A Phase 2 Open-Label Proof of Concept Study to Assess the Efficacy, Safety, and Pharmacokinetics of ACH-0144471 in Untreated Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH)

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STATISTICAL ANALYSIS PLAN
ACH471-100

Study Title: A Phase 2 Open-Label Proof of Concept Study to Assess the Efficacy, Safety, and Pharmacokinetics of ACH-0144471 in Untreated Patients With Paroxysmal Nocturnal Hemoglobinuria (PNH)

Study Number: ACH471-100

Study Phase: 2

Product Name: ACH-0144471 Tablet

Version Number: 1.0
Effective Date: 06Dec2018

Protocol Version: Amendment 7 (Version 8.0), dated 13 March 2018

TABLE OF CONTENTS

1 ABBREVIATIONS

AE	Adverse event
AP	Alternative Pathway (Complement)
AUC	Area under the plasma concentration-time curve
BLQ	Below the lower limit of quantification
C_{max}	Maximum plasma concentration
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Plasma trough (pre-dose) concentration over the dosing interval for the first daily dose
CV%	Coefficient of variation
DAIDS	Division of AIDS
ECG	Electrocardiogram
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer, 30-item Quality of Life questionnaire
FACIT	Functional Assessment of Chronic Illness Therapy
Hgb	Hemoglobin
LDH	Lactate dehydrogenase
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
ULN	Upper limit of normal
PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetic
PNH	Paroxysmal Nocturnal Hemoglobinuria
QoL	Quality of Life
QTcF	QT interval corrected using Fridericia's formula
PRO	Patient Reported Outcomes
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SD	Standard deviation
TE	Treatment Emergent
TEAE	Treatment-Emergent Adverse Event
TID	Three times daily
T_{max}	Time after administration of a drug when the maximum plasma concentration is reached

2 OVERVIEW

This statistical analysis plan (SAP) describes the statistical procedures to be implemented and data presentations for the data from Study ACH471-100.

The study is divided into two parts: the first 28 days of treatment (Part 1) and the second 56 days of treatment (Part 2), with the primary study objective of evaluating the efficacy of ACH-0144471 taking place at the end of Part 1. All analyses will include data from both Part 1 and Part 2.

Since all subjects receive the same treatment, ACH-0144471, the terms 'study drug', 'treatment', or 'ACH-0144471' are interchangeable in this document. Note also that the expressions 'subject' and 'patient' are used interchangeably throughout this document

The starting dose regimen of ACH-0144471 for the first two subjects was 100 mg TID as stated in the original protocol. Protocol amendment 3 increased the starting dose regimen to 150 mg TID, see Section 5.4 below.

3 OBJECTIVES

3.1 Primary Objectives

The primary objective of this study is to evaluate the efficacy of 28 days of oral dosing with ACH-0144471 in currently untreated PNH patients, based on decreases in lactate dehydrogenase (LDH).

3.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the efficacy of 28 and 84 days of oral dosing with ACH-0144471 in currently untreated PNH patients, based on increases in hemoglobin (Hgb) levels
- To evaluate the safety and tolerability of ACH-0144471 in currently untreated PNH patients receiving daily oral dosing by assessing SAEs, adverse events (AEs) ≥ Grade 3, laboratory abnormalities ≥ Grade 3, and AEs leading to discontinuation of study drug
- To evaluate the pharmacokinetic (PK) and pharmacodynamics (PD) profile of ACH-0144471 in currently untreated PNH patients receiving daily oral dosing for 28 days

3.3 Exploratory Objectives

The exploratory objectives of this study are:

- To evaluate the relationship between ACH-0144471 multiple-dose pharmacokinetics and pharmacodynamic biomarkers through inhibition of alternative pathway (AP) activity (PK/PD)

- To evaluate health-related quality of life (QoL) based on patient-reported outcome (PRO) instruments and its evolution over the course of ACH-0144471 treatment
- To explore the benefits of ACH-0144471 treatment, as perceived by patients with PNH, by:
  - Exploring patients' experiences of PNH, its impact on everyday lives and the disease trajectory, from first symptoms to definitive diagnosis and beyond
  - Documenting the evolution of PNH over the course of ACH-0144471 treatment from a patient's perspective
- To explore patients' expectations towards ACH-0144471 treatment

4 ENDPOINTS

4.1 Primary Endpoint

- Change in LDH level from baseline at Day 28.

4.2 Secondary Endpoints

- Change in Hgb level from baseline at Day 28 and Day 84;
- Change in LDH level from baseline at Day 84;
- PNH type III RBC clone size over the study period;
- Safety, as measured by frequency of SAEs, AEs ≥ Grade 3, laboratory abnormalities ≥ Grade 3, and AEs leading to discontinuation of study drug;
- PK parameters including AUC_{tau}, C_{max}, and T_{max} at Days 6, 13, and 20;

4.3 Exploratory Endpoints

- Complement components: AH50, CH50, C3, C4, Bb, and AP-Wieslab at scheduled time points;
- Total score and change from baseline total score on the FACIT Fatigue scale instrument at scheduled time points;
- Change in EORTC QLQ-C30 scores at scheduled time points.

5 STUDY DESCRIPTION

5.1 Study Design

This is a multiple-center, open-label, multiple dose, and single treatment arm study. Patients may be enrolled in a separate pretreatment screening protocol, ACH471-102, to establish baseline values for the pharmacodynamic (PD), efficacy and safety parameters evaluated in this study, or may be directly enrolled into this study.

In addition to meeting the study eligibility criteria, patients will also be evaluated for history of vaccination against *Neisseria meningitidis* (*N. meningitidis*), *Haemophilus influenzae (H. influenza*e), and *Streptococcus pneumoniae* (*S. pneumoniae*). Those who have not been vaccinated will receive vaccinations during this study. Those who have been previously vaccinated will receive recommended boosters. Vaccination procedures during the study are described in Section 6.3 of the protocol.

Patients will receive multiple doses of ACH-0144471 daily for up to 84 days (12 weeks) in two sequential study parts: Part 1 and Part 2.

Part 1 consists of 28 days: Day 1 through Day 28 with Day 1 being first day of dosing. Patients will be evaluated for potential dose escalations after review of safety data and LDH values on Days 6 and 13. Intensive pharmacokinetic (PK) sampling and other assessments will also be evaluated for dose escalation.

Based on a review of safety and efficacy data through Day 20, patients with reductions in LDH meeting specified criteria will be offered continued dosing beyond Day 28 for up to 8 additional weeks (up to Day 84) which is Part 2 of the study. Patients who do not meet the pre-specified criteria also may be offered participation in Part 2 if there has been clinically significant improvement during Part 1. After Day 84, dosing will be tapered over 6 days. Note that dosing for patients not continuing to Part 2 will also be tapered over 6 days after Day 28. The 6-day dose tapering schedule is as follows:

Dose at Termination	**Taper Period 1 (Taper Days 1-3)**	**Taper Period 2 (Taper Days 4-6)**
150 mg TID	100 mg TID	50 mg TID
175 mg TID	100 mg TID	50 mg TID
200 mg TID	125 mg TID	75 mg TID
225 mg TID	150 mg TID	75 mg TID
250 mg TID	175 mg TID	75 mg TID

The FACIT Fatigue Scale (Version 4) questionnaire and the EORTC-QLQ-C30 (Version 3) will be administered to collect patients' health-related quality of life at baseline and after treatment with ACH-0144471.

For all patients, a final follow-up visit will be conducted approximately 14 days after the last dose of ACH-0144471.

A long-term extension study of treatment with ACH-0144471 beyond the 84 days (12 weeks) of dosing included in this study, may be offered to patients, if supported by clinical and nonclinical data. Pending regulatory and ethics committee approval of such a study, patients who, in the opinion of the Principal Investigator (PI), are receiving benefit from ACH-0144471 may be enrolled directly into that study without interruption from this study, and will continue to receive daily treatment with ACH-0144471 and safety and efficacy monitoring. Any patients so enrolled will not require a dosing taper or the follow-up visits described above.

5.2 Treatment Assignment

All patients will receive ACH-0144471 and will be assigned to the same treatment group. Each patient will be assigned a sequential subject identification number within each study center.

5.3 Blinding and Unblinding

Not applicable for this single arm trial.

5.4 Protocol Amendments

There are seven amendments to the original protocol.

Amendment No.	Amendment Date	Main Purposes of Amendment
1	07-MAR-2017	1. Update the dose levels based on the current PK modeling and clinical safety in healthy volunteers. 2. Reword the primary objective for clarity. 3. Update the previous human experience. 4. Address discrepancies between this protocol and the ACH471-102 screening protocol.
2	19-APR-2017	1. Update the AE grading criteria to be used in the study from the DAIDS Criteria to Common Terminology Criteria for Adverse Events (CTCAE) criteria and to clarify language around the classification of AEs. 2. Update the previous human experience. 3. Clarify the collection of information about RBC transfusions at each visit (similar to the collection of concomitant medication information).
3	18-MAY-2017	1. Increase the starting dose to 150 mg TID. 2. Increase the maximum permitted dose to 200 mg TID. 3. Allow vaccination concurrent with dosing, if local practice dictates.
4	09-OCT-2017	1. For Italy only; to allow for use of written interview questionnaire in lieu of telephone interview.
5	05-DEC-2017	1. Update the contraception section to include some definitions requested by Health Authorities. 2. Update the contact information for SAE reporting. 3. Add wording to permit the conducting of patient reported outcomes interviews as questionnaires where required.
6	09-OCT-2017	1. Increase the maximum dose from 200 to 250 mg TID. 2. Update the contact information for SAE reporting.
7	13-MAR-2018	1. Specify that vaccination against bacterial infections should be performed, when necessary based on vaccination history, according to national and/or local guidelines. 2. Update and clarify requirements for “acceptable” and “highly effective” methods of contraception.

6 SAMPLE SIZE

The sample size is determined based on the very limited clinical cases of untreated PNH patients and the exploratory nature of this study to evaluate effectiveness of ACH-0144471.

7 POPULATIONS FOR ANALYSIS

Populations consist of Enrolled and Treated subjects:

- Enrolled subjects are those who signed an informed consent form and were assigned a subject identification number. This cohort is used to assess subject status and deaths.
- Treated subjects are Enrolled subjects who receive at least 1 dose of study medication, ACH-0144471, and will be included in efficacy, safety, PK, and PD analyses.

8 STATISTICAL ANALYSES

As noted in the Overview (Section 2) of this document, the original protocol called for starting dose regimen being 100 mg TID. Protocol amendment 3 increased the starting dose regimen to 150 mg TID.

Since the majority of subjects will have starting dose regimen 150 mg or higher TID, safety and efficacy summary tables will summarize data from all subjects together as one treatment group, regardless of their starting dose regimens and subsequent changes in dose levels. However, additional summary tables by various dose levels may be presented for treatment emergent adverse events (TEAEs), FACIT-Fatigue scale and EORTC QLQ-C30 scores, if clinically meaningful.

8.1 General Methods

Data listings by subject identification will be provided for all data collected during the study. Efficacy, PK/PD, and safety parameters for which summary results will be provided are detailed in following sections. As stated above, safety and efficacy summary tables will be presented with all subjects combined as one treatment group. Additional summary tables by various dose levels may be presented for treatment emergent adverse events (TEAEs), FACIT-Fatigue scale and EORTC QLQ-C30 scores, if clinically meaningful.

To summarize continuous data, descriptive statistics will include: number of subjects, mean, standard deviation, median, minimum, and maximum. For the calculation of summary statistics and analysis, unrounded data will be used.

To summarize categorical data, frequency counts and percentages will be presented.

Non protocol unscheduled assessments will not be used in summarizations.

Longitudinal summaries of efficacy and safety parameters use pre-defined visit day as described in Appendix 1, schedule of assessments, of the protocol. Note that ‘visit day’ and ‘time point’ are synonymous for an efficacy or a safety parameter when only one measurement is taken for that parameter on a visit day.

For laboratory test results, when both local and central laboratory values are collected on the same date, the central laboratory value will be used.

Baseline values for efficacy / PD and safety parameters are defined as the last measurement, including unscheduled visits, prior to first dose of ACH-0144471.

8.2 Study Population

8.2.1 Subject Disposition and Discontinuation

The summary table(s) will include the following:

- Number of patients (enrolled / treated)
- Number of patients who completed 28 and 84 days of dosing
- Reasons for not completing 28 and 84 days of dosing

8.2.2 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

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

8.2.3 Medical History

Medical history terms will be coded with the most current version of Medical Dictionary for Regulatory Activities (MedDRA®) and will be summarized by preferred term and system organ class and listed by subject.

8.2.4 Prior Treatments

Prior medications will be listed and summarized. These are medications taken before the first dose of ACH-0144471. Medications will be summarized by preferred term and system organ class using the most recent version of WHO dictionary.

Data from transfusions received up to 3 years before first dose of ACH-0144471 will also be listed by subject. Note that the transfusion summary results are presented as part of baseline characteristics described in section 8.2.2 above.

8.3 Extent of Exposure

Treatment durations will be computed for each patient as (last date of dose – first date of dose + 1). The last date of dose will be the date prior to any tapering period. Number of doses taken during the 'treatment' period will also be provided for each patient.

Compliance with study drug will be estimated for each patient as: (number of tablets actually taken / number of tablets should have been taken) *100. The tablet counts are collected in the case report form (CRF) form "Study Drug Dispensing/Accountability Record".

Treatment duration, doses taken, and compliance will be summarized and listed by subject.

8.4 Concomitant Therapies

Concomitant medications will be listed and summarized. These are medications taken any time on or after the first dose of ACH-0144471 and on or before the last dose of ACH-0144471. Medications will be summarized by preferred term and system organ class using the most recent version of WHO dictionary.

Transfusions received while taking the study drug, ACH-0144471, will also be listed by subject.

8.5 Efficacy Assessment

8.5.1 Primary Outcome Measure

Reductions in LDH values over time are the primary parameter used to evaluate the efficacy of ACH-0144471. Observed and change from baseline values as well as LDH values relative to the upper limit of normal (ULN) will be listed and summarized at protocol defined time points for all patients (one treatment group).

The primary efficacy endpoint is LDH change from baseline value at Day 28. A 95% confidence interval, based on t-distribution, will be provided for the mean changes from baseline for all patients (one treatment group).

Observed and change from baseline values as well as LDH values relative to the upper limit of normal (ULN) versus time will also be plotted to depict LDH reduction profiles over the course of the study period.

8.5.2 Secondary Outcome Measures

An increase in Hgb values over time is another measure of effectiveness of ACH-0144471. Both observed and change from baseline values will be listed and will be summarized at protocol defined time points for all patients (one treatment group).

Secondary efficacy endpoints include changes from baseline in Hgb at Day 28 and Day 84 and change from baseline in LDH at Day 84. Similar to the primary efficacy endpoint above, ninety-five percent (95%) confidence intervals, based on t-distribution, will be provided for each of the secondary endpoints on mean changes from baseline for all patients.

Both observed and change from baseline Hgb values versus time points will also be plotted.

The PNH type III and type II/III combined RBC clone size values, in %, will be listed and summarized at baseline, Days 28, 42, 56, 84, and the post-treatment follow-up visit. The PNH type III and type II/III combined RBC clone size values will also be plotted against each time points to examine the improvement in the disease status.

8.5.3 FACIT Fatigue Scale (Version 4)

There are 13 items in the FACIT Fatigue scale questionnaire. 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 protocol pre-defined time points.

Negatively stated items must be reversed before being added to obtain the scale total score. Therefore, the negatively stated items will be reversed by subtracting the response from “4”. Note that all items, except for items #7 and #8, are negatively stated.

The FACIT Fatigue scale and the calculation of total score are presented in Appendix 2 of this document. Note that the total score range is 0 to 52, with higher total scored indicating better quality of life.

Subject listings for total score and change from baseline in total score will be provided for protocol pre-specified time points.

Summary statistics for total score and change from baseline in total score will be provided for all subjects (one treatment group) and also by various dose levels, if clinically meaningful.

8.5.4 EORTC QLQ-C30 (version 3)

There are 30 items in the EORTC QLQ-C30 questionnaire which is composed of both multi-item scales and single-item measures (refer to Appendix 2 of the protocol). These include 5 functional scales, 3 symptom scales, a global health status / QoL scale, and 6 single items. The items which form the scales and global health status are listed in Table 1 of Appendix 3 of this document. 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".

All of the scales and single-item measures are transformed into scores from 0 to 100. The procedures of computing the scores for each functional scales, single-item measures, and global health status /QoL are presented in Appendix 3 of this document. A high scale score represents a higher response level:

- a high score for a functional scale represents a high / healthy level of functioning,
- a high score for the global health status / QoL represents a high QoL,
- but a high score for a symptom scale / item represents a high level of symptomatology / problems.

For each functional scale, single-item measure, and global health status / QoL, score and change from baseline score will be provided for each patient at protocol pre-specified time points.

Summary statistics for the scale / score and change from baseline in the scale / score will be provided for all subjects (one treatment group) and also by various dose levels, if clinically meaningful.

8.6 Safety Assessment

Evaluation of safety includes assessment of the following clinical parameters and will be described in detail in the subsequent subsections. Summary tables will be provided for selected clinical parameters. All summary tables will include data points during treatment and dose tapering periods, unless otherwise specified. The summary table will be presented by dose group and both groups combined. By-subject listings will provide all data points throughout the entire study period.

1. TEAEs, including discontinuation due to adverse even
2. Clinical laboratory parameters
3. 12-lead ECG parameters
4. Vital signs, including body temperatures
5. Physical findings.

8.6.1 Treatment-Emergent Adverse Events (TEAE)

Adverse events (AEs) will be coded with the most current version of Medical Dictionary for Regulatory Activities (MedDRA®).

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during treatment with ACH-0144471, including the 6-day dose tapering period, having been absent pre-treatment, or worsens relative to the pre-treatment state.

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

AEs will be listed by subject including preferred term, verbatim term, system organ class (SOC), days from first dosing date, onset and resolution dates/times, duration, frequency, severity, seriousness, outcome, action taken, and relationship to ACH-0144471.

TEAEs will be summarized by preferred term and SOC for the number of subjects reporting the TEAE, the number of TEAEs reported, and the number of events by severity and relationship to study drugs as described in Section 3.2. Summaries of AEs include both non-serious and SAEs as defined in the protocol. AEs with missing severity are included only in summaries of all severity grades (related or regardless of relationship to study drug). If a subject had an AE with different severities during treatment, then only the greatest severity is reported, unless otherwise specified. In addition, a TEAE summary table with decreasing frequencies in terms of MedDRA® preferred terms, based on overall patient population, will also be provided.

Note that there could be two separate summary tables for the number of subjects reporting the TEAE and the number of TEAEs reported. In addition, the summary TEAE tables will be presented for all subjects combined and also by various dose levels as stated in Section 8.

It is not anticipated to encounter AE with missing start date in this study. Any AE with missing start time will be treated as TEAE. AEs that are missing resolution dates are considered to be lost-to-follow-up.

All events captured in the database will be listed in by-subject data listings. However, only TEAEs will be summarized. Separate subject listings will be provided for pre-treatment AEs, TEAEs, and AEs occurred during the optional long-term follow-up visits.

Should any serious adverse events (SAEs) or discontinuation of ACH-0144471 due to adverse events (TEAE or SAE) occur, subject listings for such adverse events will be displayed in a tabulated format and narratives will be included in the study report. If no such event occurs during the study, the tables should provide a statement clearly indicating as such, e.g. ‘No SAE reported’, ‘No TEAE led to discontinuation of study drug’.

8.6.2 Clinical Laboratory Parameters

Descriptive statistics will be provided, at a minimum, for the following laboratory test results of hematology, serum chemistry, and urinalysis as listed in Table 2 of the protocol. Descriptive statistics may be provided for additional laboratory parameters, if warranted.

- hematocrit (Hct), Hgb, platelet count, white blood cell (WBC) count with differential, reticulocyte count;
- albumin, alkaline phosphatase, ALT, AST, BUN, calcium, HCO3, chloride, creatinine, calculated creatinine clearance, creatine kinase (CK), GGT, potassium, sodium, total bilirubin, direct and indirect bilirubin, total cholesterol, total protein, triglycerides, uric acid, glucose;
- urine pH, specific gravity.

Levels and changes from baseline in the laboratory measurements will be summarized at baseline and at pre-defined visits. Baseline is the last assessment before the first dose of ACH-0144471, including unscheduled assessments.

As noted in Section 8.1, when both local and central laboratory values are collected on the same date, the central laboratory value will be used. Selected lab parameters may be converted to SI or US standard units, as clinically deemed appropriate. Laboratory abnormalities are determined from laboratory measurements analyzed at the central or local laboratories, and are graded using Common Terminology Criteria for Adverse Events (CTCAE), as presented in Appendix 1 of this document.

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.

Laboratory abnormalities during treatment period will be further summarized by baseline toxicity grade and treatment therapy (shift tables). Shift tables will be provided for liver function test (LFT) results and other selected laboratory test results based on CTCAE grades. The other selected laboratory tests may include: albumin, serum calcium, serum creatinine, eGFR or CrCL, urine protein, urine WBC, urine RBC.

Values from unscheduled visits after first dose of study drugs will be excluded from descriptive statistics. Unscheduled values will be labeled as unscheduled in the listings.

Exploratory graphic presentations may be provided when data indicate that such analyses are appropriate and clinically meaningful.

8.6.3 12-lead ECG

Subject listing will be provided for ECG parameters: HR, RR, PR interval, QRS interval, QT interval, and QTcF. Abnormal and clinically significant findings will also be included in the listing.

Values and changes from baseline in ECG measurements are summarized at baseline and at each scheduled time points. Baseline ECG is the last assessment before first dose of ACH-0144471.

ECG results will also be classified as normal, abnormal (not clinically significant), and abnormal (clinically significant). Summary table will be provided for clinically significant abnormalities by dose group and both groups combined. If no clinically significant abnormalities are found, the table should state 'No clinically significant ECG abnormality reported'.

The frequency of subjects with a maximum increase from baseline in QTcF interval will be summarized according to the following categories: >30, >60, and ≤30 ms. All incidences of >30 and >60 ms will be flagged on the listing.

The treatment-emergent (TE) ECG events indicate that the abnormality / prolongations were not present at baseline. TE abnormalities will be summarized for the following parameters. Note that TE QTcF interval abnormalities are based on CTCAE criteria.

- Treatment-emergent (TE) PR interval > 200 msec;
- TE QTcF interval:
    - Grade 1: 450 – 480 msec
    - Grade 2: 481 – 500 msec
    - Grade 3: ≥ 501 msec on at least 2 separate ECG readings
    - Grade 4: ≥ 501 msec or > 60 msec change from baseline and Torsade de pointes, polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia

The maximum interval (or increase from baseline) during Treatment Period is reported for each ECG parameter

ECG readings from unscheduled visits after first dose of study medication will be excluded from descriptive statistics. Unscheduled readings will be labeled as unscheduled in the listings.

8.6.4 Vital Signs, Temperatures, and Weights

Subject listing will be provided for vital signs parameters: systolic and diastolic blood pressures, pulse rate, respiration rate and temperature. In addition, the same listing will also include weight measurements at the following time points after Screening: Days 1, 28, and 84.

8.6.5 Physical Exam

Data collected from physical exams, both complete and brief, will be listed by patient and by time points, including unscheduled visit time points.

8.7 Pharmacokinetic (PK) Assessments

PK assessments will be performed based on plasma concentrations from patients receiving ACH-0144471.

8.7.1 PK Parameters

PK parameters from plasma concentrations for ACH-0144471 will be calculated using a non-compartmental approach based on the concentration vs time data. The parameters listed in the table below will be obtained using Phoenix WinNonlin® Version 6.4 or higher, as data permit.

Subjects for whom there is insufficient data to calculate the PK parameters will have available data included in the concentration tables with descriptive statistics only.

For the calculation of the PK parameters, concentrations that are below the lower limit of quantification (BLQ) prior to the T_{max} will be set to 0 and those thereafter as missing. Concentrations that are missing or not reportable will be treated as missing values. For concentration summary statistics, concentrations that are BLQ will be set to 0. At least 3 time points with measurable concentration will be required for the calculation of AUC.

For Days 6, 13, and 20, the following PK parameters will be estimated:

Parameter	Definition/Calculation
AUC_{tau}	Area under the plasma concentration-time curve from time of administration to the end of dosing interval, calculated by linear trapezoidal summation
AUC_{0-24}	Area under the plasma concentration-time curve from time of administration to 24 hours, calculated by linear trapezoidal summation
C_{max}	Maximal plasma concentration
C_{trough}	Plasma trough (pre-dose) concentration over the dosing interval for the first daily dose
T_{max}	Time to reach the maximal plasma concentration

AUC values will be estimated using the linear trapezoidal rule. Actual sampling times relative to dosing will be used in the computation.

Unless otherwise specified below, missing sampling or concentration values should not be imputed, but left missing in the calculation of derived PK parameters. If the actual sampling time is missing, but a valid concentration value has been measured, the scheduled protocol time will be used for the calculation of derived PK parameters.

On a case by case basis, it may be necessary to exclude individual PK concentration values for the calculation of derived PK parameters because they are erroneous, abnormal or appear implausible to the pharmacokineticist in charge of the analysis. Any excluded data will be flagged in the individual data listings. The reason for exclusion will also be documented. If the exclusion has a meaningful impact on the overall interpretation of the results, then it will be discussed.

Actual post-dose time will be used in calculation of PK parameters and in the generation of individual concentration-time profiles. Scheduled (nominal) sampling times will be used as a replacement for unknown or missing actual times and will be used for the pre-dose values. Nominal sampling times will be used in the generation of summary concentration-time profiles and the concentration-time listings.

In addition, the trough concentrations from Days 28, 42, 56, 70, and 84 will be provided.

Greater detail will be provided in a separate PK Data Analysis Plan.

8.7.2 PK Analysis

Individual PK parameters will be listed. Descriptive statistics (number of non-missing observations (N), arithmetic mean, SD, median, coefficient of variation (CV%), minimum, maximum, geometric mean and geometric CV%) will be used to summarize the calculated PK parameters of ACH-0144471 by dose group, if data allow.

Individual concentration profiles with actual post-dose time will be listed. Descriptive summary statistics (N, arithmetic mean, SD, median, CV%, minimum, maximum, geometric mean and geometric CV%) will be used to summarize the concentration profiles by dose group, if data allow.

Individual time-concentration graphs will be provided for each subject in both linear and semi-log scales. Mean time-concentration graphs will also be provided by dose group, if data allow.

8.8 Pharmacodynamic (PD) Assessment

PD markers include selected laboratory tests to assess the effects of ACH-0144471 on complement alternative pathway activity. Analysis on data from LDH measurements has already been described in Section 8.4.1 above. Other PD parameters are exploratory and subject listings will be provided.

AP-Wieslab values, in %, along with complement Bb, are central for assessing the inhibitory effect of ACH-0144471 on the complement alternative pathway activity. Change from baseline on Bb concentrations will be provided at protocol pre-specified time points. AP-Wieslab values, in %, and Bb concentrations versus time points will be plotted for visual examination.

8.9 PK/PD Assessment

The relationships between selected AP component measurements (e.g., AP-Wieslab reported percentages, etc.) with corresponding plasma concentrations and/or PK parameters may be explored if available data deem such assessment being clinically meaningful. If a PK/PD relationship assessment is warranted, details on the assessment will be provided in a separate PK/PK Analysis Plan.

9 CHANGES FROM PROTOCOL SPECIFIED ANALYSIS

There are no changes from protocol specified analysis.

10 DOCUMENT HISTORY

Version No.	Author(s)	Descriptions
Draft	PPD	Original dated 31JUL2017
Draft revised		01Aug2018
Draft V1		30Nov2018
V1		06Dec2018

Appendix 1. Grading the Severity of Laboratory Values

The Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (v4.03: June 14, 2010) does not provide a separate laboratory toxicity grading table. All the laboratory grades are part of the descriptions within various system organ classes (SOCs). The following table has been created as SAS programming specifications for producing tables and listings for clinical study report. The criteria for each grade are the same as in CTCAE descriptions.

Grading the Severity of Laboratory Values, Unmodified from CTCAE, Version 4.0 (v4.03: June 14, 2010)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 LIFE-THREATING
CHEMISTRIES				
Acidosis	pH < normal, but ≥7.3	-	pH <7.3	Life-threatening consequences
Albumin, Low	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated
Alkaline Phosphatase, High	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Alkalosis	pH > normal, but ≤7.5	-	pH >7.5	Life-threatening consequences
ALT, High	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Amylase, High	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN
AST	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Bilirubin, High	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
Calcium, High	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L
Calcium (Ionized), High	Ionized calcium >ULN - 1.5 mmol/L	Ionized calcium >1.5 - 1.6 mmol/L	Ionized calcium >1.6 - 1.8 mmol/L	Ionized calcium >1.8 mmol/L
Calcium, Low	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L
Calcium (Ionized), Low	Ionized calcium <LLN - 1.0 mmol/L	Ionized calcium <1.0 - 0.9 mmol/L	Ionized calcium <0.9 - 0.8 mmol/L	Ionized calcium <0.8 mmol/L
Creatine Kinase, High	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN
Creatinine, High	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 LIFE-THREATING
eGFR or CrCl	<LLN - 60 ml/min/1.73 m^2 or proteinuria 2+ present; urine protein/creatinine >0.5	59 - 30 ml/min/1.73 m^2	eGFR or CrCl 29 - 15 ml/min/1.73 m^2	eGFR or CrCl <15 ml/min/1.73 m^2
Glucose, *Fasting , High*	>ULN - 160 mg/dL; >ULN - 8.9 mmol/L	>160 - 250 mg/dL; >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8 mmol/L;	>500 mg/dL; >27.8 mmol/L
Glucose, Low	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L
GGT, High	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Lipase, High	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN
Lipid Disorders, Cholesterol, High	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L
Triglycerides, High	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L
Magnesium, High	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L
Magnesium, Low	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L
Phosphate, Low	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L;
Potassium, High	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
Potassium, Low	<LLN - 3.0 mmol/L	-	<3.0 - 2.5 mmol/L;	<2.5 mmol/L
SODIUM, High	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
SODIUM, Low	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L
URICACID	>ULN - 10 mg/dL (0.59 mmol/L)	-	-	>10 mg/dL; >0.59 mmol/L
HEMATOLOGY				
CD4 Lymphocytes decreased	<LLN - 500/mm^3; <LLN - 0.5 x 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 x 10^9 /L	<200 - 50/mm^3; <0.2 - 0.05 x 10^9 /L	<50/mm^3; <0.05 x 10^9 /L

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 LIFE-THREATING
(Absolute) Lymphocyte Count, low	<LLN - 800/mm^3; <LLN - 0.8 x 10^9 /L	<800 - 500/mm^3; <0.8 - 0.5 x 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 x 10^9 /L	<200/mm^3; <0.2 x 10^9 /L
Absolute Neutrophil Count (ANC), low	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9 /L	<1500 - 1000/mm^3; <1.5 – 1.0 x 10^9 /L	<1000 - 500/mm^3; <1.0 - 0.5 x 10^9 /L	<500/mm^3; <0.5 x 10^9 /L
Fibrinogen, Decreased	<1.0 – 0.75 x LLN or <25% decrease from baseline	<0.75 – 0.5 x LLN or 25 - <50% decrease from baseline	<0.5 – 0.25 x LLN or 50 - <75% decrease from baseline	<0.25 x LLN or 75% decrease from baseline or absolute value <50 mg/dL
Hemoglobin, Low	Hgb<LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated
INR, High (not on anticoagulation therapy)	>1 - 1.5 x ULN;	>1.5 - 2.5 x ULN;	>2.5 x ULN; >2.5	-
INR, High (on anticoagulation therapy)	>1 - 1.5 times above baseline	>1.5 - 2.5 times above baseline	>2.5 times above baseline	-
Platelets, Decreased	<LLN - 75,000/mm^3; <LLN -75.0 x 10^9 /L	<75,000 - 50,000/mm^3; <75.0 -50.0 x 10^9 /L	<50,000 - 25,000/mm^3; <50.0 - 25.0 x 10^9 /L	<25,000/mm^3; <25.0 x 10^9 /L
WBC, Decreased	<LLN - 3000/mm^3; <LLN - 3.0 x 10^9 /L	<3000 - 2000/mm^3; <3.0 - 2.0 x 10^9 /L	<2000 - 1000/mm^3; <2.0 - 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
APTT or PTT	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN;	-
Proteinuria (Dipstick)	1+	2+	-	-
Proteinuria (24-hour urine)	<1.0 g/24 hrs	1.0 - 3.4 g/24 hrs	>=3.5g/24 hrs	-

APPENDIX 2. FACIT Fatigue Scale and Calculation of Total Score

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

		Not At All	A Little Bit	Somewhat	Quite a Bit	Very Much
1	I feel fatigued	0	1	2	3	4
2	I feel weak all over	0	1	2	3	4
3	I feel listless ("washed out")	0	1	2	3	4
4	I feel tired	0	1	2	3	4
5	I have trouble starting things because I am tired	0	1	2	3	4
6	I have trouble finishing things because I am tired	0	1	2	3	4
7	I have energy	0	1	2	3	4
8	I am able to do my usual activities	0	1	2	3	4
9	I need to sleep during the day	0	1	2	3	4
10	I am too tired to eat	0	1	2	3	4
11	I need help doing my usual activities	0	1	2	3	4
12	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
13	I have to limit my social activity because I am tired	0	1	2	3	4

Scoring: Items are scored as follows: 4=Not At All; 3=A Little Bit; 2=Somewhat; 1=Quite A Bit; 0=Very Much, EXCEPT items #7 and #8 which are reversed scored. Total score range 0-52.

Item Number	Reverse Item?		Item Response	Item Score
1	4	-		=
2	4	-		=
3	4	-		=
4	4	-		=
5	4	-		=
6	4	-		=
7	0	+		=
8	0	+		=
9	4	-		=
10	4	-		=
11	4	-		=
12	4	-		=
13	4	-		=

Sum individual item scores: ____

Appendix 3. EORTC QLQ-C30 Scoring Procedure

For information about terms and conditions for using the questionnaire, please contact the Quality of Life Unit, EORTC Data Center.[1]

Scoring procedures

[1] From EORTC QLQ-C30 Scoring Manual, third edition, 2001, pages 5-7.

General principles of scoring

The QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QoL scale, and six single items. Each of the multi-item scales includes a different set of items - no item occurs in more than one scale.

All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level.
Thus a **high score for a functional scale** represents a *high / healthy level of functioning*, a **high score for the global health status / QoL** represents a *high QoL*, but a **high score for a symptom scale / item** represents a *high level of symptomatology / problems*.

The principle for scoring these scales is the same in all cases:

1. Estimate the average of the items that contribute to the scale; this is the *raw score*.

2. Use a linear transformation to standardize the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.

Coding of the scoring procedure is presented in Appendix 3 for three major statistical packages.

Technical Summary

In practical terms, if items I_1, I_2,... I_n are included in a scale, the procedure is as follows:

Raw score

Calculate the raw score

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

Linear transformation

Apply the linear transformation to 0-100 to obtain the score S,

Functional scales: $S = \left[1 - \frac{(RS - 1)}{range}\right] \times 100$

Symptom scales / items: $S = \{(RS - 1)/range\} \times 100$

Global health status / QoL: $S = \{(RS - 1)/range\} \times 100$

Range is the difference between the maximum possible value of *RS* and the minimum possible value. The QLQ-C30 has been designed so that all items in any scale take the same range of values. Therefore, the range of *RS* Equals the range of the item values. Most items are scored 1 to 4, giving *range* =3. The exceptions are the items contributing to the global Health status / QoL, which are 7-point questions with *range* =6 , and the initial yes/no items on the earlier versions of the QLQ-C30 which have *range*=1.

Scoring the EORTC QLQ-C30 version 3.0

Table 1: Scoring the QLQ-C30 version 3.0

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

* *Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.

† (revised) 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.

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

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

Then for **Functional scales**:

$$Score = \left(1 - \frac{(RS - 1)}{range}\right) \times 100$$

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

$$\text{Score} = \{(\text{RS} - 1)/\text{range}\} \times 100$$

Examples:

Emotional functioning

$$RawScore = (Q_{21} + Q_{22} + Q_{23} + Q_{24})\ 4$$

$$\text{EF } Score = \{1 - (RawScore - 1)\ 3\} \times 100$$

Fatigue

$$RawScore = (Q_{10} + Q_{12} + Q_{18})\ 3\ \text{FA}$$

$$Score = \{(RawScore - 1)\ 3\} \times 100$$

STATISTICAL ANALYSIS PLAN

APPROVAL PAGE

A Phase 2 Open-Label Proof of Concept Study to Assess the Efficacy, Safety, and Pharmacokinetics of ACH-0144471 in Untreated Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH)

Protocol ACH471-100

Prepared by:

PPD

2/26/2019 | 3:37 PM EST
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PPD

2/26/2019 | 3:37 PM EST
Date

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2/26/2019 | 3:43 PM EST
Date