A Phase 2 Open-label Study of ACH-0144471 in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) Who Have an Inadequate Response to Eculizumab Monotherapy

Unique Protocol ID:	ACH471-101
NCT Number:	NCT03472885
EudraCT Number:	2016-003526-16
Date of SAP:	09 March 2020

STATISTICAL ANALYSIS PLAN
ACH471-101

Study Title: A Phase 2 Open-label Study of ACH-0144471 in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) Who Have an Inadequate Response to Eculizumab Monotherapy

Study Number: ACH471-101

Study Phase: 2

Product Name: ACH-0144471 Tablet

Version Number: v.1
Effective Date: 09MAR2020

Protocol Version: Amendment 3.1 (Version 4.1), dated 19 February 2019

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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
CSR	Clinical study report
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
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 data presentations and the statistical procedures to be implemented for the data from Study ACH471-101.

There will be 4 groups studied based on initial dose of ACH-0144471, which will be enrolled sequentially. Group 1 will start at 100 mg three times daily (TID). Group 2 will start at 150 mg TID. Group 3 will start at 200 mg TID. Group 4 will start at the optimal dose determined from Groups 1-3. The initial dose level of Groups 2 and 3 could be lower based on emerging safety data from the prior group(s).

A minimum of 4 weeks of treatment are required at each dose level before dosing of the subsequent group of patients at the next highest dose level. The first three groups include 2 patients per group to determine an optimal ACH-0144471 dose for the remaining 8 patients in the fourth group. ACH-0144471 dose may be increased within each patient, to a maximum of 200 mg TID based on safety and Hgb values at protocol-specified time points, after a minimum of 4 weeks of treatment at the lower dose level during the 24-week treatment phase.

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 analysis and summary presentations of study results will, therefore, combine data from 4 groups into one grouping regardless of initial dose regimens.

At the writing of this SAP, the enrollment to the study has been completed. All patients have reached 24 weeks of treatment with ACH-0144471 plus eculizumab. Most of them are participating in the long-term extension phase of the study.

3 OBJECTIVES

3.1 Primary Objectives

The primary objective of this study is to evaluate the efficacy of ACH-0144471 plus eculizumab based on the increase in hemoglobin (Hgb) relative to baseline during 24 weeks of treatment.

3.2 Secondary Objectives

The secondary objectives of this study are:

- to evaluate the efficacy of ACH-0144471 plus eculizumab based on the reduction in the number of RBC units transfused during the 24 weeks of treatment with ACH-0144471 compared to the 24 weeks prior to initiation of treatment with ACH 0144471

- to evaluate the efficacy of ACH-0144471 plus eculizumab based on the percentage of patients who are RBC transfusion-independent during 24 weeks of treatment
- to evaluate the efficacy of ACH-0144471 plus eculizumab based on the change from baseline in lactate dehydrogenase (LDH) during 24 weeks of treatment
- to evaluate the safety and tolerability of 24 weeks of treatment with ACH-0144471 plus eculizumab based on serious adverse events (SAEs), Grade 3 and Grade 4 adverse events (AEs), and events leading to discontinuation of study drug.

3.3 Exploratory Objectives

The exploratory objectives of this study are:

- to explore the effect of ACH-0144471 plus eculizumab on complement biomarkers including alternative pathway (AP) activity, Bb, fD, and C3 fragment deposition during 24 weeks of treatment
- to evaluate health-related quality of life (QOL) measures during 24 weeks of treatment
- To explore the benefits of ACH-0144471 plus eculizumab 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, including prior treatment with eculizumab alone
  - documenting the evolution of PNH over the course of treatment with ACH-0144471 plus eculizumab from a patient's perspective
  - comparing patients' experience with eculizumab alone and ACH-0144471 plus eculizumab treatment
- to explore patients' expectations towards treatment with ACH-0144471 plus eculizumab.

4 ENDPOINTS

4.1 Primary Endpoint

- Change in hemoglobin (Hgb) level from baseline at Week 24.

4.2 Secondary Endpoints

- Reduction in the number of red blood cell (RBC) units transfused and transfusion instances during the 24 weeks of treatment with ACH-0144471 compared to the 24 weeks prior to initiation of treatment with ACH-0144471;
- Number and proportion of patients who are RBC transfusion independent at 24 weeks of treatment;

- Change in lactate dehydrogenase (LDH) level from baseline at Week 24;
- Safety, as measured by frequency of SAEs, AEs ≥ Grade 3, laboratory abnormalities ≥ Grade 3, and AEs leading to discontinuation of study drug.

4.3 Exploratory Endpoints

- PNH type III RBC clone size at Week 24;
- Complement components: C3, C3 fragments, 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 from baseline 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 Phase 2 study in patients with PNH who have inadequate response to eculizumab treatment. Eligible PNH patients must have RBC-transfusion-dependent anemia and are receiving a stable dose of eculizumab.

This study plans to include up to 14 patients who will receive 24 weeks of daily oral treatment with ACH-0144471 plus intravenous (IV) eculizumab administered at the patient's usual dose and schedule.

Four groups, based on initial dose of ACH-0144471, are to be enrolled sequentially. Initial dose for Group 1 plans to be 100 mg TID. Group 2 plans to start at 150 mg TID. Group 3 plans to start at 200 mg TID. Group 4 start at the optimal dose determined from Groups 1-3. The initial dose level of Groups 2 and 3 could be lower based on emerging safety data from the prior group(s).

A minimum of 4 weeks of treatment are required at each dose level before dosing of the subsequent group of patients at the next highest dose level. The first three groups include 2 patients per group to determine an optimal ACH-0144471 dose for the remaining 8 patients in the fourth group. ACH-0144471 dose may be increased within each patient, to a maximum of 200 mg TID based on safety and Hgb values at protocol-specified time points, after a minimum of 4 weeks of treatment at the lower dose level during the 24-week treatment phase. Refer to Section 3.1 of the protocol for details of study design and dose escalation criteria.

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, depending on evolving recommendations in this patient population. Vaccination procedures during the study are described in Section 6.3 of the protocol.

Patients return to the clinic for safety, PK, and other assessments at protocol-specified time points. At the Week 12 visit, subjects remain at the clinic for 8 hours for intensive PK/PD sampling and collection of a time-matched ECG at the maximum plasma concentration of ACH 0144471 (3 hours after dosing).

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

In addition, Patient Reported Outcomes (PRO) interviews by independent outcomes researchers chosen by the Sponsor will be conducted with patients enrolled in the trial at pre-determined time points to collect patients' experience of PNH, its impact on everyday lives and the disease trajectory.

After Week 24, if patients are receiving clinical benefit, they continue treatment in a (long-term) extension phase with ACH-0144471 and the same dose and schedule of eculizumab that they have been receiving prior to the start of extension phase. Patients not entering the extension phase, or discontinue from the study, will have the dose of ACH-0144471 tapered over 6 days, and two follow-up visits will be conducted approximately 14 days and 28 days after the last dose of ACH-0144471.

5.2 Treatment Assignment

All patients receive ACH-0144471 (plus eculizumab) and will be assigned to one of the four sequential groups as described above. Each patient will be assigned a subject identification number within each study center.

Note that patients receive the same eculizumab regimens as they have received prior to initiation of ACH-0144471. Eculizumab is considered as a concomitant / background medication, as opposed to a study therapy.

5.3 Blinding and Unblinding

Not applicable for this single arm trial.

5.4 Protocol Amendments

There are five amendments to the original protocol.

Amendment No.	Amendment Date	Main Purposes of Amendment
1	13-DEC-2017	1. Update the contraception section to include definitions requested by Health Authorities. 2. Update the contact information for SAE reporting.
1.1	17-JAN-2018	1. Add wording to permit the conducting of patient reported outcomes interviews as questionnaires where required.
2	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 the requirements for "acceptable" and "highly effective" methods of contraception. 3. The time window for definition of a missed dose has been reduced from 6 hours to 4 hours.
3	15-FEB-2019	1. Amend the exclusion criteria to allow enrollment of participants with a history of hematopoietic stem cell transplant if HSCT engraftment has failed. 2. Amend the exclusion criteria to allow enrollment of participants with direct bilirubin > 1.5 × ULN if the elevated bilirubin is due to extravascular hemolysis, in the opinion of the investigator. 3. Permit participants to switch from eculizumab to an approved eculizumab biosimilar or ravulizumab after completion of the primary endpoint at Week 24. 4. Expands potential enrolment to a maximum of 14 participants.
3.1	19-FEB-2019	1. Shorten the time (from 12 to 8 weeks) for which participants must be receiving a stable dose of eculizumab prior to study entry.

6 SAMPLE SIZE

The sample size is based on the small number of PNH patients who have an inadequate response to eculizumab monotherapy and the goal of achieving an optimal dose level of ACH-0144471 in combination with eculizumab treatment. It is estimated that 14 patients enrolling sequentially will be sufficient to identify an optimal dose level of ACH-0144471 plus eculizumab for use in future studies.

7 POPULATIONS FOR ANALYSIS

There are three study populations for analysis.

- Enrolled population consists of subjects who signed an informed consent form and were assigned a subject identification number. This cohort is used to assess subject status and deaths.
- Treated population includes Enrolled subjects who receive at least 1 dose of study medication, ACH-0144471. Data from treated subjects are used for safety analyses.
- The modified intent-to-treat (mITT) population includes Treated subjects who receive at least 4 weeks of study medication, ACH-0144471. Data from mITT subjects are used for efficacy, PK, and selected PD biomarkers analyses. Note that there are a total of 11 patients completing 24 weeks of study medication.

8 STATISTICAL ANALYSES

As noted in the Overview (Section 2) of this document, the protocol indicated 4 sequentially enrolled groups with subjects in Group 4 starting at the optimal dose determined from Groups 1-3. Since the majority of subjects have received a similar dose regimen, safety and efficacy summary tables will summarize data from all subjects together as one treatment group.

The primary analysis and summary presentations will focus on data from 24 weeks of ACH-0144471 treatment period, unless otherwise specified. Subject listings will include data from the entire study, including the long-term extension of the study. Presentations and discussions on the data from long-term extension phase will be undertaken in a separate report.

Note that results from PRO interviews will be presented in a separate report.

8.1 General Methods and Baseline Considerations

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 and will only include data from 24-week treatment period.

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 points will be used.

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

Longitudinal summaries of efficacy and safety parameters use protocol pre-defined visit Week as described in Appendix 1, schedule of assessments, of the protocol.

For longitudinal summaries of data, windows around planned measurement times are based on the midpoint between planned study visits unless specified otherwise. If there are multiple measurements

within the same window, use the value in the visit window closest to the day of the planned visit for each time point (as determined by the absolute difference in days between the planned visit and the collection date, and the absolute difference in days between the planned visit and the assay date).

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.

Since subjects are allowed to have RBC transfusions between screening and first day of dosing of ACH-014471, the baseline Hgb is determined according to the following rules:

- If **no** RBC transfusions are given between screening and dosing, the baseline Hgb is the last measurement prior to the first dose of ACH-0144471, as described above.
- If RBC transfusions are given between screening and dosing, the baseline Hgb will be determined as follows,
    - if the Hgb measurement prior to the first dose of ACH-0144471 after transfusions (Day 1 pre-dose) is within 3 g/dL of the screening Hgb value, then the Day 1 pre-dose measurement will be the baseline for the subject;
    - if the Hgb measurement prior to the first dose of ACH-0144471 after transfusions (Day 1 pre-dose) is more than 3 g/dL higher than the screening Hgb value, the baseline Hgb will be the screening Hgb measurement for the subject.

  The value of 3 g/dL is chosen because more than 3 g/dL increase in Hgb immediately after RBC transfusions is biologically and clinically implausible.

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 24 weeks of treatment
- Reasons for not completing 24 weeks of treatment
- Number of patients entering long-term extension phase

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)
- Transfusion history
    - Number and unit of RBC transfusions 52 weeks prior to screening
    - Number of patients with RBC transfusions between screening and first dose of ACH-0144471
- Hemoglobin (g/dL)
- LDH (U/L)
- Reticulocyte counts (10^3/uL)
- Direct Coombs (positive / negative)
- Total Bilirubin (mg/dL)
- Indirect bilirubin (mg/dL)
- Direct bilirubin (mg/dL)
- C3 fragment (%)
- PNH type III RBC clone size (%)
- Platelet counts (10^3/uL)
- Absolute neutrophil counts (10^3/uL)
- ALT (IU/L)
- AST (IU/L)
- ALP (IU/L)
- GGT (IU/L)

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. All patients should have received stable dose regimen of eculizumab at least 8 weeks prior to first dose of ACH-0144471. Separate listing will be provided for eculizumab.

Data from transfusions 52 weeks 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

Note that all treated patients, except for one patient, completed 24-week treatment period. Treatment durations, therefore, will be computed for each patient as (last date of dose – first date of dose + 1) during the study. The last date of dose will be the date prior to any tapering period or database lock date when patients are in long-term extension phase. In addition, a contingency table will be provided to

display the number of patients with exposure in the following categories: 1-4 weeks, 5-12 weeks, 13-24 weeks, 25-48 weeks, and >48 weeks.

Number of doses at different dose regimen and length of each dose regimen taken during the entire treatment period, including dose regimen taken during long-term extension phase, will also be provided and listed for each patient.

Compliance with study drug will be estimated and listed 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".

8.4 Concomitant Therapies

Concomitant medications will be listed. 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.

Concomitant medications will be summarized only for the duration of 24-week treatment period.

As eculizumab is considered a concomitant medication, a separate listing will be provided which also includes other approved C5 inhibitors that patients are allowed to switch to during long-term extension phase.

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

8.5 Efficacy Assessment

All efficacy analysis will be carried out on data from mITT subjects. A total of 11 subjects are included in the mITT analysis.

8.5.1 Primary Outcome Measure

The primary efficacy endpoint is Hgb change from baseline value at Week 24. Summary statistics will be provided for the changes from baseline for all patients (one treatment group).

Reductions in Hgb values over time are the primary parameter used to evaluate the efficacy of ACH-0144471. Observed and change from baseline values will be listed and summarized at protocol pre-defined time points (Weeks) during 24 weeks of treatment period.

Observed and change from baseline values versus time will also be plotted to depict Hgb reduction profiles over the course of the 24-week treatment period.

8.5.2 Secondary Outcome Measures

The secondary efficacy endpoints are listed in Section 4.2.

Similar to primary efficacy endpoints, only descriptive statistics will be provided for the secondary outcome measures.

- Mean, median, minimum, and maximum reduction in the number of RBC units transfused during the 24 weeks of treatment compared to the 24 weeks prior to first dose of ACH-0144471 will be presented;

- Mean, median, minimum, and maximum reduction in the number of RBC transfusion instances during the 24 weeks of treatment compared to the 24 weeks prior to first dose of ACH-0144471 will be displayed;

- Number and percentage of patients who are RBC transfusion independent at 24 weeks of treatment will be presented;

- Mean, standard deviation, median, minimum and maximum of change in LDH level from baseline at protocol pre-specified visits, including Week 24, will be presented. Similar presentation may be available for the observed LDH levels and LDH relative to upper limit of normal (ULN). Observed and change from baseline values and LDH relative to ULN versus time may also be plotted for LDH measurements over the course of the 24-week treatment period.

8.5.3 Exploratory Outcome Measures

PNH type III RBC clone size will be presented at protocol pre-specified time points, including Week 24. Similarly, observed and change from baseline values of the complement components of C3, C3 fragments, Bb, and AP-Wieslab will be summarized at protocol pre-specified time points.

The analysis and summarization of the FACIT Fatigue scale instrument and EORTC QLQ-C30 scores are described as below.

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.

Summary statistics for total score and change from baseline in total score will be provided at protocol pre-specified time points up to and including Week 24. Subject listings for total score and change from baseline in total score will be provided for all protocol pre-specified time points.

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 all protocol pre-specified time points.

Summary statistics for the scale / score and change from baseline in the scale / score will be provided at protocol pre-specified time points up to and including Week 24.

8.6 Safety Assessment

Evaluation of safety includes assessment of the following clinical parameters and will be described in detail in the subsequent subsections. All patients receiving at least one dose of ACH-0144471 (Treated population) will be included in the safety assessment. Note that there are 11 patients treated with ACH-0144471 for this study.

Summary tables will be provided for selected clinical parameters. All summary tables will include data points during 24-week treatment period and dose tapering period. By-subject listings will provide all data points throughout the entire study, including long-term extension phase.

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 drug. 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 safety 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.

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. For subjects having discontinued from the study, AEs that are missing resolution dates will be 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 may be provided for pre-treatment AEs, TEAEs, and AEs occurred during the long-term extension phase of the study.

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 at protocol pre-specified visits up to and including Week 24, will be provided, at a minimum, for the laboratory test results of hematology, serum chemistry, and urinalysis as listed in Table 3 of the protocol. Descriptive statistics may be provided for additional laboratory parameters, if warranted.

Levels and changes from baseline in the laboratory measurements will be summarized at baseline and at protocol pre-specified visits. Baseline is the last assessment before the first dose of ACH-0144471, including unscheduled assessments, unless otherwise specified (refer to Section 8.1).

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 24-week treatment period will be further summarized by baseline toxicity grade and worst grade during treatment period (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: hemoglobin, platelet counts, total bilirubin, and others as clinically deemed meaningful.

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 up to and including visit Week 24. 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. 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 in 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 24-week treatment period is reported for each ECG parameter

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.

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 mITT subjects receiving ACH-0144471 during 24 weeks of treatment period.

8.7.1 PK Parameters and Analysis

PK parameters from plasma concentrations for ACH-0144471 will be calculated using a non-compartmental approach based on the concentration vs time data. The standard PK parameters outlined below, will be derived from the individual plasma concentration time data at Week 12 with intensive PK sampling, 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.

Trough plasma concentrations will be listed and summarized to assess the amounts of ACH-144471 at steady state prior to the first daily dose. Graphic presentations will also be provided to depict PK profiles of ACH-0144471 from the patients.

PK Analysis Parameters

AUC	Area under the curve
C_{max}	Maximum observed plasma concentration
t_{max}	Time after administration of a drug when the maximum plasma concentration is reached
C_{trough}	Observed plasma concentration prior to the first daily dose

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.

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 assessment will be based on data from mITT subjects receiving ACH-0144471 during 24 weeks of treatment period.

PD markers include selected laboratory tests to assess the effects of ACH-0144471 (plus eculizumab) on complement alternative pathway activity. Analyses on data from Hgb, LDH measurements and various biomarkers in Section 8.5.1 to 8.5.3 above have provided detailed description on PD assessment of ACH-0144471. Other PD parameters may be explored, if clinically deemed meaningful.

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 the clinical study report (CSR).

9 CHANGES FROM PROTOCOL SPECIFIED ANALYSIS

There are changes from protocol specified analysis:

- Since the majority of subjects have received a similar dose regimen, safety and efficacy summary tables will summarize data from all subjects together as one treatment group. The primary efficacy endpoint measure is mean change from baseline, rather than median change from baseline as specified in the protocol.
- No 95% confidence intervals will be provided as there are only 11 patients completing 24 weeks of treatment. Summary statistics and longitudinal presentations for Hgb and other efficacy parameters would be sufficient to describe the effectiveness of ACH-0144471 in addition to eculizumab.
- The protocol uses ‘analysis sets’ (Section 9.3 of the protocol) to identify groupings of subjects. The SAP uses simple word ‘populations’ to identify various groupings of subjects in the study.

10 DOCUMENT HISTORY

Version No.	Author(s)	Descriptions
Draft	PPD	Original dated 13JAN2020
v.1		Minor edits from draft

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

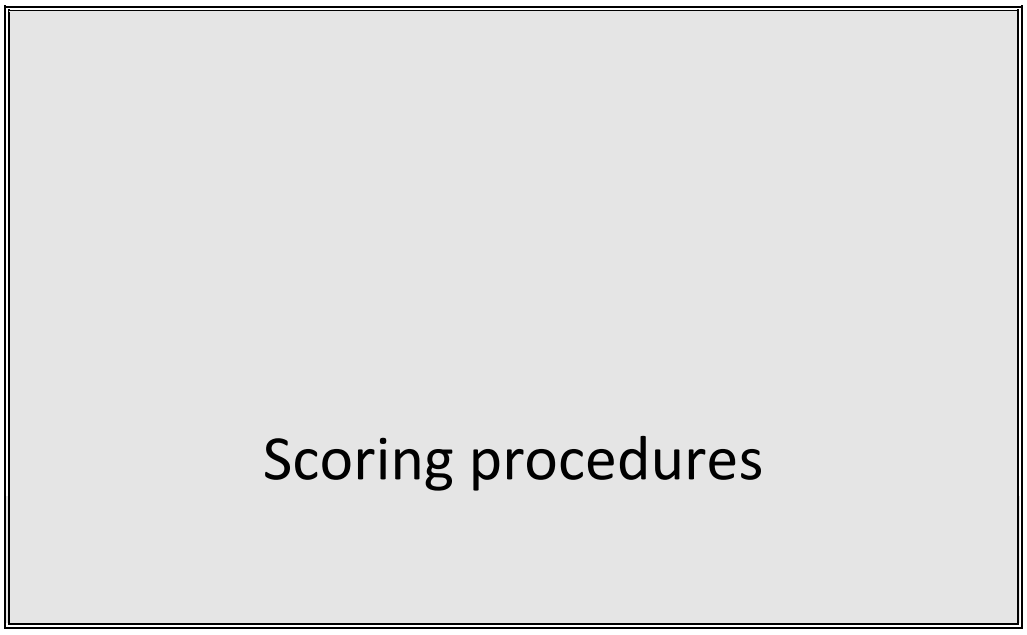
Scoring: Items are scored as follows: 4=Not At All; 3=A Little Bit; 2=Somewhat; 1=Quite A Bit; 0=Very Much, EXCEPT items #7 and #8 which are reversed scored. Total score range 0-52.

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]



[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:

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

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 Study of ACH-0144471 in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) Who Have an Inadequate Response to Eculizumab Monotherapy

Protocol ACH471-101

Prepared by:

PPD

	Signature	Date

Approved by:

PPD

	Signature	Date
	Signature	Date