A Phase 2a Proof-of-Mechanism, Open-Label Study to Determine the Effect of ACH-0144471 on C3 Levels in Patients with Low C3 Levels Due to Either C3 Glomerulopathy (C3G) or Immune-Complex Membranoproliferative Glomerulonephritis (IC-MPGN)

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STATISTICAL ANALYSIS PLAN
ACH471-201

Study Title: A Phase 2a Proof-of-Mechanism, Open-Label Study to Determine the Effect of ACH-0144471 on C3 Levels in Patients with Low C3 Levels Due to Either C3 Glomerulopathy (C3G) or Immune-Complex Membranoproliferative Glomerulonephritis (IC-MPGN)

Study Number: ACH471-201

Study Phase: 2 a

Product Name: ACH-0144471 Tablet

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List of Abbreviations

ACR	(Urine) albumin:creatinine ratio
AE	Adverse event
AP	Alternative Pathway (Complement)
AUC_{tau}	Area under the plasma concentration-time curve from time of administration to the end of dosing interval
BLQ	Below the lower limit of quantification
C3G	C3 glomerulopathy
C_{max}	Maximum plasma concentration
CL/F	Apparent oral drug clearance
CTCAE	Common Terminology Criteria for Adverse Events
CV%	Coefficient of variation
ECG	Electrocardiogram
IC-MPGN	Immune-Complex Membranoproliferative Glomerulonephritis
LLN	Lower limit normal
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamic
PK	Pharmacokinetic
QTcF	QT interval corrected using Fridericia's formula
SAP	Statistical Analysis Plan
SD	Standard deviation
TE	Treatment emergent
TEAE	Treatment-emergent adverse event
T_{max}	Time after administration of a drug when the maximum plasma concentration is reached
ULN	Upper limit normal

1 Overview

This statistical analysis plan (SAP) document describes in detail the statistical procedures and presentations to be implemented for the data from Study ACH471-201.

All eligible patients are expected to complete the three sequential study periods: 14-day Treatment Period, 7-day Taper Period, and 28-day Follow-Up Period as briefly described in section 4.1 of this document. Afterwards, patients can participate in the optional long-term no-treatment observational follow-up visits for up to a year. Statistical procedures and presentations described in the SAP will focus on data collected during Treatment, Taper, and Follow-Up study periods. Data available from long-term follow-up visits will be listed, but will not be analyzed.

Note that the expressions 'subject' and 'patient' are used interchangeably throughout this document.

2 Objective

2.1 Primary Objectives

The primary objective(s) of this study is to determine whether ACH-0144471 can increase blood C3 levels in patients with low C3 levels due to either C3G or IC-MPGN.

2.2 Secondary Objectives

The secondary objective(s) of this study is (are):

- To evaluate the safety and tolerability of oral dosing with ACH-0144471 in patients with C3G or IC-MPGN by assessing SAEs, Grade 3 and higher adverse events (AEs), and AEs leading to discontinuation of study drug
- To evaluate the PK profile of ACH-0144471 following oral dosing in patients with C3G or IC-MPGN
- To evaluate the effect of ACH-0144471 on biomarkers of alternative pathway activity in patients with C3G or IC-MPGN
- To explore the relationship between study drug exposure and changes in C3 levels and other biomarkers of alternative pathway activity.

2.3 Other Objectives

The exploratory objective(s) of this study is (are):

- To explore patients' experience of their disease (C3G or IC-MPGN), its impact, and its management on everyday lives, from first symptoms to definitive diagnosis and beyond
- To explore patients' expectations of ACH-0144471 in the treatment of their disease.

3 Endpoints

The following sections intend to provide a list of outcome measures from data collected on efficacy, including pharmacodynamics (PD), safety, and pharmacokinetics (PK) to address the study objectives.

3.1 Efficacy Outcome Measures

3.1.1 Primary Efficacy Outcome Measures

There are two related outcome measures of evaluating the increases of blood C3 levels in patients with low C3 levels due to either C3G or IC-MPGN for this study:

- Change from baseline in serum C3 level after 14 days of ACH-0144471 treatment, as measured by conventional Roche immunoturbidimetric assay method
- Change from baseline in plasma intact C3 level after 14 days of ACH-0144471 treatment, as measured by a novel multiplex assay method

3.1.2 Secondary Efficacy Outcome Measures

- Changes from baseline after 14 days of ACH-0144471 treatment for the following (serum) biomarkers:
  - Total complement classical pathway activities, Total CP activities (IU/L)
  - AP Complement Functional Activity (AP Wieslab)
- Time (in days) to achieving peak serum C3 levels from the first day of dosing to last day of Treatment Period

3.1.3 Other Efficacy / PD Outcome Measures

- Changes from baseline after 14 days of ACH-0144471 treatment for the following (serum / plasma) biomarkers:
  - fD (Factor D)
  - fB (Factor B)
  - Bb
  - Bb / fB ratio
  - C4
  - sC5b-9
  - C3 fragment (iC3b)
  - C3 fragment (C3b+iC3b)
  - C3 fragment (C3b+iC3b) / intact C3 ratio
- Change from baseline after 14 days of ACH-0144471 treatment in urine albumin:creatinine ratio (ACR)

Note that the patient-reported outcome measures through patient interviews will be assessed and stored in a separate database (from study clinical database). Therefore, they are excluded from this SAP.

3.2 Safety Outcome Measure

- Frequency of SAE
- Frequency of TEAEs leading to discontinuation of the study medication
- Frequency of TEAEs (related and regardless of relationship to study medication)
- Frequency of treatment-emergent laboratory abnormalities by toxicity grade
- Change from baseline on selected laboratory test results over treatment duration and Follow-Up Period
- Change from baseline on parameters of vital signs and weight over treatment duration and Follow-Up Period
- Treatment emergent abnormalities on selected ECG parameters
- Change from baseline on ECG parameters over treatment duration and Follow-Up Period

Note that 'treatment duration' includes data from both Treatment Period and Taper Period.

3.3 Pharmacokinetic (PK) Parameters

- C_{max}, $AUC_{0\text{-}tau}$, t_{max}, CL/F for Days 1 and 7
- C_{trough} concentrations for other days

4 Study Description

4.1 Study Design

This is an open-label study. The study has planned to enroll up to 10 patients with biopsy-confirmed C3G or idiopathic IC-MPGN and a low C3 level. All patients receive ACH-0144471 and enroll into two sequential groups. Group 1 serves as a sentinel group consisting of two patients receiving ACH-0144471 at a dose of 100 mg three times daily (TID). Group 2 is initiated upon confirmation that dosing was well-tolerated - based on the available safety, PK, and PD data - in Group 1. The dose regimen for Group 2 would not exceed 200 mg TID.

Patients receive study drug for 14 days (Treatment Period), followed by a taper over the next 7 days (Taper Period) to minimize the potential adverse effects of a rapid surge in complement activity following drug withdrawal. Patients have daily clinic visits for the first 3 days of the taper, and then continue to be followed for 28 days after the last dose of study drug (Follow-Up Period). Long-term follow up visits to allow collection of longitudinal observational data are included but not required. During the long-term follow up period, patients are asked to return for an outpatient clinic visit approximately every 45 days for a maximum of 1 year.

If a patient has a C3 level that, at 2 consecutive evaluations, is greater than 125% the upper limit of normal (ULN), or is greater than 3× their baseline and greater than or equal to the lower limit of normal (LLN), then the taper period will be initiated before completion of the 14 days of dosing, as proof-of-mechanism will already be established for that patient. Furthermore, early tapering and possible prevention of supraphysiologic C3 levels may mitigate the theoretical risk for acute precipitation of C3 into the glomerulus upon drug discontinuation.

4.2 Treatment Assignment

All patients receive ACH 0144471. Each patient is assigned a sequential subject identification number within the study site.

The first two patients from Group 1 and receive ACH-0144471 at a dose of 100 mg TID. The remaining enrolled patients are included in Group 2. The dose for Group 2 is selected based on the data from Group 1 but does not exceed 200 mg TID.

4.3 Blinding and Unblinding

This is an open-label study.

4.4 Protocol Amendments

There are two amendments to the original protocol.

Amendment No.	Amendment Date	Main Purposes of Amendment
1	07-APR-2017	1. Change Study Phase from 1b to 2a. 2. Update the dose levels based on the current PK modeling and clinical safety in healthy volunteers. 3. The circumstances under which an early dosing taper would be initiated are modified. 4. Potential long-term follow-up visits are added. 5. Adverse Event definitions are clarified. 6. The grading of Adverse Events is changed from the DAIDS criteria to CTCAE.
2	09-JUN-2017	1. Update the maximum dose based on the current PK modeling and clinical safety in healthy volunteers. 2. The eGFR calculation method is revised. 3. The approximate blood volume to be collected is updated to include blood drawn in the optional long-term follow-up visits. 4. Adverse Event definitions are (further) clarified. 5. The previous human experience is updated.

5 Sample Size

The sample size is determined based on very limited clinical cases of C3G and IC-MPGN and the exploratory nature of this study to evaluate effectiveness of ACH-0144471.

6 Analysis Set

All patients receiving at least one dose of ACH-0144471, with baseline and at least one measurement during Treatment Period, will be included in the efficacy, safety, pharmacokinetic (PK), and pharmacodynamic (PD) analyses.

7 Statistical Analyses

Statistical analyses and data presentations are performed using the version of SAS 9.12.

7.1 General Methods

Data listings by subject identification will be provided for all data, including efficacy, safety, PD, and PK parameters. Note that data listings also include data from the optional long-term follow-up visits whenever available.

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.

Summary results for all patients will be presented alongside Group 1 and Group 2 for all summary tables. In addition, if there are more than two dose levels administered to the patients and it is deemed clinically meaningful, summary tables may be presented by dose levels, instead of, or in addition to, Group 1 and Group 2.

Both inferential and descriptive statistical procedures will be performed on most of the efficacy outcome measures. For safety measures, only descriptive statistical procedures will be utilized, unless otherwise specified.

As stated in section 1 Overview, summary tables and statistical procedures will be presented for data collected during Treatment, Taper, and Follow-Up study periods. Data from the optional long-term follow-up visits will be listed; no planned summary tables will be provided.

Unscheduled assessments taken after dosing will not be used in the summarization.

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

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.

Separate analysis and presentation by diagnosis, C3G or IC-MPGN, may be provided if it is deemed clinically feasible and meaningful.

7.2 Study Population

7.2.1 Subject Discontinuation and Disposition

The summary table(s) will include the following:

- Number of patients (enrolled / treated)
- Number of patients who completed 14 days of Treatment Period
- Reasons for not completing 14 days of Treatment Period
- Number of patients entering Taper Period:
    - Number of patients who completed dose tapering
    - Reasons for not completing dose tapering
- Number of patients entering Follow-Up Period:
    - Number of patients who completed Follow-Up Period
    - Reasons for not completing Follow-Up Period

7.2.2 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized by treatment group and both group combined:

- demographics: age, gender, race, country / geographic region
- physical measurement at baseline: height, weight, BMI
- disease characteristics at baseline: duration of the disease, biopsy results
- selected PD markers and laboratory tests at baseline
- prior medications.

Demographic and physical measurements will be listed together.

7.2.3 Medical History

Medical history 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.

7.3 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 end date of Treatment Period. Number of doses taken during Treatment Period will also be provided for each patient.

Duration of tapering dosing period may also be provided, as a separate computation, if patients enter the 7-day Taper Period schedule. The duration will be calculated similarly as (last date of taper dose – first date of taper dose +1). Number of doses taken during Taper 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 be taken) *100.

Treatment duration, duration of tapering dosing, number of doses for both Treatment and Taper Period, and compliance will be summarized and by-patient listing will be provided.

7.4 Concomitant Medications

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 are presented alphabetically by anatomic class, therapeutic class and generic name using the most recent version of WHO dictionary.

7.5 Efficacy and Selected PD Markers Assessment

7.5.1 Analysis of Primary Efficacy Outcome Measures

Change from baseline for serum C3 levels on study Day 15, after 14 days of treatment ACH-0144471, will be computed for each patient.

Ninety-five (95%) confidence interval, based on t-distribution, will be provided for the mean changes from baseline from all patients on Day 15, Group 1 and Group 2 combined. Ninety-five (95%) confidence interval will also be provided for the mean changes from baseline from patients in Group 2, and dose levels or diagnosis (C3G or IC-MPGN) when the individual group / dose level / diagnosis has 4 or more patients.

Summary statistics will be provided for both original and change from baseline serum C3 levels at scheduled time points for the three study periods, Treatment, Taper, and Follow-Up. The serum C3 levels, both original and changes from baseline, will be plotted against time.

Same analysis and graphic procedures will also be employed for intact C3 level data.

7.5.2 Analysis of Secondary Efficacy Outcome Measures

For the biomarkers listed in section 3.1.2, similar analysis and graphic procedures as described in the above section 7.5.1 will be utilized to assess the effect of ACH-0144471 on complement pathway activities.

Mean change from baseline and corresponding 95% confidence interval on Day 15 for AP Wieslab will be provided. However, mean change from baseline and corresponding 95% confidence interval on Day 14 for total CP activities will be provided. Note that total CP activities have not been measured on Day 15 as it is not expected any change in values, if any, from Day 14 to Day 15. Graphic presentations will be provided to these secondary efficacy outcome measures.

For data on time (in days) to achieving peak serum C3 level, Kaplan-Meier plot and descriptive analysis procedure will be applied for visual examination and interpretation. The time (in days) to achieving peak serum C3 level for each patient will be summarized and listed.

7.5.3 Analysis of Other Outcome Measures

For biomarkers and laboratory tests listed in Section 3.1.3, changes from baseline at the protocol-defined time points will be computed. Note that the biomarkers of AH50, factor B and factor D are measured with less frequency than the other biomarkers and laboratory tests. In addition, spot urine laboratory measurements of albumin and creatinine may also be summarized similarly.

Ninety-five confidence intervals may be constructed on mean changes from baseline on Day 15 for selected other outcome measures as clinically deemed beneficial in interpreting the biological effects of ACH-0144471.

7.6 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 Period and Taper Period, unless otherwise specified. The summary table will be presented by treatment group and both groups combined. By-subject listings will provide all data points throughout the entire study period, including data from optional long-term follow-up visits.

1. Treatment emergent adverse events, including discontinuations due to adverse event
2. Clinical laboratory parameters
3. 12-lead ECG
4. Vital signs
5. Body weights
6. Physical findings.

7.6.1 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 (Treatment Period and Taper Period) and Follow-Up 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.

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’.

7.6.2 Clinical Laboratory Parameters – Safety and Complement Biomarkers

Descriptive statistics will be provided, at a minimum, for the following laboratory test results of hematology, serum chemistry, urinalysis, coagulation tests, and complement biomarkers as listed in Table 5 of the protocol. Descriptive statistics may be provided for additional laboratory parameters, if clinically warranted.

- hematocrit (Hct), hemoglobin (Hgb), mean corpuscular volume (MCV), platelet count, and WBC count
- all chemistry laboratory test results
- pH, specific gravity
- urine albumin, urine creatinine, albumin:creatinine ratio

- PT/PTT/INR
- all complement biomarker results

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.

Laboratory parameters are summarized using US standard values and units. 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 and complement biomarkers.

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.

7.6.3 12-lead ECG

Subject listing will be provided for ECG parameters: HR, RR, PR interval, QRS interval, QT interval, and QTcF. The 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 treatment group. 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.

7.6.4 Vital Signs and Body Weights

Subject listing will be provided for vital signs parameters: body temperature, systolic and diastolic blood pressures in triplicate, heart rate, and respiration rate.

Body weights are taken at the same time points as vital signs and will be included in the listing.

Summary of changes from baseline at individual time points will be provided for each parameter of vital signs and body weight. Additional analysis and presentations may be required based on the emerging data.

7.6.5 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.

7.7 Pharmacokinetic (PK) Assessments

PK assessments will be performed on plasma concentrations from patients whose PK profiles can be determined. PK parameters may be presented by dose levels when clinically appropriate.

7.7.1 PK Parameters

PK parameters from plasma concentrations for ACH-0144471 will be calculated using a non-compartmental approach based on the concentration versus 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 Tmax 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 1 and 7, 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
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
CL/F	Apparent oral drug clearance during a dosing interval, calculated as $Dose/AUC_{tau}$

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 at protocol specified visits will be provided.

7.7.2 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.

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.

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.

7.8 PK/PD Assessment

To assess the relationships between C3 levels and the PD markers listed in section 3.1.2 with corresponding plasma concentrations and/or PK parameters, graphic presentations on time-matched PK concentration and C3 levels / selected PD markers will be provided for visual examinations and clinical interpretations.

8 Changes from Protocol Specified Analysis

There are no changes from protocol specified analysis for efficacy / PD and safety variables.

Note that the efficacy endpoints described in the protocol have been expanded to include specific biomarkers / laboratory tests of clinical interest.

The protocol Section 9.8 states “derivation from the raw data of AP Wieslab assay to the reported percentages will be presented in the SAP”. Since the derivation is now detailed in the appropriate laboratory manual, it is not included in this document.

9 Document History

Version No.	Author(s)	Descriptions
1.0	PPD	Original dated 02Jan2019

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	-

STATISTICAL ANALYSIS PLAN
APPROVAL PAGE

A Phase 2a Proof-of-Mechanism, Open-Label Study to Determine the Effect of ACH-0144471 on C3 Levels in Patients with Low C3 Levels Due to Either C3 Glomerulopathy (C3G) or Immune-Complex Membranoproliferative Glomerulonephritis (IC-MPGN)

Protocol ACH471-201

Prepared by:

PPD

PPD

Sig

03 Jan 2019
Date

Approved by:

PPD

PPD

1/11/2019 | 2:03 PM
Date

1/12/2019 | 1:01
Date