for PK analysis and potential measurement of PD biomarkers as described in Section 6.9.

12 Every 6 months for the first 2 years, and then annually for the duration of the study.

## 9.2. Scoring the EORTC QLQ-C30 version 3.0

**Table 4. Scoring of EORTC QLQ-C30 version 3.0**

The following table shows the component questions of QLQ-C30 included in each of the scales and single-item measures and their ranges.

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

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

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

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

*RawScore= RS= ( $I_1$ + $I_2$ +…+ $I_n$)/n*

Then for **Functional scales**: *Score*= $\{1 - {(RS-1)range}/\ \} \times 100$

and for **Symptom scales/items** and **Global health status/QoL**:

*Score = [ (RS −1)/ range] ×100*

## 9.3. Technical Specifications for Derived Variables

**Missing and Partial Dates**

In cases where only the month and year are provided for a date, the day for the date will be imputed as 15. Missing months will be imputed as June. In cases where the day is observed but the month is missing, the date will be imputed as June 15. Should the date created with these imputation rules place it outside the possible range of values established by complete, known dates (such as the birth date, death date, or the ICF date for study procedures), the closest known date will be used. For example, a patient with a partial AE start date of June 2011 and a death date of June 5th 2011 would have the AE date imputed as June 5th 2011 instead of the 15th.

**Analysis Relative Day**

Analysis relative day is the day relative to the first dosing day in the primary study. It will be calculated as: analysis date – first dose date + 1 if analysis date is after the first dose date, or else as: first dose date – analysis date. Similarly, analysis relative day will also be calculated relative to the first dosing day in study ACH471-103.

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