An Open-Label Phase 2 Proof-of-Concept Study in Patients with C3 Glomerulopathy (C3G) or Immune-Complex Membranoproliferative Glomerulonephritis (IC-MPGN) Treated with ACH-0144471

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Date of Protocol:	15 May 2020

CLINICAL TRIAL PROTOCOL
ACH471-205

Study Title: An Open-Label Phase 2 Proof-of-Concept Study in Patients with C3 Glomerulopathy (C3G) or Immune-Complex Membranoproliferative Glomerulonephritis (IC-MPGN) Treated with ACH-0144471

Study Number: ACH471-205

Study Phase: Phase 2

Product Name: ACH-0144471 Tablets

IND Number: 129,916

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WHO UTN: U1111-1203-9136

Indication: C3 Glomerulopathy (C3G) or Immune-Complex Membranoproliferative Glomerulonephritis (IC-MPGN)

Investigators:

Sponsor: Achillion Pharmaceuticals, Inc. (a subsidiary of Alexion Pharmaceuticals, Inc.)

Medical Monitor:
PPD
PPD
nader.najafian@alexion.com
Direct PPD Mobile PPD

	Date
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Confidentiality Statement

SPONSOR SIGNATURE(S)

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Study Number:	ACH471-205
Protocol Version and Date	15 May 2020 (Version 7.0)

This clinical study protocol has been approved by the sponsor.

PPD

Date

Alexion Pharmaceuticals, Inc.
121 Seaport Blvd
Boston, MA 02210

PPD

22-May-2020 | 12:32:29 EDT

INVESTIGATOR'S SIGNATURE(S)

Study Title:	An Open-Label Phase 2 Proof-of-Concept Study in Patients with C3 Glomerulopathy (C3G) or Immune-Complex Membranoproliferative Glomerulonephritis (IC-MPGN) Treated with ACH-0144471
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I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

<Name and Credentials/Title> <Affiliation/Company> <Address> <Address> <Phone Number>	Date

SYNOPSIS

Sponsor	Achillion Pharmaceuticals, Inc. (a subsidiary of Alexion Pharmaceuticals, Inc.) 121 Seaport Blvd Boston, MA 02210 Phone: IPPD
Name of Finished Product	ACH-0144471 Tablet: 50 and 100 mg
Name of Active Ingredient	ACH-0144471
Name of Inactive Ingredient	ACH-0144471 Tablet: CCI [redacted]
Study Title	An Open-Label Phase 2 Proof-of-Concept Study in Patients with C3 Glomerulopathy (C3G) or Immune-Complex Membranoproliferative Glomerulonephritis (IC-MPGN) Treated with ACH-0144471
Study Number	ACH471-205
Study Phase	Phase 2
Primary Objective	To evaluate the efficacy of 12 months of oral ACH-0144471 in participants with C3G or IC-MPGN based on histologic scoring and proteinuria
Secondary Objectives	• To evaluate the clinical effect of 12 months of oral ACH-0144471 in participants with C3G or IC-MPGN based on significant improvement in slope of estimated glomerular filtration rate (eGFR) relative to baseline over time • To evaluate for improvement in eGFR following treatment with ACH-0144471 • Where available evaluate the change in measured (m) eGFR relative to baseline at the end of 12 months of treatment with ACH-0144471 • To evaluate the safety and tolerability of ACH-0144471 in participants with C3G or IC-MPGN by assessing serious adverse events (SAEs)

Study Design	This is an open-label study in which all participants will receive active treatment with ACH-0144471 for approximately 40 months. The study will enroll approximately 20 participants with biopsy-confirmed C3G or IC-MPGN, 12 years of age or older, who have not undergone renal transplant. Participants who completed ACH471-201 are eligible to participate, as long as they do not meet any exclusion criteria. For all participants, eligibility will be confirmed based on the results from the screening eligibility assessments. Once eligibility is confirmed, arrangements can be made for a renal biopsy (if necessary to confirm the diagnosis or to establish a baseline for adult participants who chose to participate in the renal biopsy sub-study) and/or vaccinations, as discussed below. Biopsies will not be obtained from participants less than 18 years of age (unless a biopsy is determined to be clinically indicated by the treating provider), or from participants for whom a biopsy is contraindicated. The initial screening visit must occur no more than 75 days before the first dose date. All participants should be vaccinated against *Haemophilus influenzae* (*H. influenzae*), *Streptococcus pneumoniae* (*S. pneumoniae*), and *Neisseria meningitidis* (*N. meningitidis*) as recommended by the Advisory Committee on Immunization Practices (ACIP) guidelines at least 2 weeks before the start of dosing ACH-0144471, as described in Section 6.4, to minimize the risk of serious infection with an encapsulated organism, unless otherwise recommended by local vaccination guidelines, or precluded by licenses or availability. The PI may institute additional prophylactic measures, including the use of prophylactic antibiotics, if deemed appropriate by local clinical practice and/or guidelines for treatment with a complement inhibitor. The starting dosage will be 100 mg of ACH-0144471 TID, for a total daily dose of 300 mg. After 2 weeks of treatment, dosing will be escalated to 200 mg TID (or 150 mg TID for participants less than 60 kg). Additional dosage regimens may be investigated if supported by emerging data from this and other clinical studies. Upon treatment discontinuation, regardless of the timing or reasons for discontinuation, a 6-day taper period is required unless the PI determines this taper period poses a risk to the participant. The taper period is in place to prevent the theoretical risk of marked increase or rebound in complement activity, as described in Section 5.1.1. **Renal Biopsies and Renal Biopsy Sub-Study** Participants must have biopsy-confirmed primary C3G or IC-MPGN. This can be a historical biopsy. If no historical biopsy is available, a renal biopsy should be performed during the screening period, and the results must be available and reviewed before the first dose of ACH-0144471. Biopsy will be obtained from participants at the 12 months timepoint (Week 52) if older than 18 years of age and not contraindicated. A sub-study is being conducted to evaluate the effects of ACH-0144471 on renal pathology; participation in this study is not required. For participants in the renal biopsy sub-study, biopsies will be obtained prior to dosing and after approximately 6 and/or 24 months of dosing. If for any reason, any additional renal biopsies are performed (e.g.

	for a clinical indication), then every effort will be made to make these biopsy samples and results available to the central pathology laboratory for evaluation.
Study Visit Schedule	On Day 1, the required pre-dose assessments will be obtained, followed by administration of the first dose of ACH-0144471. At each visit, safety and efficacy will be assessed. Safety assessments may include physical examination, vital signs, electrocardiogram (ECG) measurements and safety laboratory testing. Samples will be collected for measurement of complement biomarkers and PK analysis at selected visits as specified in the Schedule of Assessments (Appendix 1). Quality of Life and Patient Reported Outcomes assessments will occur according to the Schedule of Assessments. If a participant discontinues from the study prior to Week 104, study participation is not necessarily immediately terminated. Instead, whenever possible, dosing of ACH-0144471 should be tapered over 6 days. Whether dosing is tapered or not, all participants should return for two follow-up visits, 2 and 4 weeks after the last dose of ACH-0144471.
Treatment Groups:	There will be a single treatment group, and all participants will receive active treatment with ACH-0144471
Study Population	Participants must have biopsy-confirmed C3G or IC-MPGN, must have an eGFR >30 mL/min/1.73 m^2, and must not have undergone renal transplant
Number of Participants	Approximately 20
Inclusion Criteria	Each participant must meet all of the following criteria to be enrolled in this study: 1. Must have completed the C3G Proof of Mechanism (POM) study (ACH471-201) (participation in the long-term follow-up portion of ACH471-201 is not required), followed by a washout period of at least 30 days OR Must meet all the following criteria: a. Must have biopsy-confirmed primary C3G or IC-MPGN b. Must have clinical evidence of ongoing disease based on significant proteinuria (defined as ≥500 mg/day of protein in a 24-hour urine) attributable to C3G disease or IC-MPGN in the opinion of the PI, and present prior to study entry and confirmed during Screening. c. If a pre-treatment biopsy is obtained, or if a historical biopsy is available for review, it must have no more than 50% global fibrosis and no more than 50% of glomeruli with cellular crescents d. Must be 12 years or age or older and capable of swallowing tablets

	2. If on corticosteroids, anti-hypertensive medications, anti-proteinuric medications (e.g., ACE inhibitors or angiotensin receptor blockers [ARBs]), or mycophenolate mofetil (MMF), must be on a stable dose for at least 2 weeks prior to screening 3. Female participants of childbearing potential must agree to use an acceptable method of contraception (as defined in Section 5.5.4) from the date of signing the informed consent to the first day of dosing (Day 1), and must agree to use a highly effective form of contraception (as defined in Section 5.5.4) from the first day of dosing to 30 days after their last dose of study drug. Female participants of childbearing potential must also have a negative serum pregnancy test during Screening and negative urine pregnancy test on Day 1. Female participants of non-childbearing potential need not employ a method of contraception. 4. Non-sterile male participants must agree to use a highly effective form of contraception (as defined in Section 5.5.4) with their partner(s) of childbearing potential from the first day of dosing to 90 days after their last dose of study drug. Male participants who are surgically sterile need not employ additional contraception. Male participants must agree not to donate sperm while enrolled in this study and for up to 90 days after their last dose of study drug. 5. Adult participants must be capable of providing written informed consent and adolescent participants must be capable of providing written assent. All participants must be willing and able to comply with the requirements and restrictions listed in the consent form and with all procedures in the protocol, including, the visit schedule, the treatment plan, the schedule for laboratory testing, and other study procedures 6. Must be up-to-date on routine vaccinations, or willing to be brought up-to-date, based on local guidelines 7. Must have access to emergency medical care
Exclusion Criteria	Participants who meet any of the following criteria will be excluded from the study. 1. Have a history of a major organ transplant (e.g., heart, lung, kidney, liver) or hematopoietic stem cell/marrow transplant 2. Have a history or presence of any clinically relevant co-morbidities that would make the participant inappropriate for the study (for example, a comorbidity which is likely to result in deterioration of the participant's condition, affect the participant's safety during the study, or confound the results of the study), in the opinion of the PI 3. Have an estimated GFR <30 mL/min/1.73 m^2 at the time of screening or at any time over the preceding four weeks 4. Is a renal transplant recipient or receiving renal replacement therapy 5. Have other renal diseases that would interfere with interpretation of the study 6. Have evidence of monoclonal gammopathy of unclear significance (MGUS), infections, malignancy, autoimmune diseases, or other conditions to which C3G or IC-MPGN is secondary 7. Have been diagnosed with or show evidence of hepatobiliary cholestasis 8. Females who are pregnant, nursing, or planning to become pregnant during the study or within 90 days of ACH-0144471 administration or participants with a

	female partner who is pregnant, nursing, or planning to become pregnant during the study or within 90 days of ACH-0144471 administration 9. Have a history of febrile illness, a body temperature >38°C, or other evidence of a clinically significant active infection, within 14 days prior to ACH-0144471 administration 10. Have evidence of human immunodeficiency virus (HIV), hepatitis B infection, or active hepatitis C infection at Screening 11. Have a history of meningococcal infection within the prior year 12. Have a history of hypersensitivity reactions to commonly used antibacterial agents, including beta-lactams, penicillin, aminopenicillins, fluoroquinolones, cephalosporins, and carbapenems, which, in the opinion of the investigator and/or an appropriately qualified immunology or infectious disease expert, would make it difficult to properly provide either empiric antibiotic therapy or treat an active infection. 13. Have participated in a clinical study in which an investigational drug was given within 30 days, or within 5 half-lives of the investigational drug, whichever is longer, prior to the first dose of ACH-0144471 14. Have received eculizumab at any dose or interval within the past 50 days prior to the first dose of ACH-0144471 15. Have received tacrolimus or cyclosporine within 2 weeks of the first dose of ACH-0144471 16. Have a 12-lead ECG with a QTcF >450 msec for males or >470 msec for females, or have ECG findings which, in the opinion of the PI, could put the participant at undue risk 17. Have received any drug known to prolong the QTc interval within 2 weeks of the first dose of ACH-0144471 and which, in the opinion of the PI, could put the participant at undue risk 18. Have any of the following laboratory abnormalities at screening: ▪ Alanine transaminase (ALT) > upper limit of normal (ULN) ▪ Aspartate aminotransferase (AST) > ULN ▪ Absolute neutrophil counts (ANC) <1,000/μL ▪ Total bilirubin >1.5× ULN ▪ Indirect bilirubin > ULN ▪ Any laboratory abnormality that, in the opinion of the PI, would make the participant inappropriate for the study 19. Are unwilling or unable to comply with the study protocol for any reason
Study Stopping Rules	The safety of dose continuation will be assessed within 24 hours if one or more of the following occurs: • Two or more participants experience the same or similar study drug-related serious adverse event • Two or more participants experience the same or similar study drug-related Grade 4 or higher adverse events

	• Two or more participants discontinue study therapy due to study drug-related liver function test abnormalities detailed in the Stopping Rules for Individual Participants If dosing is terminated in one or more study participants, all these participants will be expected to complete the study by complying with the schedule for the Taper Period (if relevant) and Follow-Up Period. Of note, additional visits beyond those specified in the protocol may be required if needed to ensure adequate safety monitoring.

Stopping Rules for Individual Participants	Any individual participant who meets any of the following criteria may be discontinued from further dosing:
	• The participant experiences a serious, unexpected suspected adverse reaction
	• The PI believes that participant continuation in the study is not advisable or the participant withdraws from the study or meets one of the conditions described in Section 6.22, including, but not limited to:
	  • The participant becomes pregnant
	  • Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree
	  • Participant requests to discontinue for any reason
	
	Discontinuation of treatment should also be considered if:
	• ALT or AST >8× ULN
	• ALT or AST >5× ULN for more than 2 weeks
	• ALT or AST >3× ULN and concomitant total bilirubin >2× ULN and/or International Normalized Ratio [INR]* >1.5
	• ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
	
	* Participants, particularly those with nephrotic syndrome, may be receiving ongoing warfarin, resulting in increased INR values. The PI should evaluate INR in the context of any concomitant medications to determine if any observed increases are due to an effect on liver function or are secondary to anticoagulation.
	
	Upon dosing termination, a participant will be expected to complete the study, if possible, by complying with the schedule for the Taper Period (if relevant) and Follow Up Period. Of note, additional visits beyond those specified in the protocol may be required if needed to ensure adequate safety monitoring.

Duration of Treatment, Confinement, and Total Study Participation	Screening is up to 75 days, treatment is approximately 40 months (including the taper), and follow-up is an additional 28 days. Therefore, the total duration of participation will be up to 44 months.
Safety Assessments:	Safety assessments will include assessment of AEs, clinical laboratory tests, physical examination findings, and vital signs measurements, and 12-lead ECG recordings at screening, baseline, and at various time points during the study as listed in the schedule of assessments (Appendix 1).

Pharmacokinetic Assessments:	Single trough PK samples will be taken at the time points as listed in the schedule of assessments (Appendix 1).
Pharmacodynamic and Efficacy Assessments	Pharmacodynamics will be evaluated using serum, plasma, and/or urine collected at the time points as listed in the schedule of assessments (Appendix 1). Samples will be collected and retained for non-genetic complement-associated biomarker testing.
Patient-Reported Outcomes Assessments	Patient-reported outcome (PRO) questionnaires will be administered at screening, Week 28, 52 and 104, and at follow-up as specified in the Schedule of Assessments in Appendix 1, to assess participants' health-related quality of life, fatigue, and kidney-related symptoms, and to determine health states value over the course of treatment with ACH-0144471. The questionnaires are: Adult participants: • KDQOL-SF v1.3 questionnaire • FACIT-Fatigue scale version 4.0 • EQ-5D-3L questionnaire Adolescent participants: • Peds-FACIT-F questionnaire • EQ-5D-Y questionnaire
Statistical Methods:	Primary efficacy endpoints: • Change from baseline in biopsy, based on a score incorporating changes in both the activity index and C3 staining at the end of 12 months of treatment. • Number and percent of participants with reduction in proteinuria relative to baseline at the end of 12 months of treatment Secondary efficacy endpoints: Number and proportion of participants with significant (≥25%) increase in eGFR relative to baseline at the end of 12 months of treatment • Change and percent change from baseline in proteinuria and eGFR over 12 months of treatment period for all participants • Change and percent change from baseline in eGFR over 12 months of treatment for participants meeting eGFR inclusion criterion at study entry • Descriptive analysis of slope of GFR over the treatment period of ACH-0144471 therapy Safety endpoints: • Number and incidence of – SAEs

	– AEs leading to discontinuation of the study medication – Grade 3 or 4 AEs (related and regardless of relationship to study medication) – Grade 3 or 4 Laboratory abnormalities – Treatment-emergent vital signs, physical exam results, and ECG abnormalities Descriptive statistical and confidence interval procedures will be utilized for both primary and secondary efficacy endpoints. Summary statistics will be provided for safety endpoints. No inferential statistical procedures will be used for safety endpoints, unless clinically deemed necessary and appropriate. Details of statistical analysis strategies and methodologies will be described in the statistical analysis plan (SAP).

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
Ab	Antibody
ACE	Angiotensin converting enzyme
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANC	Absolute neutrophil count
AP	Alternative Pathway (of complement)
ARBs	Angiotensin receptor blockers
AST	Aspartate aminotransferase
AUC	Area under the curve
BA	Bioavailability
Ba	Ba fragment of complement factor B
Bb	Bb fragment of complement factor B
BID	"bis in die" or twice daily
BMI	Body mass index
BP	Blood pressure
°C	Degrees Celsius
C3	C3 complement protein
C3a	Complement cleavage fraction of C3
C4	C4 complement protein
C5	C5 complement protein
C5a	Complement cleavage fraction of C5
C6	C6 complement protein
CFHR-5	Complement Factor H Related – 5 gene
C3G	C3 glomerulopathy
C3GN	C3 glomerulonephritis
CFU	Colony-forming unit
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease - Epidemiology collaboration
C_{max}	Maximum plasma concentration
CP	Classical pathway (of complement)
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DDD	Dense deposit disease
DDI	Drug-drug interaction
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
EM	Electron microscopy
EQ-5D-3L	Three-level version of EuroQol 5 Dimensions questionnaire
ESRD	End stage renal disease
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue scale version 4.0
fB	(Complement) Factor B
fD	(Complement) Factor D
FDA	Food and Drug Administration
fH	(Complement) Factor H
fI	(Complement) Factor I

Abbreviation	Definition
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
HbsAg	Hepatitis B surface antigen
Hct	Hematocrit
HCV	Hepatitis C virus
Hgb	Hemoglobin
H&E	Hematoxylin & eosin stain
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	Human immunodeficiency virus
HRQOL	Health-related quality of life
HR	Heart rate
iC3b	Complement cleavage fragment of C3b
IC-MPGN	Immune-Complex Membranoproliferative Glomerulonephritis
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional review board
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
kDa	Kilodalton
KDQOL-SF v1.3	Kidney Disease Quality of Life short form questionnaire version 1.3
LFC	Liquid filled capsule
LLN	Lower limit of normal
LP	Lectin pathway (of complement)
MAD	Multiple-ascending dose
MCP	Membrane Co-Factor Protein
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MenB	Meningococcal B
MGUS	Monoclonal gammopathy of unclear significance
MM	Medical monitor
MMF	Mycophenolate mofetil
MPA	Mycophenolic acid
msec	Millisecond
NIH	National Institute of Health (US)
NOAEL	No observed adverse effect level
PAS	Periodic acid-Schiff
PD	Pharmacodynamic(s)
PI	Principal investigator
PK	Pharmacokinetic(s)
POC	Proof of Concept
PR interval	Period that extends from the beginning of the P wave until the beginning of the QRS complex
PRO	Patient-reported outcome
PT	Prothrombin time
PTT	Partial thromboplastin time
QRS	Group of electrocardiogram waves comprising the Q, R, and S waves
QT	Period (in milliseconds) from the beginning of the QRS complex until the end of the T wave
QTcF	QT interval Fridericia Correction Formula
RBC	Red blood cells
Relative BA	Relative bioavailability study
RR	Respiration rate
SAD	Single-ascending dose

Abbreviation	Definition
SAE	Serious adverse event
SAP	Statistical Analysis Plan
sC5b-9	Soluble terminal complement complex
SD	Standard deviation
SLE	Systemic lupus erythematosus
SUSAR	Serious, unexpected suspected adverse reaction
TEAE	Treatment-emergent adverse event
THBD	Thrombomodulin
t_{max}	Time after administration of a drug when the maximum plasma concentration is reached
UGT	UDP-gluronosyltransferase
ULN	Upper limit of normal
WBC	White blood cells
Wk	Week

1. INTRODUCTION

ACH-0144471, a small molecule, orally administered, factor D (fD) inhibitor, is in development by Achillion Pharmaceuticals, Inc. ("Achillion", or the sponsor), a subsidiary of Alexion Pharmaceuticals, Inc., for the treatment of complement-related diseases, such as paroxysmal nocturnal hemoglobinuria (PNH) and C3 glomerulopathy (C3G). Factor D is a serine protease that catalyzes the cleavage of factor B, a rate-limiting step in the alternative pathway (AP) of complement. By inhibiting fD, ACH-0144471 potently and specifically inhibits AP activity.

Because C3G is a disease of AP hyperactivity, ACH-0144471 represents an ideal therapeutic approach to C3G, as it has the potential to reverse the underlying pathophysiology of the disease. Primary immune-complex membranoproliferative glomerulonephritis (IC-MPGN), which shares many clinical, pathologic, genetic, and laboratory features with C3G and in which complement also likely plays a key role, may also be an attractive therapeutic target.

This protocol is a multiple-center, open-label study in which participants with C3G or primary IC-MPGN will receive ACH-0144471 for approximately 40 months (including the taper period). In preceding studies, it has been demonstrated that ACH-0144471 inhibits AP activity. This study will assess the ability of ACH-0144471 to inhibit AP activity, in the setting of AP over-activation in participants with C3G or primary IC-MPGN. Doses for this study were selected based on available data from the completed and ongoing studies in healthy volunteers, and from PNH patients and C3G patients treated in other clinical studies.

1.1. Previous Experience with ACH-0144471

A detailed description of the chemistry, pharmacology, efficacy, and safety of ACH-0144471 is provided in the Investigator's Brochure [1].

1.2. Background

1.2.1. Complement Factor D

Factor D is one of nine serine proteases in the complement system. It is a highly specific enzyme with only one known substrate, fB. Of all the complement proteins, it has the lowest abundance in serum with a concentration of approximately 2 µg/mL and is the rate-limiting step of AP activation [2, 3]. It is a low molecular weight protein (24 kDa) that is primarily produced by adipocytes, but can also be produced and secreted by monocytes/macrophages and astrocytes in humans [2, 3]. Due to its small size, it is freely filtered at the glomerulus, and then taken up by the proximal tubule cell where it is catabolized with an estimated fractional catabolic rate of 60% per hour. It is this rapid catabolism that is responsible for maintaining low circulating fD levels. As a result, renal dysfunction is associated with elevated fD levels, which may lead to increased alternative pathway activity and inflammation [4, 5]. The biochemical, physiological, and functional features of fD make it an attractive target for pharmacological inhibition as this may prove useful in the treatment of a wide spectrum of complement-mediated diseases, including C3G and IC-MPGN.

1.2.2. C3 Glomerulopathy

C3 glomerulopathy (C3G) is an ultra-rare disease with an incidence rate of approximately 2 per million people worldwide [6, 7]. It is widely accepted that C3G is attributable to excessive alternative pathway (AP) activity [8]. Although the disease is typically diagnosed during early adulthood in a majority of patients, the manifestations of glomerular C3 deposition can be detected in childhood and thus, it may be clinically meaningful to treat patients as young as 12 years of age [7, 9, 10]. The clinical course of C3G is characterized by variable amounts of proteinuria, hematuria, hypertension, and decreased renal function, with approximately 30% to 50% of patients reaching end-stage renal disease (ESRD) within 10 years of diagnosis [7, 11, 12, 13]. The diagnosis is based on predominant deposition of C3 in the glomerulus on renal biopsy along with clinical evidence of AP hyperactivity. C3G can be further subdivided into two separate entities, dense deposit disease (DDD) and C3 glomerulonephritis (C3GN), based on electron microscopic features of the renal pathology [8]. Although the two disorders have similar clinical features, DDD tends to present earlier in life than C3GN. However, both diseases can present in either childhood or adulthood [13].

Unfortunately, no specific therapy has proven effective for the treatment of C3G. Care is therefore largely non-specific and supportive. Given the lack of available therapeutic options, immunosuppressive and plasma infusion/exchange therapy are often attempted, as a subset of patients may benefit [13, 14]. Treatment is otherwise focused on management of hypertension, proteinuria and the manifestations of chronic kidney disease.

The overall prognosis of C3G is poor, with approximately 30% to 50% of patients progressing to ESRD within 10 years of diagnosis. Dialysis and renal transplantation are options available for patients who reach ESRD; however, disease recurrence is frequent after transplantation, occurring in more than 50% of patients. Only about 50% of patients have a functioning graft 5 years after transplantation, which is significantly lower than renal graft survival in other settings [13, 14, 15].

Studies in animal models have indicated that the pathophysiology of C3G strongly relates to an excessive AP activity at the level of the C3 convertase. Specifically, mouse factor H-deficient animals have evidence of uncontrolled alternative pathway activation, with low plasma levels of intact C3, high levels of C3 breakdown product and renal pathology consistent with C3G; yet, in mice deficient in both factor H (fH) and fD (knock-out mice), serum C3 levels were similar to wild-type and dense deposits were not present in the kidneys [16, 17]. These studies confirmed that removal of fD prevented the renal pathogenesis of C3G in the factor H-deficient mice.

Given that the pathophysiology of C3G derives from excessive C3 activation through the AP, treatment of the disease with an AP complement inhibitor is logical. Eculizumab, the only commercially available complement inhibitor, has been tested in patients with C3G, even though its mechanism of action (targeting the terminal complement pathway) would not be expected to affect C3 activation. Based on the published results of an open-label trial in 20 patients, the general consensus is that only a subset of patients appears to benefit from eculizumab therapy; however, identification of these patients prior to treatment remains a challenge [8, 13, 14, 18]. It has been suggested that response to eculizumab may be more likely in those patients with elevated soluble C5b-9 levels, indicative of excessive terminal pathway activity, although this hypothesis remains to be established [18].

A fD inhibitor like ACH-0144471, which inhibits directly at the level of the AP C3 convertase formation, provides a more targeted rationale for efficacy than existing complement inhibitors that target the terminal complement pathway. This hypothesis is supported by animal data in which the renal disease observed with factor H deficiency, which is similar to human C3G, was completely prevented in the setting of simultaneous fD or fB deficiency [16, 17]. In contrast C5 deficiency only ameliorated, but did not prevent, renal disease. Furthermore, C6 deficiency had no effect on the renal disease in fH deficient mice. Taken together, the data from the C5 and C6 deficient mice provide evidence that the membrane attack complex itself plays little role in renal pathogenesis of C3G in the setting of fH deficiency, but that C5a production may be a factor contributing to disease [13, 19].

1.2.3. Immune-Complex Membranoproliferative Glomerulonephritis (IC-MPGN)

Immune-complex membranoproliferative glomerulonephritis (IC-MPGN) is a renal disease which shares many clinical, pathologic, genetic, and laboratory features with C3G, and therefore can be considered a sister disease of C3G. In the majority of patients with IC-MPGN, an underlying disease or disorder (most commonly infections, autoimmune diseases or monoclonal gammopathies) are identified to which the renal disease is secondary. Of note, the most common infections associated with IC-MPGN are hepatitis B and C. Up to 40% of patients with IC-MPGN have no identifiable underlying etiology and are considered to have primary IC-MPGN. Patients with primary IC-MPGN can have low C3 and normal C4 levels, similar to those observed in C3G, as well as many of the same genetic or acquired factors that are associated with abnormal alternative pathway activity. Although IC-MPGN pathology is at least in part attributable to overactivity of the classical pathway, evidence of C3 and/or C3 fragment staining on renal biopsy suggests alternative pathway-related pathophysiology [20]. IC-MPGN patients should therefore benefit from fD inhibition.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of this study is to evaluate the efficacy of 12 months of oral treatment with ACH-0144471 in participants with C3G or IC-MPGN.

Evaluation of efficacy will be based on significant improvement in histologic scoring and proteinuria relative to baseline.

2.2. Secondary Objectives

The secondary objectives of this study are:

- To evaluate the clinical effect of 12 months of oral ACH-0144471 in participants with C3G or IC-MPGN based on significant improvement in slope of estimated glomerular filtration rate (eGFR) relative to baseline over time
- To evaluate for improvement in eGFR following treatment with ACH-0144471
- Where available evaluate the change in measured (m) eGFR relative to baseline at the end of 12 months of treatment with ACH-0144471
- To evaluate the safety and tolerability of ACH-0144471 in participants with C3G or IC-MPGN by assessing serious adverse events (SAEs)

2.3. Other Objectives

The exploratory objectives of this study include:

- To evaluate whether changes in histopathology scoring correlate with observed clinical changes in those participants with biopsy results before and after treatment with ACH-0144471
- To explore the effect of ACH-0144471 on complement biomarkers including alternative pathway (AP) activity in participants with C3G or IC-MPGN over a 12-month treatment period
- To evaluate plasma concentrations of ACH-0144471 in participants with C3G or IC-MPGN
- To evaluate kidney disease and health-related quality of life instruments in participants with C3G or IC-MPGN, over the course of ACH-0144471 treatment
- To explore participants' experience of their disease (C3G or IC-MPGN), its impact, and its management on their everyday lives, from first symptoms to definitive diagnosis and beyond
- To explore participants' expectations and perceptions of ACH-0144471 treatment

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This is an open-label study in which all participants will receive active treatment with ACH-0144471 for approximately 40 months. The study will enroll approximately 20 participants with biopsy-confirmed C3G or IC-MPGN, 12 years of age or older, who have not undergone renal transplant. Participants who completed ACH471-201 are eligible to participate, as long as they do not meet any exclusion criteria.

Participants who did not participate in ACH471-201 must meet all inclusion and exclusion criteria to be eligible. In particular, they must have a biopsy-confirmed diagnosis of C3G or IC-MPGN. The initial diagnosis should have been made at least 3 months prior to dosing, unless otherwise approved by the sponsor. Participants must also have clinical evidence of ongoing disease (defined as proteinuria of ≥500 mg/day of protein in a 24-hour urine) that is attributable to C3G or IC-MPGN in the opinion of the Principal Investigator (PI). Participants who completed ACH471-201 may enroll in this study following a washout period of at least 30 days between the last dose of ACH-0144471 in study ACH471-201 and the renal biopsy (if collected during screening; Section 6.3) or the 24-hour urine collection during screening. These participants will not be required to re-establish their diagnosis of C3G or IC-MPGN, but must meet the other eligibility requirements described in Section 4.

For all participants, eligibility will be confirmed based on the results from the screening eligibility assessments. Once eligibility is confirmed, arrangements can be made for a renal biopsy (if necessary to confirm the diagnosis of C3G or IC-MPGN as described in Section 6.3.1, or to establish a baseline for adult participants who choose to participate in the renal biopsy sub-study) and/or vaccinations. Biopsies will not be obtained from participants less than 18 years of age (unless a biopsy is determined to be clinically indicated by the treating provider), or from participants for whom a biopsy is contraindicated. The initial screening visit must occur no more than 75 days before the first dose date.

All participants should be vaccinated against *Haemophilus influenzae (H. influenzae)*, *Streptococcus pneumoniae* (*S. pneumoniae*), and *Neisseria meningitidis* (*N. meningitidis*) as recommended by the Advisory Committee on Immunization Practices (ACIP) guidelines at least 2 weeks before the start of dosing with ACH-0144471, as described in Section 6.4, to minimize the risk of serious infection with an encapsulated organism, unless otherwise recommended by local vaccination guidelines, or precluded by licenses or availability. The PI may institute additional prophylactic measures, including the use of prophylactic antibiotics, if deemed appropriate by local clinical practice and/or guidelines for treatment with a complement inhibitor.

The starting dosage will be 100 mg of ACH-0144471 TID, for a total daily dose of 300 mg. After 2 weeks of treatment, dosing will be escalated to 200 mg TID (or 150 mg TID for participants less than 60 kg). Additional dosage regimens may be investigated if supported by emerging data from this and other clinical studies. For each participant, the medical monitor will consult with the investigator before making the decision to dose escalate. Upon treatment discontinuation, regardless of the timing or reasons for discontinuation, a 6-day taper period is required unless the PI determines this taper period poses a risk to the participant. The taper

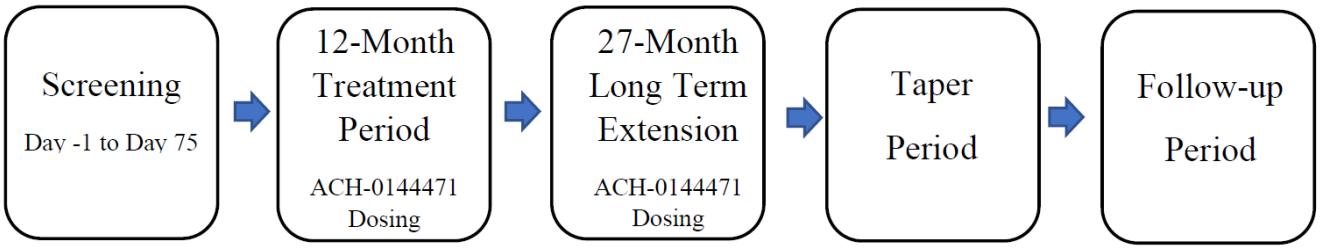
period is in place to prevent the theoretical risk of marked increase or rebound in complement activity, as described in Section 5.1.1.

A sub-study is being conducted to evaluate the effects of ACH-0144471 on renal pathology; participation in this study is not required. For participants in the renal biopsy sub-study, biopsies will be obtained prior to dosing and after approximately 28 and 104 weeks of dosing. If for any reason, any additional renal biopsies are performed (e.g., for a clinical indication), then every effort will be made to make these biopsy samples and results available to the central pathology laboratory for evaluation.

Patient-reported outcome (PRO) questionnaires will be administered to participants at various time points as specified in the Schedule of Assessments (Appendix 1), to assess participants' health-related quality of life (HRQOL), fatigue, and kidney-related fears and worries (e.g. kidney failure, dialysis, kidney transplant), and to determine health states value, over the course of treatment with ACH-0144471.

Figure 1 provides the study schematic.

Figure 1. Study Schematic



3.2. Rationale for Study Design

3.2.1. Justification of Design

This trial is one of two proof-of-concept studies planned to obtain data demonstrating that fD inhibition can reduce AP hyperactivity, and thereby halt, and possibly even reverse, progression of C3G and IC-MPGN. Disease progression and activity will be assessed using evaluation of clinical manifestations of the disease, namely proteinuria and abnormal eGFR, and the sponsor will attempt to correlate any such improvements in clinical manifestations with changes in histopathology, to the extent biopsy data is available. This proof-of-concept trial enables participants with C3G or IC-MPGN (including those who have completed the non-therapeutic ACH471-201 trial) to receive ACH-0144471 for what we expect to be a therapeutic duration. The open-label design, in which all participants receive active treatment, ensures that all participants have the opportunity to receive active drug. Further rationale is provided below for the participant population selected, the endpoints to be evaluated, the duration of treatment, and the safety monitoring plan. Rationale for dose selection and dose adjustment parameters are detailed in Section 3.2.2.

3.2.1.1. Participant Population

The participant population enrolled in this study will be patients with biopsy-confirmed C3G or IC-MPGN. For those who participated and completed study ACH471-201, additional inclusion/exclusion criteria are designed to ensure that there are no new circumstances that would make the participant inappropriate for an ACH-0144471 clinical trial.

Achillion hypothesizes that a fD inhibitor will reduce AP hyperactivity, halting deposition of complement by-products in the kidney. These complement by-products induce an inflammatory response that affects glomerular function, and over time this chronic inflammation can lead to irreversible scarring of the renal parenchyma. As discussed in Section 3.2.1.2.1, the primary clinical manifestations of these processes are proteinuria and/or abnormal eGFR, and intervention during the period of active inflammation is expected to reverse damage and yield improvements in the clinical manifestations of the disease. In contrast, intervention once the kidney is irreversibly damaged may only provide minimal benefit, and even in non-ESRD participants, there is likely to be some component of irreversible renal damage that could limit the maximal response to a fD inhibitor. Therefore, we aim to enrich the population for those participants with the greatest likelihood for significant improvements by targeting participants with enough reversible renal disease to enable a detectable response to a fD inhibitor (proteinuria of at least 500 mg/day) but who do not have ESRD.

Because C3G and IC-MPGN are diseases that can present in childhood, and because early intervention is ideal for the greatest potential benefit, this study will enroll both adult and adolescent (12 years of age and older) participants.

The remaining criteria further ensure that the appropriate population is enrolled based on the available supporting data from the clinical and nonclinical programs for ACH-0144471 at the time of study conduct.

3.2.1.2. Endpoints

Demonstrating definitive efficacy with well-established endpoints for renal diseases, such as time to end-stage renal disease, or doubling of serum creatinine, is impractical in clinical trials for ultra-rare diseases such as C3G and IC-MPGN where these endpoints typically occur over many years, and unfortunately, there are no existing validated surrogate endpoints for progression of these diseases. [redacted] In the absence of validated surrogate endpoints, proteinuria and reduced eGFR are mechanistically important markers for glomerular loss and inflammation, as discussed in Section 3.2.1.2.1, and as such will be endpoints measured in this study.

In patients with reversible renal disease due to C3G or IC-MPGN, successful treatment should be marked by improvement in the clinical, pathologic, and laboratory evidence of the disease, namely improvements in proteinuria and/or eGFR (clinical), improvements in complement deposits and glomerular inflammation (pathologic), and correction of AP hyperactivity reflected by improvements in systemic C3 levels, as well as changes in factor B breakdown products (Bb and Ba), and other complement components (laboratory). Improvements in clinical findings are selected as primary endpoints for this Phase 2 clinical trial, as these are believed to most closely correlate with improvement in long-term outcomes such as time to end-stage renal disease.

Pathology-based endpoints will be examined as an exploratory endpoint for correlation, noting that improvements in histology may lag behind clinical improvements.

3.2.1.2.1. Clinically-Based Endpoints

Since there are no validated surrogate endpoints for C3G or IC-MPGN for use in clinical trial design, Achillion has considered meaningful clinical endpoints that would be indicative of improvements in disease, based on currently available information for C3G, IC-MPGN, and other primary glomerular diseases. Based on two large case series, clinical features of C3G at the time of biopsy diagnosis included proteinuria >3.5 g/day and/or nephrotic syndrome in 26.8% to 44.0%, microscopic hematuria in 64.3% to 76%, and high blood pressure in 20.7% to 44% of patients. It should be noted that at the time of diagnosis, many patients were on steroids and/or other immunosuppressive agents as well as treatment with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), which confounds interpretation of the frequency and extent of both proteinuria and high blood pressure. With regard to blood pressure, there is little additional data in the literature on the extent of high blood pressure, or its responsiveness to anti-hypertensive therapy and management, either at presentation or during the disease course. Up to 50% of patients may also have an abnormal creatinine/eGFR at time of the biopsy diagnosis. Of note, the disease can present with acute kidney injury and/or as a rapidly progressive glomerulonephritis, although these represent a minority of cases [6, 9, 21, 22, 23, 24, 25].

Considering that the primary clinical manifestations of both C3G and IC-MPGN are proteinuria and/or abnormal eGFR, and that current treatment strategies heavily focus on management of these clinical features, Achillion has focused its attention on these two parameters. It is well-accepted within the nephrology community that for glomerular diseases, especially glomerulonephritis, the following earlier changes will translate to long-term clinical benefit, including renal survival: conversion of nephrotic to non-nephrotic proteinuria, decreasing proteinuria (assuming baseline proteinuria is significant [≥500 mg/day]), eliminating proteinuria or reducing it to less than 300 mg/day, normalizing serum creatinine if abnormal at baseline, and/or improving or stabilizing eGFR relative to baseline if abnormal at baseline [26, 27, 28, 29]. Further data in the literature supports a relationship between reduction in proteinuria and improved renal survival across chronic kidney disease (CKD), and especially across multiple different primary glomerular diseases with multiple different types of interventions [30, 31, 32, 33]. Therefore, it is reasonable to expect that improvement in these clinical markers of C3G (proteinuria and/or eGFR) would be indicative of reduced glomerular injury and inflammation, and would translate to improved renal survival.

As the clinical presentation and course of both C3G and IC-MPGN are quite heterogeneous, patients are likely to have only a subset of the possible clinical manifestations. Given the small number of participants, it is not practical to create multiple stratified response criteria (e.g., as often done in trials for SLE nephritis) [28, 29]. Instead, the study will focus on two clinical endpoints, which are among those expected to translate to clinical benefit: decrease in proteinuria relative to baseline, and/or improvement in eGFR relative to baseline.

3.2.1.2.2. Pathology-Based Endpoints

Renal biopsy scoring is a proximal and direct measure of renal disease. An improvement in disease activity scoring by renal histopathology is expected to translate into observed improvements in clinical manifestations, and hopefully into improvements in long-term renal outcomes. There has been no formal assessment correlating histologic features and outcomes in C3G or IC-MPGN, however, there are some data showing that the presence of crescents and more tubular atrophy in the initial biopsy are associated with worse outcomes [10, 34, 35]. In addition, the extent of C3c staining will be a key feature for biopsy analysis for this disease and considering the mechanism of action for ACH-0144471. Achillion is therefore conducting an optional sub-study to evaluate the effects of ACH-0144471 on renal pathology, as described in Section 6.3.1. Since this study is not powered to show improvements in histologic scoring and it is not known if improvements in histology are synchronized with clinical changes, the pathology endpoint will be exploratory, however, histopathologic findings will be important in confirming a mechanistic reason for improvements in other markers if all are present in this study.

Biopsies will not be obtained from participants less than 18 years of age (unless they are determined to be clinically indicated by the treating provider), or from adult participants for whom a biopsy is contraindicated.

The pathology assessments will be described in more detail in a Pathology Manual, and the specific analysis of pathology endpoints for this study will be described in the Statistical Analysis Plan.

3.2.1.2.3. PRO-Based endpoints

Findings from the analysis of qualitative interviews conducted with C3G and IC-MPGN adult patients (n = 10) and with key opinion leaders (n = 7; clinicians and patient advocacy group leaders) have shown that C3Gand IC-MPGN have a detrimental impact on patients' everyday lives. The C3G and IC-MPGN populations appear highly heterogeneous in terms of disease symptomatology, occurrence and evolution of symptoms, and level of impact on patients' lives. However, fatigue and lack of energy are the symptoms the most frequently reported. In addition, patients expressed their fear and worries, mainly due to the likelihood of kidney failure, dialysis and/or transplant. In turn, this significantly affects their everyday lives and quality of life. These symptoms and impacts were salient in C3G patient testimonials during the 04 August 2017 FDA Patient-Focused Drug Development Meeting that was organized by the National Kidney Foundation. Therefore, the PRO strategy for this study will include questionnaires selected to focus on these facets of patients' lives. In particular, participants will complete PRO questionnaires (adult participants will complete the KDQOL-SF v1.3, FACIT-Fatigue, and EQ-5D-3L questionnaires; adolescent participants will complete the Peds-FACIT-F and EQ-5D-Y questionnaires) during the screening period and at Week 28, Week 52 and Week 104, and follow-up (or, in case of a participant's early termination, at the termination visit) as specified in Appendix 1, to assess their HRQOL, fatigue, and kidney-related fears and worries (e.g. kidney failure, dialysis, kidney transplant), and to determine health states value, over the course of treatment with ACH-0144471..

3.2.1.2.4. Safety Endpoints

Safety endpoints:

- Number and incidence of
  - SAEs
  - AEs leading to discontinuation of the study medication
  - Grade 3 or 4 AEs (related and regardless of relationship to study medication)
  - Grade 3 or 4 Laboratory abnormalities
  - Treatment-emergent vital signs, physical exam results, and ECG abnormalities

Descriptive statistical and confidence interval procedures will be utilized for both primary and secondary efficacy endpoints. Summary statistics will be provided for safety endpoints. No inferential statistical procedures will be used for safety endpoints, unless clinically deemed necessary and appropriate.

Details of statistical analysis strategies and methodologies will be described in the statistical analysis plan (SAP).

3.2.1.3. Duration of Treatment

Unfortunately, there is no precedent available for this disease to guide our decision about the length of therapy required to see improvements in clinical manifestations of renal disease (e.g., proteinuria and/or eGFR). A 12-month treatment period with an additional up to 27-month long term extension was selected CCI [redacted] as a feasible timeframe for changes in proteinuria and/or eGFR.

3.2.1.4. Safety Monitoring Plan

The primary focus of the safety monitoring plan will be to regularly monitor safety, including any adverse events, safety laboratory measurements including liver function test and serum creatinine, and the urine albumin: creatinine ratio. In addition, there are specific safety monitoring plans for the potential risk of infection (Appendix 2) and elevation in liver function tests (Section 3.2.3.2).

3.2.1.4.1. Infection

Since one of the primary functions of the complement system is to fight infections, pharmacologic inhibition of the complement system could theoretically result in an increased rate or severity of infections. However, high doses of C1 esterase inhibitor in transplant patients with rejection did not show a signal for infection [36]. Thus, it remains unclear as to whether fD inhibition would increase risk for infection.

In vitro work was done to understand potential infection risk, especially meningococcal infection risk that is associated with AP inhibition. As summarized in Sections 4.1.2 and 6.5.1 of the Investigator's Brochure [1], ACH-0144471 showed minimal inhibition of protective bactericidal and opsonophagocytic activities in studies that included several strains of the clinically important pathogen *N. meningitidis* and blood samples from immunized individuals, suggesting that

vaccination should provide protection from meningococcal infections in participants receiving ACH-0144471.

Nonetheless, this study takes steps to minimize the risk of serious infection. Participants should be vaccinated according to applicable national and/or local guidelines or local clinical practice for *N. meningitidis*, *H. influenza*, and *S. pneumonia* (see Section 6.4), and antibiotic prophylaxis is permitted if deemed appropriate by local clinical practice and/or guidelines, as described in Section 6.5. Achillion will also create and distribute a wallet card for outpatient studies with warning signs and symptoms of serious infection, and appropriate steps of action for all participants. Finally, a fever management plan has been incorporated into the study protocol (see Appendix 2).

3.2.1.4.2. Hepatic Injury

Hepatobiliary cholestasis has been observed in dog toxicology studies at exposures higher than those intended for clinical use, and higher than those planned for this study. Based on clinical observations, the cholestasis is reversible and can be monitored with hepatic safety biomarkers.

Elevations of transaminases have occurred clinically with ACH-0144471. Grade 3 or Grade 4 liver enzyme elevations occurred in 2 active phase 1 study participants receiving higher doses of ACH-0144471 (500 mg twice daily [BID] and 800 mg BID), although these elevations occurred after dosing was completed (3 days and 7 days after last dose). One PNH participant had elevated transaminases associated with breakthrough hemolysis and discontinued ACH-0144471. All abnormal transaminase findings were transient, were not associated with evidence of hepatic decompensation, and resolved within a short time period. Transaminases will be monitored in this study.

Stopping criteria have been included ensuring prompt discontinuation of any participant with evidence of unexplained liver injury. Finally, participants with evidence of active hepatic or hepatobiliary disease will be excluded.

3.2.2. Justification of Dose

The starting dosage will be 100 mg TID. This dose has been demonstrated to inhibit the alternative pathway in PNH patients and in C3G patients, and dosing regimens with similar exposures (e.g., 200 mg BID) have demonstrated AP inhibition in healthy volunteers. Early data shows some clinically relevant reduction in proteinuria associated with AP inhibition, and ACH-0144471 has been well tolerated to date in participants with C3G or IC-MPGN. In order to maximize inhibition of the AP, the dosage will be escalated after 2 weeks, unless the participant has not tolerated treatment, or the investigator feels escalation would not be in the participant's interest. Participants of 60 kg or more will be escalated to a dosage of 200 mg TID, and participants of less than 60 kg will be escalated to a dosage of 150 mg TID.

Based on adult pharmacokinetic data, a PBPK (physiologically-based pharmacokinetics) model was developed and validated to determine a dose of ACH-0144471 in adolescents equivalent to the starting dose of 100 mg TID in adults. A range of doses were simulated in virtual pediatric (adolescent) participants (n=500/1000) to find a dose level that resulted in exposures comparable to those of adults (Figure 2 and Figure 3).

Figure 2. Simulated Adult PK Profile of ACH-0144471 after 200 mg TID for 14 days

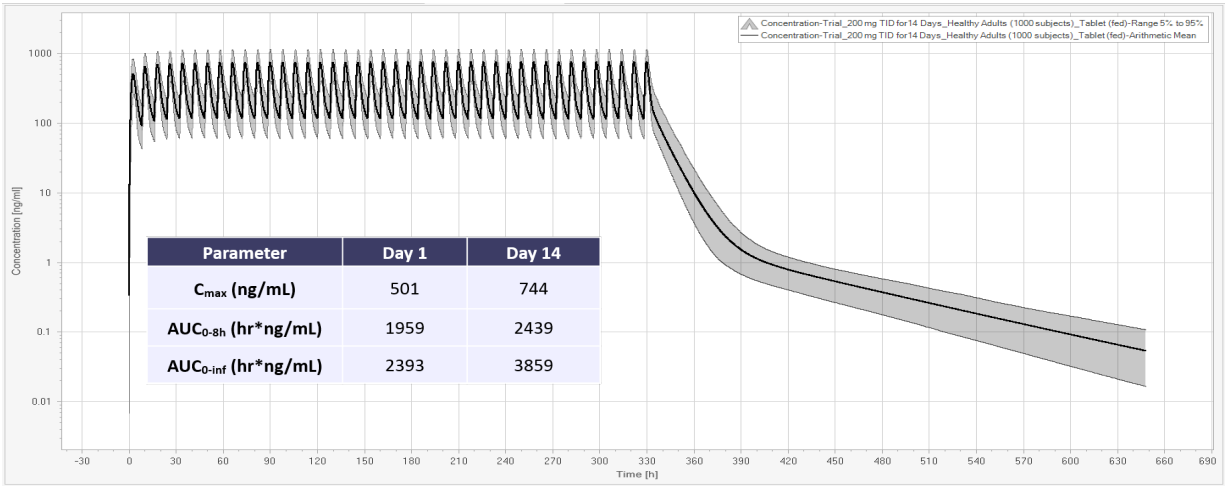
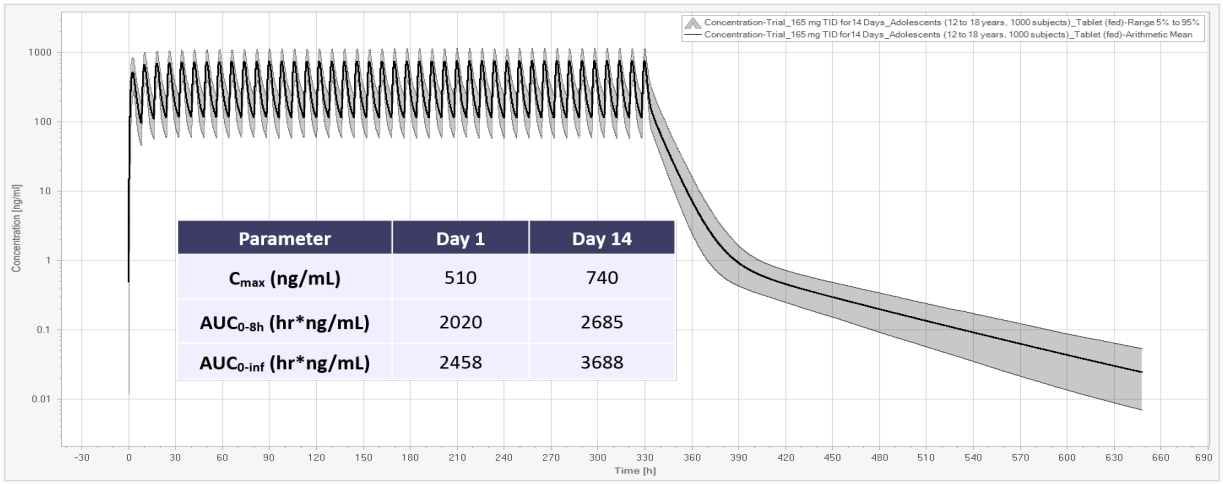


Figure 3. Simulated Adolescent PK Profile of ACH-0144471 after 165 mg TID for 14 days



The result of these simulations was that a mean dosage regimen of 165 mg TID in adolescents (age ≥12 to <18 years) resulted in comparable exposure to adults receiving 200 mg TID. Since ACH-0144471 exhibits linear pharmacokinetic behavior, for a 100-mg TID dosage in adults, the equivalent dosage in adolescents would be 82.5 mg TID. Based on these modeling data, adolescents will receive the same 100 mg TID starting dosage as adults. Adolescents of 60 kg or more may be escalated to the same 200 mg TID dosage as adult participants of 60 kg or more; adolescents of less than 60 kg may be escalated to a dosage of 150 mg TID.

3.2.3. Stopping Criteria and End-of-Study Definition

The Sponsor reserves the right to close a study site or terminate the study at any time for any reason at the sole discretion of the Sponsor.

Study and Individual Stopping Rules are provided below in Sections 3.2.3.1 and 3.2.3.2, respectively. The Achillion Medical Monitor (MM) will review safety data from all enrolling sites on an ongoing basis. If at any time, a Group Stopping Rule is met, then dosing continuation will be assessed. If a PI becomes aware that a Group Stopping Rule has been met, then he/she should inform the Achillion MM immediately. If dosing is terminated in any participant in the study, the Achillion MM in consultation with the PI will decide whether or not the taper should be implemented.

The PI may stop dosing in any participant who meets an Individual Stopping Rule (Section 3.2.3.2); however, the Achillion MM should be notified immediately, and if possible, before dosing is terminated. When dosing is stopped in an individual participant, the PI should consider whether it is in the best interest of the participant to discontinue dosing immediately or to taper (as described in Section 5.2). Whenever possible, the taper decision should also be discussed with the Achillion MM prior to dosing termination.

When dosing is terminated, study participation is not necessarily immediately terminated. Instead, whenever possible, the participant should advance to the Taper and/or Follow-Up Periods, as relevant, and complete all activities as described in Appendix 1.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the Schedule of Assessments.

3.2.3.1. Study Stopping Rules

The safety of dose continuation will be assessed within 24 hours if one or more of the following occurs:

- Two or more participants experience the same or similar study drug-related SAE
- Two or more participants experience the same or similar study drug-related Grade 4 or higher AE
- Two or more participants discontinue study therapy due to study drug-related liver function test abnormalities detailed in the Stopping Rules for Individual Participants

If dosing is terminated in one or more study participants, all these participants will be expected to complete the early termination activities described in Section 7.5, and comply with the schedule for the Taper Period (if relevant) and Follow-Up Period. Of note, additional visits beyond those specified in the protocol may be required if needed to ensure adequate safety monitoring.

3.2.3.2. Stopping Rules for Individual Participants

Any individual participant who meets any of the following criteria may be discontinued from further dosing:

- The participant experiences a SUSAR
- The PI believes that participant continuation in the study is not advisable, or the participant withdraws from the study or meets one of the conditions described in Section 6.22, including, but not limited to:

- The participant becomes pregnant
- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree
- Participant requests to discontinue for any reason

Discontinuation of treatment should also be considered for:

- ALT or AST >8× ULN
- ALT or AST >5× ULN for more than 2 weeks
- ALT or AST >3× ULN and concomitant total bilirubin >2× ULN and/or International Normalized Ratio [INR]* >1.5
- ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

* Participants, particularly those with nephrotic syndrome, may be receiving ongoing warfarin, resulting in increased INR values. The PI should evaluate INR in the context of any concomitant medications to determine if any observed increases are due to an effect on liver function or are secondary to anticoagulation.

Upon dosing termination, a participant will be expected to complete the study, if possible, by complying with the schedule for the Taper Period (if relevant) and Follow Up Period. Of note, additional visits beyond those specified in the protocol may be required if needed to ensure adequate safety monitoring.

4. STUDY POPULATION SELECTION

4.1. Study Population

This study will be conducted in approximately 20 participants with biopsy-confirmed C3G or IC-MPGN. Participants may not have undergone renal transplant and must have an eGFR >30 mL/min/1.73 m^2.

4.2. Inclusion Criteria

Each participant must meet all the following criteria to be enrolled in this study.

1. Must have completed the ACH471-201 Proof of Mechanism (POM) study (participation in the long-term follow-up portion of ACH471-201 is not required), followed by a washout period of at least 30 days,

OR

Must meet all the following criteria:

a. Must have biopsy-confirmed primary C3G or IC-MPGN
b. Must have clinical evidence of ongoing disease based on significant proteinuria (defined as ≥500 mg/day of protein in a 24-hour urine) attributable to C3G disease or IC-MPGN in the opinion of the PI, and present prior to study entry and confirmed during Screening.
c. If a pre-treatment biopsy is obtained, or if a historical biopsy is available for review, it must have no more than 50% global fibrosis and no more than 50% of glomeruli with cellular crescents
d. Must be 12 years of age or older and capable of swallowing tablets

2. If on corticosteroids, anti-hypertensive medications, anti-proteinuric medications (e.g., ACE inhibitors or angiotensin receptor blockers [ARBs]), or mycophenolate mofetil (MMF), must be on a stable dose for at least 2 weeks prior to screening
3. Female participants of childbearing potential must agree to use an acceptable method of contraception (as defined in Section 5.5.4) from the date of signing the informed consent to the first day of dosing (Day 1), and must agree to use a highly effective form of contraception (as defined in Section 5.5.4) from the first day of dosing to 30 days after their last dose of study drug. Female participants of childbearing potential must also have a negative serum pregnancy test during Screening and negative urine pregnancy test on Day 1. Female participants of non-childbearing potential need not employ a method of contraception.
4. Non-sterile male participants must agree to use a highly effective form of contraception (as defined in Section 5.5.4) with their partner(s) of childbearing potential from the first day of dosing to 90 days after their last dose of study drug. Male participants who are surgically sterile need not employ additional contraception. Male participants must agree not to donate sperm while enrolled in this study and for up to 90 days after their last dose of study drug.

5. Adult participants must be capable of providing written informed consent, and adolescent participants must be capable of providing written assent. All participants must be willing and able to comply with the requirements and restrictions listed in the consent form and with all procedures in the protocol, including, the visit schedule, the treatment plan, the schedule for laboratory testing, and other study procedures
6. Must be up-to-date on routine vaccinations, or willing to be brought up-to-date, based on local guidelines
7. Must have access to emergency medical care

4.3. Exclusion Criteria

Participants who meet any of the following criteria will be excluded from the study.

1. Have a history of a major organ transplant (e.g., heart, lung, kidney, liver) or hematopoietic stem cell/marrow transplant
2. Have a history or presence of any clinically relevant co-morbidities that would make the participant inappropriate for the study (for example, a comorbidity which is likely to result in deterioration of the participant's condition, affect the participant's safety during the study, or confound the results of the study), in the opinion of the PI
3. Have an estimated GFR <30 mL/min/1.73 m^2 at the time of screening or at any time over the preceding four weeks
4. Is a renal transplant recipient or receiving renal replacement therapy
5. Have other renal diseases that would interfere with interpretation of the study
6. Have evidence of monoclonal gammopathy of unclear significance (MGUS), infections, malignancy, autoimmune diseases, or other conditions to which C3G or IC-MPGN is secondary
7. Have been diagnosed with or show evidence of hepatobiliary cholestasis
8. Females who are pregnant, nursing, or planning to become pregnant during the study or within 90 days of ACH-0144471 administration or participants with a female partner who is pregnant, nursing, or planning to become pregnant during the study or within 90 days of ACH-0144471 administration
9. Have a history of febrile illness, a body temperature >38°C, or other evidence of a clinically significant active infection, within 14 days prior to ACH-0144471 administration
10. Have evidence of human immunodeficiency virus (HIV), hepatitis B infection, or active hepatitis C infection at Screening
11. Have a history of meningococcal infection within the prior year
12. Have a history of hypersensitivity reactions to commonly used antibacterial agents, including beta-lactams, penicillin, aminopenicillins, fluoroquinolones, cephalosporins, and carbapenems, which, in the opinion of the investigator and/or an appropriately

qualified immunology or infectious disease expert, would make it difficult to properly provide either empiric antibiotic therapy or treat an active infection.

13. Have participated in a clinical study in which an investigational drug was given within 30 days, or within 5 half-lives of the investigational drug, whichever is longer, prior to the first dose of ACH-0144471
14. Have received eculizumab at any dose or interval within the past 50 days prior to the first dose of ACH-0144471
15. Have received tacrolimus or cyclosporine within 2 weeks of the first dose of ACH-0144471
16. Have a 12-lead ECG with a QTcF >450 msec for males or >470 msec for females, or have ECG findings which, in the opinion of the PI, could put the participant at undue risk
17. Have received any drug known to prolong the QTc interval within 2 weeks of the first dose of ACH-0144471 and which, in the opinion of the PI, could put the participant at undue risk
18. Have any of the following laboratory abnormalities at screening:
    - Alanine transaminase (ALT) > upper limit of normal (ULN)
    - Aspartate aminotransferase (AST) > ULN
    - Absolute neutrophil counts (ANC) <1,000/μL
    - Total bilirubin >1.5× ULN
    - Indirect bilirubin > ULN
    - Any laboratory abnormality that, in the opinion of the PI, would make the participant inappropriate for the study
19. Are unwilling or unable to comply with the study protocol for any reason

5. STUDY TREATMENT(S)

5.1. Description of Treatment(s)

5.1.1. Study Drug

ACH-0144471 will be dosed orally as a tablet formulation containing the drug substance, [redacted] Tablets will be provided in 50 and 100-mg strengths.

5.2. Treatment(s) Administered

5.2.1. ACH-0144471

ACH-0144471 tablets will be administered at a starting dosage of 100 mg TID. Study drug administration will then continue for the remainder of the 40-month Treatment Period. When dosing is to be discontinued, the dose will be tapered over approximately 6 days (Taper Period) to minimize the potential adverse effects of a rapid surge in complement activity following drug withdrawal.

The dosing taper regimen is described in Table 1. If a dosing regimen not specified in the Table 1 is used, then the taper schedule will be defined by the Achillion MM prior to dosing termination. In addition, the taper schedule may be adjusted to allow for slower taper in a participant who is not tolerating discontinuation of drug.

Table 1. ACH-0144471 Taper Schedule

Dose at Termination	Taper Period 1 (Taper Days 1-3)	Taper Period 2 (Taper Days 4-6)
100 mg TID	100 mg BID	0mg
150 mg TID	100 mg TID	50 mg TID
200 mg TID	100 mg TID	100 mg BID

5.2.2. Vaccines

Depending on the participant's vaccination history, the vaccines described in Section 6.4 may need to be administered according to the ACIP guidelines unless otherwise recommended by local vaccination guidelines or precluded by licenses or availability. Because these are commercially available products, information about the specific vaccines can be found on the package inserts/product labels for those products. Full identifying information for any administered vaccines, including the brand, should be recorded in the participant's CRF.

5.2.3. Prophylactic Antibiotics

As described in Section 6.5, antibiotic prophylaxis is not mandated but allowed if deemed necessary by local clinical practice and/or guidelines for treatment with a complement inhibitor. Because commercially available products will be used, information about any specific antibiotics administered can be found on the package inserts/product labels for those products. Full

identifying information for any antibiotics given as part of this study, including the brand, should be recorded in the participant's CRF.

5.3. Selection of Timing and Dose for Each Participant

For the starting dose, participants will take one 100-mg ACH-0144471 tablet three times daily (TID): a dose in the morning, a second dose 8 hours later, and a third dose 8 hours after the second dose. Doses should be taken at approximately the same time each day and as close as possible to 8 hours apart. All doses should be taken approximately 15 to 30 minutes after completion of a meal. Water intake is not restricted. If a dose is missed, it should be taken within 4 hours of the originally scheduled time. After 4 hours, the missed dose should be skipped. In either case, the next dose should be taken according to the original dosing schedule.

If a dosing interval other than TID is used during the study, then interval between doses should be equally distributed over a 24-hour period, and dosing should otherwise comply with the guidelines provided for a TID interval.

5.3.1. Clinic Visit Dose Administration Instructions

The morning doses on the days of each visit to the study center will be administered in the clinic by study site personnel, who will instruct participants on how to take their study medication at home between visits. Participants will be instructed to fast for at least 8 hours before their clinic visit and to drink enough water to ensure they are adequately hydrated. Participants must abstain from taking their study medication on the mornings of their study visits so that they can be dosed in the clinic following safety and pharmacokinetic assessments. All doses should be taken approximately 15 to 30 minutes after completion of a meal. Participants will be required to bring back their study drug at each visit so that study site personnel may perform drug accountability. If morning clinic visits are not possible, participant visits may be scheduled so that safety and pharmacokinetic assessments can be made before the second daily dose. The 8-hour interval between doses should be maintained, as should the relative timing of dosing and all study-related activities.

5.3.2. Home Dose Administration Instructions

Participants should be instructed to finish a meal or snack approximately 15 to 30 minutes prior to dosing. Participants should also take their medication such that doses are as close as possible to 8 hours apart (or the relevant interval in the event of a non-TID schedule).

Participants should be instructed to keep their study medications at room temperature.

5.3.3. Dose Adjustment

After 2 weeks of treatment, dosing will be escalated to 200 mg TID (or 150 mg TID for participants less than 60 kg) unless the participant has not tolerated treatment. While the intent is to maintain a steady dose for the duration of the study, dose adjustments are permitted for participant safety or in order to create the best opportunity for each participant to have a therapeutic benefit. Dosing may be adjusted by the MM (or designee) in consultation with the PI, within the parameters provided below and based on review of available safety, PK, and PD results.

Dose increases should be such that the new total daily dose is no more than 2× the prior total daily dose.

5.4. Method of Assigning Participants to Treatment Groups

All participants will receive ACH 0144471 and will be assigned to the same treatment group. Participants entering following completion of ACH471-201 will retain the same participant identification as in study ACH471-201. Newly enrolled participants will be assigned a sequential participant identification number within each study site.

5.5. Restrictions

5.5.1. Prior and Concomitant Therapy

Participants who complete ACH471-201 are eligible to enter this study, following a washout period of at least 30 days between the last dose of ACH-0144471 in study ACH471-201 and the pre-treatment renal biopsy (if collected; Section 6.3). This is to allow the renal histopathology to return toward baseline after completion of study drug administration in ACH471-201. In addition, this 30-day window will also meet the study's exclusion criteria that requires no administration of an investigational agent within 30 days or 5 half-lives. Of note, based on healthy volunteer data, the half-life of ACH-0144471 is 7 to 10 hours.

Participants may not have received another investigational agent within 30 days or 5 half-lives of the investigational agent prior to the first dose of study drug, whichever is greater. Participants may not have received eculizumab within 50 days prior to the first dose of study drug. Participants may not have received tacrolimus or cyclosporine within 2 weeks prior to the first dose of study drug.

Based on in vitro data, ACH-0144471 has the potential to interact with several CYP enzymes as well as some transporters as a perpetrator but not as a victim drug. In vitro results for various CYP enzymes and transporters are described in the Investigator's Brochure [1].

A drug-drug interaction study with ACH-0144471 has been conducted to determine the potential for ACH-0144471 to affect the PK of midazolam (substrate for CYP3A), fexofenadine (substrate for P-gp), and mycophenolic acid (substrate of UGT). Preliminary results indicate that ACH-0144471 is a weak inhibitor of CYP3A, a moderate inhibitor of P-gp, and had no effect on UGT.

Although QT prolongation has not been observed in the studies with ACH-0144471 conducted to date a conservative approach is being taken for drugs that are known to prolong the QT interval since a thorough QT/QTc study has not yet been completed. The use of drugs that are known to prolong the QT interval will be considered in the context of available information.

Use of specific concomitant medications will be considered on a case-by-case basis, with decisions made jointly between the PI and Sponsor, based on available and emerging knowledge of ACH-0144471 as well as the characteristics of the potential concomitant medication. Details of all concomitant medication use, including all medications administered for the treatment of AEs, must be recorded in the participant's case report form (CRF).
The following are some general guidelines for concomitant medication use based on currently available data:

- Concomitant administration of cyclosporine and tacrolimus are not allowed and must be stopped at least two weeks prior to study drug administration.
- Concomitant administration of corticosteroids is permitted if on stable doses for at least 4 weeks prior to the first screening visit. Doses should be maintained at the same dose throughout the study, whenever possible, unless the PI deems it necessary to do otherwise.
- Concomitant administration of mycophenolate mofetil (MMF) is allowed if on stable doses for at least 2 weeks prior to the first screening visit. Doses should be maintained at the same dose throughout the study, whenever possible, and unless the PI deems it necessary to do otherwise.
- Concomitant administration of warfarin or low molecular weight heparin is permitted with prior approval.
- Oral, injectable, implantable, transdermal, or intravaginal hormonal therapies are allowed for either contraception or hormonal replacement therapy.
- Concomitant administration of anti-proteinuric medications (e.g., ACE inhibitors or ARBs) or anti-hypertensive medications is permitted if on stable doses for at least 4 weeks prior to the first screening visit. Doses should be maintained at the same dose throughout the study, whenever possible, unless the PI deems it necessary to do otherwise.
- If it is necessary to treat a fever (see Appendix 2), or any minor ailment occurring while on study, ibuprofen (maximum 400 mg/day and up to 1200 mg/week) and/or acetaminophen (maximum 1000 mg/day) are permitted without prior approval.
- Concomitant administration of drugs with the potential to cause QTc prolongation will be evaluated on a case-by-case basis by the medical monitor.
- Antibiotic prophylaxis is allowed if deemed appropriate by local clinical practice and/or guidelines for treatment with a complement inhibitor.

No new therapy for C3G/IC-MPGN should be added during the study unless the participant's condition deteriorates to the extent that the PI deems it in the best interest of the participant to do so. In addition, doses of medications for C3G (e.g., immunosuppressive agents, ACE inhibitors, etc.) should be maintained at the same dose throughout the study whenever possible, and unless the PI deems it necessary to do otherwise.

5.5.2. Fluid and Food Intake

Participants should be instructed to take each dose of ACH-0144471 with food. As described in Section 5.2.3, ACH-0144471 should be taken three times daily, approximately 8 hours apart. An appropriate schedule would be to take the three daily doses within 15 to 30 minutes of finishing breakfast, dinner, and a bedtime snack.

Water or other non-alcoholic fluid intake is not restricted.

5.5.3. Participant Activity and Other Restrictions

Participants should refrain from heavy exercise 24 hours prior to and after having blood drawn for safety laboratory evaluations. Walking and light exercise are acceptable.

5.5.4. Contraception

5.5.4.1. Contraception for Male Participants

All non-sterile male participants must use highly effective or acceptable contraception with their partner(s) of childbearing potential from the first day of dosing (Day 1) through 90 days after their last dose of study drug.

Sterile is defined as having bilateral orchiectomy.

Highly effective contraception for males is defined as any of the following:

- Vasectomy with confirmed medical assessment of surgical success
- Condom plus use of one of the following by partner(s) of child-bearing potential:
  - Oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
  - Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation
  - Intrauterine device (IUD) or Intrauterine hormone-releasing system (IUS)
  - Bilateral tubal occlusion (including bilateral tubal ligation)
- Sexual abstinence, defined as refraining from heterosexual intercourse during the entire period from the first day of dosing (Day 1) through 90 days after their last dose of study drug. Periodic abstinence (e.g., calendar, symptothermal, post-ovulation methods) is not an acceptable method of contraception. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. If a participant is usually not sexually active but becomes active, they, with their partner(s), must comply with the contraceptive requirements described in this section.

Acceptable contraception for males or female partner of childbearing potential is defined as any of the following:

- Progestin-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide
- Cap, diaphragm, or sponge with spermicide
- Combinations of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)

Male participants must agree to refrain from sperm donation from the date of screening until 90 days after their last dose of study drug.

5.5.4.2. Contraception for Female Participants

Female participants of child-bearing potential and/or their male partners must use a highly effective or acceptable method of contraception from the date of signing the informed consent to the first day of dosing (Day 1) through 30 days after their last dose of study drug. Highly effective contraception for females is defined as any of the following:

- Oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
- Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation
- Intrauterine device (IUD) or Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion (including bilateral tubal ligation)
- Vasectomised partner(s) with confirmed medical assessment of surgical success
- Sterile partner(s) (bi-lateral orchiectomy)
- Sexual abstinence, defined as refraining from heterosexual intercourse during the entire period from the first day of dosing (Day 1) through 30 days after their last dose of study drug. Periodic abstinence (e.g., calendar, symptothermal, post-ovulation methods) is not an acceptable method of contraception. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. If a participant is usually not sexually active but becomes active, they, with their partner(s), must comply with the contraceptive requirements described in this section.

Acceptable contraception for females is defined as any of the following:

- Progestin-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide
- Cap, diaphragm or sponge with spermicide
- Combinations of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)

Female participants of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline in order to enter the study, and must have urine pregnancy tests throughout the study at the intervals defined in the Schedule of Assessments (Appendix 1).

Female participants of non-childbearing potential, as defined by one of the following, need not employ a method of contraception:

- Surgical sterilization by hysterectomy, bilateral salpingectomy, or bilateral oophorectomy

- Postmenopausal with amenorrhea for at least 1 year prior to dosing and FSH serum levels consistent with postmenopausal status

5.6. Treatment Compliance

Treatment compliance assessments shall be performed at each visit. Participants will be required to bring their supply of study drug to each visit so that study site personnel may perform drug accountability. Site personnel will keep a record of all drug dispensed and returned at each visit. Drug dispensing records will be updated at each visit.

Participants will be asked to confirm they take each daily dose of study drug and may receive automated reminders (e.g., via SMS text or phone call) in an effort to ensure compliance. The site will receive notification of any non-response or non-compliance to follow up and address with the participant directly.

5.7. Packaging and Labeling

Labels for ACH-0144471 tablets will include, at a minimum, the following information:

- Clinical Study Number
- Sponsor Name and Address
- Product Name and Strength
- Dosage Form and Route of Administration
- Direction for Use
- Contents (Number of Tablets)
- Lot Number (or Code)
- Storage Instructions
- Caution statement to keep out of the reach of children
- Caution Statements such as “For Clinical Trial Use Only” or “Caution: New Drug—Limited by Federal (or United States) law to investigation use” or similar statements

5.8. Storage and Accountability

At the pharmacy, the ACH-0144471 tablets must be stored as provided at controlled room temperature (20°C to 25°C), with allowed excursion of 15°C to 30°C. Participants should be instructed to keep their study medications in the original container at room temperature.

Participants will be required to bring back their study drug at each clinic visit so that study site personnel may perform drug accountability.

The PI or designee (e.g., pharmacist) is responsible for ensuring storage as per the label on the drug product at the site and adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study drug (quantity and condition) and participant dispensing records and returned or destroyed drug. Dispensing records will document quantities received from Achillion Pharmaceuticals (or designee) and quantities

dispensed to participants, including lot number, date dispensed, participant identifier number, participant initials, and the initials of the person dispensing the medication. All drug supplies and associated documentation will be periodically reviewed and verified by the Study Monitor over the course of the study.

5.9. Investigational Product Retention at Study Site

At study initiation, the Study Monitor will evaluate the site's Standard Operating Procedure for study drug disposal/destruction in order to ensure that it complies with Achillion Pharmaceuticals requirements. Drug may be returned to the Sponsor (or designee) or destroyed on an ongoing basis during the study, if appropriate, after drug accountability has been verified by the Study Monitor. At the end of the study, following final drug inventory reconciliation by the Study Monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet Achillion Pharmaceuticals requirements for disposal, arrangements will be made between the site and Achillion Pharmaceuticals or its representative, for destruction or return of unused study drug supplies.

6. STUDY PROCEDURES

The required study procedures are detailed in this section. The timeline for these procedures may be found in Appendix 1.

6.1. Informed Consent or Assent

The PI or designee is responsible for administering and obtaining freely given consent, in writing, before the participant enters into the study and any study-related procedures are performed. Each adult participant will sign an Ethics Committee (EC) or Institutional Review Board (IRB)-approved written informed consent form (ICF). This may include additional consent forms for HIV testing or other procedures which may be performed prior to participants being accepted into the study. Each participant 17 years of age or less will sign an EC or IRB-approved written assent form, and their parent(s) or guardian(s) will sign an EC or IRB-approved written informed consent form (ICF).

6.2. Medical History

At Screening, the PI or designee will interview each participant and obtain a complete medical and medication history to determine whether the participant meets the eligibility criteria. The history should include the specific type of C3 glomerulopathy (for participants with C3G), date of initial C3G or IC-MPGN diagnosis, family history of renal disease, all surgeries and past medical procedures, all past significant illnesses or current chronic conditions, all medication use currently and within the past 90 days (including over the counter medications, and use of herbal and nutrient supplements), any prior use of alcohol, illicit drugs and/or controlled substances, and any other relevant information. Other relevant information should include any extrarenal manifestations of C3G or IC-MPGN, including ophthalmic manifestations such as drusen. If any ophthalmic exams are performed (including any exams performed for reasons unrelated to the conduct of this study), then every effort will be made to include an anonymized copy of the exam results in the participants' source documents. The history should also include the results of any genetic testing related to the disease, and a full vaccination history. The medical history must be recorded in the participant's source documents and in the participant's CRF.

6.3. Percutaneous Renal Biopsy

Percutaneous renal biopsies should be performed according to local practices for this procedure, including appropriate pre-biopsy evaluation, biopsy technique, choice of imaging technique (e.g., ultrasound-guided, CT-guided, or other), anesthesia, and post-biopsy care. Biopsies will not be obtained from participants less than 18 years of age (unless they are determined to be clinically indicated by the treating provider), or from participants for whom a biopsy is contraindicated. All biopsies will be reviewed by the designated central pathology laboratory, and will be evaluated by light microscopy, electron microscopy, and immunofluorescence.

Details on the processing of the biopsy sample and discussion of the final renal pathology assessment and scoring for this study will be provided in the Pathology Manual, and the method for analyzing the pathology data will be provided in the Statistical Analysis Plan. However, the approach will be similar to that described for lupus in that it will assess features that indicate active glomerular inflammation, and those that indicate chronic fibrotic irreversible injury. Each

of these will be quantitated and may be combined into a composite scoring system. If a composite scoring system is not used, the score of each feature at baseline and post-treatment can be compared.

If, for any reason, any additional renal biopsies are performed (e.g., for a clinical indication), then every effort will be made to make these biopsy samples and results available to the central pathology laboratory for evaluation.

6.3.1. Renal Biopsy Assessment

Participants must have biopsy-confirmed primary C3G or IC-MPGN. This can be a historical biopsy. If no historical biopsy is available, a renal biopsy should be performed during the screening period, and the results must be available and reviewed before the first dose of ACH-0144471.

Participants who choose to participate in the sub-study should have a renal biopsy before the first dose of ACH-0144471 to establish a baseline histology score. Only one biopsy will be obtained prior to dosing; if a biopsy is required to confirm the diagnosis of C3G or IC-MPGN. It will be considered the pre-treatment biopsy for the sub-study. If a pre-treatment biopsy is required for a participant who completed study ACH471-201, the biopsy should be at least 30 days after the last dose of ACH-0144471 in that study. If a participant has had a recent renal biopsy it may not be clinically reasonable to repeat the procedure, and in this situation, a biopsy collected within approximately 6 months of the first dose of ACH-0144471 may be accepted in lieu of a biopsy during screening if it meets the requirements for analysis, and with written sponsor approval prior to study enrolment.

For all subjects, biopsy should be obtained approximately 12 months of treatment, as described in the Schedule of Assessments (Appendix 1), to allow evaluation of changes in renal pathology.

A sub-study is being conducted to evaluate the effects of ACH-0144471 on renal pathology; participation in this sub-study is not required. A separate informed consent will be required for participation.

Participants who choose to participate in the sub-study should have a renal biopsy at Week 28 and 104 as detailed on the Schedule of Assessments. The biopsy at the end of the treatment period should be performed during the last 2 weeks of study drug treatment.

6.4. Vaccination

Information regarding the risk of infection can be found in Section 6.5.1 of the Investigator's Brochure [1].

As discussed in Section 6.2, a full vaccination history will be gathered. Based on the vaccination history, the need for vaccinations against *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* in this study will be evaluated. Participants who do not have a sufficient history for some or all of these vaccines should receive vaccinations as recommended in the ACIP guidelines at least 2 weeks before the start of dosing with ACH-0144471, unless otherwise recommended by national and/or local guidelines or local clinical practice. If local and/or national guidelines do not exist or do not fully address vaccination against these organisms, investigators should

consider consulting the ACIP guidelines (available at https://www.cdc.gov/vaccines/acip/index.html).

Full identifying information for any vaccines given as part of this study, including the brand, should be recorded in the participant's CRF. Laboratory samples will be collected at the times indicated in the Schedule of Assessments (Appendix 1) for possible evaluation of participant response to the vaccines.

6.5. Prophylactic Antibiotics

As described in Section 6.4, Achillion expects that participants will be vaccinated according to ACIP guidelines at least 2 weeks prior to dosing with ACH-0144471, and believes that this will provide sufficient protection against these organisms. However, this is a global study and Achillion recognizes that some vaccines may not be available in all countries, and that guidelines and clinical practices differ by region and may include the use of prophylactic antibiotics in some instances. Antibiotic prophylaxis is therefore allowed if deemed appropriate by the PI or local clinical practice and/or guidelines for treatment with a complement inhibitor.

Full identifying information for any antibiotics given as part of this study, including the brand, dosage, and times of administration should be recorded in the participant's CRF.

6.6. Urine Collection

6.6.1. 24-Hour Urine Collection

Collection of urine over 24 hours will occur according to the schedule of assessments (Appendix 1). Urine collected will be assayed as described in Table 2 for total protein concentration, albumin, creatinine, albumin:creatinine ratio, total protein: creatinine ratio, and total volume. Complement components may also be assessed using urine, as described in Section 6.13.1.

The 24-hour urine during the screening period must be collected at least 30 days after the last dose of ACH-0144471 in study ACH471-201. If the 24-hour urine collection period is to occur after a renal biopsy, it must be at least 7 days after the biopsy procedure. If clinic visits are not possible during the COVID-19 global pandemic, urine samples may be collected during home healthcare visits or delivered to a local laboratory.

Specific instructions for urine collection, processing, and shipping will be provided in a separate laboratory manual.

6.6.2. First Morning Urine Collection

Collection of urine will occur according to the schedule of assessments (Appendix 1). Urine collected will be assayed as described in Table 2; in addition to standard urinalysis, urine collected will be assayed for total protein concentration, albumin, creatinine, and the protein: creatinine and albumin:creatinine ratios. Complement components may also be assessed, as described in Section 6.13.1.

Participants will be given a collection container to collect their first morning void. Specific instructions for urine collection, processing, and shipping will be provided in a separate

laboratory manual. If the first morning urine collection coincides with a renal biopsy, collection must be completed before or at least 7 days after the biopsy procedure. If clinic visits are not possible during the COVID-19 global pandemic, urine samples may be collected during home healthcare visits or delivered to a local laboratory.

6.7. Physical Examination

A complete physical examination will be conducted by the PI (or designee) at the times specified in the Schedule of Assessments (Appendix 1). This will include an examination of all major body/organ systems (including skin, head, eyes, ears, nose, throat, neck, thyroid, lungs, heart, abdomen, lymph nodes, and extremities), height, weight and calculation for BMI. Measurements of height and weight should be taken with the participants in light clothing or underwear and without shoes. Assessment of edema is part of the complete physical exam. If edema is present, then assessment of edema should be performed at each subsequent visit, even when a physical exam is not required.

Brief physical examinations, to include general appearance and examination of cardiovascular and respiratory systems, abdomen, extremities, and skin will be performed by the PI (or designee) at the times specified in the Schedule of Assessments (Appendix 1). Assessment of edema is part of the brief physical exam. If edema is present, then assessment of edema should be performed at each subsequent visit, even when a physical exam is not required. Additional complete, brief or targeted physical exams (e.g., targeted to any new signs or symptoms) may be performed at any time at the discretion of the Investigator or designee, for example to evaluate an AE. All clinically significant physical examination findings that are new or worsened since the last physical examination must be recorded in the participant's source documents and in the participant's CRF as an adverse event.

6.8. Vital Signs

The PI or designee will obtain blood pressure (BP), heart rate (HR), and respiration rate (RR) at the visits indicated in the Schedule of Assessments (Appendix 1). Vital signs will be measured in the supine position following a 5-minute rest. All blood pressure measurements should be taken on the same arm throughout the study. Vital signs may be measured using an automated vital signs monitor, although manual measurements of blood pressure are preferred. All vital sign measurements must be done using a calibrated instrument. For each participant, the same method of measurement should be used at all visits. All vital sign values, including whether measured manually or via an automated monitor, will be recorded in the participant's source documents and in the participant's CRF.

6.9. Body Temperature

The PI or designee will obtain body temperature using an oral thermometer at the visits indicated in the Schedule of Assessments (Appendix 1). Prior to discharge from the clinic on Day 1, the participant will:

1. Be educated and counseled by site staff regarding the potential for serious, rapidly progressive bacterial infections which may be life threatening and therefore understand the need to identify fever rapidly and seek emergency medical evaluation without delay

2. Be educated and counseled by site staff regarding high risk behaviors, which include drinking from the same beverage containers, sharing eating utensils with others, avoiding large crowds, and smoking (including second-hand exposure)
3. Be provided a thermometer and taught how to use it. All participants need to take these thermometers with them at all times. They need to be able to take their temperature if feeling warm or unwell
4. Be instructed to contact the investigator immediately and/or seek emergency medical attention for any temperature >38.0°C /100.4°F
5. Be advised not to wait for site staff to return their phone call before seeking emergency medical attention, but should go to the nearest emergency or urgent care medical facility for evaluation.
6. Be taught to be alert to the signs of possible serious infections, which are often flu-like symptoms
7. At all times, have immediate access to transportation, telephone, and emergency medical care
8. Be provided with a study contact card and instructed to carry this with them at all times. The study contact card should be provided to the emergency medical personnel who should be asked to contact the study site

All abnormal body temperature measurements must be recorded or stored in the participant's source documents and CRF. Any clinically significant finding must be reported as an adverse event. Any temperature measurement ≥38.0°C, measured either at the clinic or by the participant outside the clinic, requires action as outlined in the Fever Management Plan (Appendix 2).

6.10. Electrocardiography

The PI or designee will obtain ECG measurements at the screening visit only. The ECG recordings should be 12-lead, and should be performed after the participant has rested quietly for at least 5 minutes in a supine position prior to dosing and before blood is drawn (whenever possible). The following parameters and intervals will be assessed: HR, RR, PR, QRS, QT, and QTcF. The occurrence of depolarization or repolarization disorders, arrhythmic disorders or other abnormalities will be noted. A designation of clinical significance shall also be noted.

In some cases, it may be appropriate to repeat an abnormal ECG to rule out improper lead placement as contributing to the ECG abnormality. It is important that the leads are placed in approximately the same positions each time in order to achieve precise ECG recordings.

All ECGs must be read by the PI or designee. The PI/designee needs to evaluate the finding of ECG abnormalities promptly (refer to Section 6.19.1 for a discussion of the circumstances under which ECG findings are to be reported as AEs).

All ECG parameters and assessments must be recorded or stored in the participant's source documents and in the participant's CRF. Any clinically significant finding must be reported as an adverse event.

6.11. Clinical Laboratory Tests

Blood and urine samples will be collected for safety and PD laboratory evaluation as listed in Table 2, at the times in Appendix 1. Participants will be in a seated or supine position during the blood collection. Specific instructions for sample collection, processing, and shipping will be provided in a separate laboratory manual.

In addition to the calculation of eGFR, some investigators may choose to measure GFR based on iohexol clearance. Measurement of GFR is at the discretion of the investigator, but if performed, these measurements should be taken, at a minimum, at baseline and at Weeks 28 and 52, to align with the collection of 24-hour urine samples (or at the end of treatment, if a participant terminates early). Additional measurements may also be done at the discretion of the investigator.

Table 2. Clinical Laboratory Tests

Hematology	Chemistry	Urinalysis	Additional Tests at Screening Only	Other Assessments

Complete blood count (CBC), including:
- Red blood cell (RBC) count
- White blood cell (WBC) count
- WBC differential (absolute and percent):
  - neutrophils
  - lymphocytes
  - monocytes
  - eosinophils
  - basophils
- Hematocrit (Hct)
- Hemoglobin (Hgb)
- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Mean platelet volume (MPV)
- Platelet count
- Red cell distribution width (RDW)
- Reticulocyte count
	Alanine aminotransferase (ALT)
	Albumin
	Alkaline phosphatase
	Aspartate aminotransferase (AST)
	Bicarbonate (HCO_3)
	Bilirubin (fractionated)[1]
	Blood urea nitrogen (BUN)
	Calcium
	Calculated eGFR[2]
	Chloride
	C-reactive protein (CRP)
	Creatine kinase[3]
	Creatinine
	Cystatin C
	Gamma-glutamyl transferase (GGT)
	Glucose[4]
	GFR (iohexol clearance)[5]
	Lipid Profile including:
	- Cholesterol/HDL ratio
	- High-density lipoprotein cholesterol (HDL-C)
	- Low-density lipoprotein cholesterol (LDL-C)
	- Non-HDL-C
	- Total cholesterol
	- Triglycerides
	- Very low-density lipoprotein cholesterol (VLDL-C)
	Phosphate
	Potassium
	Sodium
	Total protein
	Uric acid
		Dipstick Analysis including:
		- Bilirubin
		- Color
		- Glucose
		- Ketones
		- Leukocytes
		- Nitrite
		- Occult blood
		- pH
		- Protein
		- Specific gravity
		- Urobilinogen
		Microscopic examination of sediment[6]
		Spot Urine sample, including[7]:
		- Total protein
		- Albumin
		- Creatinine
		- Albumin: creatinine ratio
		- Total protein: creatinine ratio
		- Complement components
		24-Hour Urine collection sample, including:
		- Total protein
		- Albumin
		- Creatinine
		- Albumin: creatinine ratio
		- Total protein:
			HCV Ab[8]
			HbsAg
			HIV Ab
			FSH[9]
			Serum Pregnancy test[10]
			Urine drug screen[11]
			Sample for potential genetic biomarker testing (white blood cells)
				Complement Biomarkers:
				- AP Wieslab
				- AP Hemolysis
				- Ba
				- Bb
				- C3
				- C4
				- CP activity
				- fB
				- fD
				- sC5b-9
				PT/PTT/INR
				Urine pregnancy test
				Samples for assessment of participant response to vaccines

		creatinine ratio - Total volume - Complement components		

Check the Schedule of Assessments (Appendix 1) for specific times when these tests should be done.

1. Fractionate and obtain measurements of direct and indirect bilirubin for all participants.
2. Provide eGFR based on CKD-EPI creatinine equation (2009) for participants ≥19 years of age, and based on the "Bedside Schwartz" equation (2009) for participants <19 years of age.
3. Perform at screening and Day 1, and then subsequently only as a reflex if AST > ULN.
4. If glucose is > ULN, reflexively test HbA1c
5. Optional, at the discretion of the investigator.
6. Only if occult blood, protein, or leukocytes present on dipstick analysis.
7. The spot urine sample should be a first-morning void.
8. If positive, HCV RNA levels should be measured. Participants with detectable HCV RNA will be excluded.
9. FSH for postmenopausal women at screening only. May be omitted if postmenopausal status confirmed in ACH471-201.
10. Serum pregnancy test at Screening Visit 1 and urine pregnancy tests at other times as per the schedule in Appendix 1 for women of childbearing potential only. Any positive urine pregnancy test will be confirmed by a serum pregnancy test.
11. Urine drug screen will be measured at Screening Visit 1. For all participants, the urine drug test should include, at a minimum, cotinine, amphetamines, barbiturates, cocaine metabolites, opiates, benzodiazepines, and cannabinoids.

6.12. Pregnancy Testing

All females of childbearing potential (as determined at screening) will have a serum pregnancy test during screening, and urine pregnancy tests for the duration of the study including follow-up, as indicated in Appendix 1. On Day 1, the urine pregnancy test must be done before dosing and be negative to begin dosing.

Female participants of childbearing potential who require vaccinations (see Section 6.4) must also have a negative urine pregnancy test before any vaccine or booster is administered.

Any positive urine pregnancy test will be confirmed by a serum pregnancy test.

6.13. Sample Collection, Storage, and Shipping

6.13.1. Blood and Urine Collection for Complement Assays

Serum/plasma samples will be collected at the time points indicated in Appendix 1. It is important that samples for PD testing be collected, prepared, and shipped in a way that ensures minimum freeze-thaw cycles and avoids potential in vitro complement activation before testing. Whole blood will be collected and processed to obtain cell-free serum or plasma which will be aliquotted into cryovials, frozen on dry ice, stored in a -80°C freezer and shipped frozen to the designated laboratories for testing.

Urine samples will be collected according to the schedule in Appendix 1 and stored for potential assessment of the concentrations of selected complement proteins in urine.

Specific instructions for sample collection, processing, and shipping will be provided in a separate laboratory manual.

Biological samples, such as serum, plasma and urine, may be kept for up to 3 years after completion of the Clinical Study Report and then will be destroyed by internationally accepted means (e.g., incineration).

6.13.2. Blood Collection for Genetic Complement-Associated Biomarker Testing

Subject to participant consent, a sample will also be collected at screening for potential genetic analysis. Genetic analyses may be conducted if a participant does not respond to the investigative drug, to better understand a potential drug-related toxicity, or to further characterize the underlying disease. Genes which may be sequenced include (but are not limited to):

- Complement component C3
- Complement factor H-related proteins (CFHR1, CFHR3, CFHR4, CFHR5)
- Complement factor B
- Complement factor D
- Complement factor H
- Complement factor I
- Membrane Co-Factor Protein (MCP/CD46)
- Thrombomodulin (THBD)

All genetic samples will be stored for a maximum of 3 years after completion of the Clinical Study Report. During that time, samples may be retested if other mutations are discovered that may be associated with C3G. Participants may withdraw their consent for genetic testing and withdraw their samples from further genetic testing at any time by notifying the study investigator verbally and in writing. After the 3-year storage period defined above, or once the sponsor is informed of withdrawal of consent for further analysis, the sample will be destroyed consistent with accepted laboratory standards and no further testing or analysis will be completed. Any data already generated from the sample may continue to be used for the purposes of this study and future research.

6.13.3. PK Plasma Samples

For samples collected for pharmacokinetic analysis, whole blood (2 mL) will be collected into 3 mL vacutainers containing K_2EDTA. The vacutainers should be gently inverted 5 to 8 times to thoroughly mix the preservative with the blood and kept chilled in an ice bath. The tubes should be centrifuged at 4°C for 15 minutes at 1300 g within 30 minutes of blood collection. Approximately 400 µL of plasma shall be pipetted into each of 2 pre-labeled cryovials (a primary and back-up sample) and stored at -80°C within one hour of having collected the blood. The primary PK samples will be shipped to the bioanalytical laboratory at pre-determined intervals, while the backup sample will remain at the clinic. Information on when and where to ship samples will be provided separately.

6.13.4. Blood Volumes

Approximate blood volumes to be drawn are detailed in Table 3 below. The total planned blood volume to be collected per individual is approximately 559 mL. This does not include discarded blood from pre-collection used to flush catheters. The discarded volume is not expected to exceed 40 mL. Unanticipated additional blood may be collected throughout the study for such things as safety monitoring and additional PK or PD assessments, if necessary, and if there are blood samples collected during any unscheduled visits.

Table 3. Approximate Total Blood Volumes

	Volume (mL)				
Period	**Screening**	**Treatment (Weeks 1 to 54)**	**Long Term Follow-up (Weeks 55 to 169)**	**Taper & Follow-up**	**Total Volume**
Totals	**34**	**269**	**176**	**80**	**559**

The maximum volume drawn in an 8-week window is 115 mL, from Day 1 to Week 8 (Day 56), inclusive. The maximum volume drawn in a 24-hour period is 35 mL, on Week 12.

6.14. Dispensing Study Drug

ACH-0144471 will be supplied as 50 and 100 mg tablets. At each visit, the site will dispense study drug as required to provide participants with sufficient study drug for dosing until their next clinic visit. If a clinic visit is not possible during the COVID-19 pandemic, study drug will be sent directly to participant's home (Section 6.24).

6.15. Safety Assessments

Safety will be evaluated by monitoring and assessment of AEs, clinical laboratory tests, physical examination findings, and vital signs measurements at Screening, Baseline, and at various time points during the study as described in Section 7 and the Schedule of Assessments (Appendix 1).

6.16. Pharmacokinetic Assessments

Single trough PK samples will be taken at the times indicated in the Schedule of Assessments (Appendix 1).

Concentrations of ACH-0144471 in plasma or serum will be measured using a validated bioanalytical method. Actual sampling times will be checked for major aberrations. Actual sampling times will be used in the PK analysis for that participant and study day.

6.17. Pharmacodynamic Assessments

PD markers monitor biological effects and are used in early drug development to assist in future decision making. Pharmacodynamics will be evaluated using serum, plasma, and urine collected during the study. Additional information on sample collection and shipping instructions will be provided in a separate laboratory manual.

Pharmacodynamics will be evaluated by assessment of Bb levels in plasma samples collected during the study, which should provide a direct readout of AP inhibition in vivo. In addition, the

CP activity assay is a functional assay to qualitatively evaluate the effect of ACH-0144471 on total CP activity.

Inhibition of AP activity will also be evaluated with the AP Wieslab ELISA assay, AP hemolysis, and C3 convertase activity, the presence of autoantibodies to complement components or regulators, and the concentrations of selected complement components and their split and terminal products in serum, plasma, and/or urine may be explored to understand their association with the underlying disease and any changes in response to ACH-0144471 treatment.

White blood cells will be collected and stored for possible genetic profiling of selected complement components and regulators (see Section 6.13.2) for possible exploration of the understanding of the underlining etiology of C3G and any correlation with participants' response to ACH-0144471.

6.18. Patient-Reported Outcomes Assessments

6.18.1. Quality of Life Questionnaires

All adult participants enrolled in the trial will self-administer questionnaires for the FACIT-Fatigue (version 4), KDQOL version 1.3, and EQ-5D-3L scales, and all adolescent participants enrolled in the trial will self-administer questionnaires for the Peds-FACIT-F and EQ-5D-Y scales at the times specified in Appendix 1 to assess their HRQOL, fatigue, and kidney-related fears and worries (e.g. kidney failure, dialysis, kidney transplant), and to determine health states value, over the course of treatment with ACH-0144471. Local language versions of each of the tools will be provided separately.

6.19. Adverse Events Assessments

6.19.1. Definitions

Adverse events (AEs) must be assessed for the investigational product(s) in this study. An investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in the study, whether blinded or unblinded. The term "adverse event" is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

Medical occurrences, including pregnancies, that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section. This does not include pre- or post-treatment complications that occur as a result of protocol-mandated procedures (e.g., invasive procedures, such as venipuncture or biopsy), which should be reported as AEs. While pregnancy itself is not considered an AE, for the purposes of tracking, a pregnancy occurring after the start of study intervention should be captured as an AE as well as reported on the pregnancy forms.

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during treatment, having been absent prior to treatment, or worsens relative to the pretreatment state. In this study, any AE first assessed after receipt of the first dose of ACH-0144471 until 28 days after the last

dose of study drug will be considered treatment-emergent, as defined in Section 6.19.5. All TEAEs will be recorded and reported.

An AE (including a TEAE) can be one or more of the following:

- Any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug and does not imply any judgment about causality.
- Any new disease or exacerbation of an existing disease.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.
- Any case of abuse of alcohol, illicit drugs, or prescription drugs; abuse of study drug(s) or protocol-specified drug(s); addiction.
- A pregnancy that occurs or becomes confirmed during a clinical study (see Section 6.19.8).
- Laboratory test or other clinical test (e.g., ECG or X-ray) with a clinically significant abnormality (as defined below).
- An effect of the study medication, including comparator.
- Any dose of medication (study drug or other concomitant medication) that is taken at a dose higher than the prescribed dose (i.e., an overdose). Overdose should be reported as an AE whether or not it is associated with any symptoms or signs.

The following are not considered to be AEs:

- Medical or surgical procedures (e.g., surgery, endoscopies, tooth extraction, transfusion, etc.) - the condition which leads to the procedure is the AE;
- Preexisting diseases or conditions or laboratory abnormalities present or detected prior to the screening evaluation that do not worsen;
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions, etc.)

Clinically significant changes in objective findings (e.g., laboratory, ECG, physical examination) should be considered AEs only if they meet one or more of the following criteria:

- Associated with accompanying symptoms;
- Require medical/surgical intervention;
- Lead to a change in study drug dosing or discontinuation from the study;
- Lead to significant additional concomitant drug treatment, or other therapy;
- Lead to any of the outcomes included in the definition of a serious adverse event;
- Are considered clinically significant by the investigator.

Whenever possible, the etiology of the abnormal finding (rather than the abnormal finding itself) should be documented as the adverse event. Repeated additional tests and/or other evaluations

required to establish the significance and etiology of an abnormal result should be obtained when clinically indicated.

Any abnormal test result that is determined to be an error does not require reporting as an AE.

Surgical procedures themselves are not AEs but are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an adverse event, if it occurs or is detected during the study period. Planned surgical measures permitted by the clinical study protocol (if any) and the condition(s) leading to these measures are not AEs, if the condition(s) was (were) known before the start of the study treatment and documented in the participant's medical record. In the latter case, the condition should be reported as medical history.

All participants who have AEs, whether considered to be associated with the use of the investigational product or not, must be monitored to determine the outcome of the event(s). The clinical course of the AE will be followed according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found, or the investigator considers it medically justifiable to terminate follow-up.

6.19.2. Criteria for Assessing Seriousness

All AEs must be evaluated as potential SAEs. If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met. An SAE is any untoward medical occurrence that occurs at any dose and meets at least one of the following criteria:

- Results in death
- Is life-threatening i.e., the participant was at immediate risk of death from the AE as it occurred. (This does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death.)
- Requires inpatient hospitalization or prolongation of existing hospitalization for the AE
  - The following types of hospitalizations are not considered SAEs for regulatory reporting purposes:
    - Hospitalization(s) for planned (pre-scheduled) medical procedures known at the time of screening
    - Protocol-specific hospital admission
    - Respite care
    - Admission for the treatment of pre-existing condition (known at the time of screening) not associated with the development of a new AE or with the worsening of the pre-existing condition
    - Observation/same day/ambulatory procedure
- Is a persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect (in the child of a participant who was exposed to the study drug)

- Is an important medical event or reaction

6.19.3. Documentation and Reporting of Adverse Events

AEs, including TEAEs, may be spontaneously reported by a participant or his/her representative, or elicited during questioning and examination of a participant. All AEs will be assessed by the Investigator and documented regardless of apparent causality from use of the study treatment(s). For each AE, the investigator will evaluate and report the date of onset and resolution, outcome, severity, relationship to study treatment(s), action taken, additional treatments required to manage the event, and determination of seriousness. All identified AEs occurring during the trial and follow-up period must be fully recorded and described on the appropriate CRF page. The AE should be reported in standard medical terminology. Whenever possible, the AE should be evaluated and reported as a diagnosis, rather than as individual signs or symptoms. A cluster of signs and symptoms that results from a single cause should be reported as a single AE (e.g., fever, elevated WBC, cough, abnormal chest X-ray, etc. can all be reported as "pneumonia").

If a definitive diagnosis is not possible, the individual symptoms and signs should be recorded. Documentation must be supported by an entry in the participant's medical record. The relationship to study drug or study procedures should be assessed using the definitions in Section 6.19.7.

6.19.4. Treatment and Follow-Up of Adverse Events

All AEs should be followed up (including obtaining relevant laboratory tests) until they have returned to baseline status or stabilized. If a clear explanation is established, it should be recorded. Follow-up of AEs will continue through the last day on study (including the follow-up period) or until the events have resolved or stabilized to the satisfaction of the PI and the Achillion Pharmaceuticals Medical Monitor (or designee). Achillion Pharmaceuticals may request that certain AEs be followed until resolution or stabilization.

6.19.5. Timeframe for Collection of Adverse Events

AEs include events that have appeared or worsened during the course of the clinical trial. AEs may also include pre- or post-treatment complications that occur as a result of protocol-mandated procedures (e.g., invasive procedures, such as venipuncture, biopsy, etc.).

Any AE (i.e., a new event or an exacerbation of a preexisting condition) with an onset date after the participant provides informed consent through the 28 days following the participant's last study drug dose will be recorded as an AE on the appropriate CRF page(s).

All SAEs, regardless of cause or relationship, occurring within 28 days of last study drug dose must be documented and reported.

Follow-up of SAEs will continue through the last day on study or until the event has resolved or stabilized to the satisfaction of the PI and the Achillion Pharmaceuticals Medical Monitor (or designee). Investigators are not obligated to actively seek out SAEs beyond the follow-up period. However, if the PI (or designee) learns of an SAE occurring after completion of the final follow-up visit, and the SAE is deemed by the PI (or designee) to be related to the study drug (s),

the PI (or designee) should promptly document and report the event to Achillion Pharmaceuticals.

6.19.6. Severity and Grading of Adverse Events

The severity of an adverse event will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.03 [37]. The PI (or designee) should determine the severity of the AE based on the overall clinical importance or significance of the finding for that individual participant. If a lab abnormality is deemed to be clinically significant, according to the criteria described in Section 6.19.1, it should be reported as an AE and the AE grade reported should correspond to the grade of the lab abnormality on the CTCAE grading scale.

If an AE that was reported during the study increases or decreases 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, the AE will be kept open through to resolution.

6.19.7. Assessment of Causality

The investigator must assess the likelihood that the study drug caused or contributed to each AE, and document this assessment assigning one of the following relatedness criteria to each AE:

- **Unrelated:** In the opinion of the investigator, there is no association between the study drug and the AE.
- **Unlikely**: In the opinion of the investigator, it is unlikely that there is an association between the study drug and the reported event.
- **Possible**: In the opinion of the investigator, treatment with the study drug may have caused or contributed to the AE, but could also have been produced by other factors (i.e., the event follows a reasonable temporal sequence from the time of drug administration and/or follows a known response pattern to the study drug, but is also known to be caused by other factors).
- **Probable:** In the opinion of the investigator, it is likely that the study drug caused or contributed to the AE based on a reasonable temporal sequence of the event with drug administration and, the known pharmacologic action and/or adverse reactions of the drug (or class of drugs) or the investigator's clinical judgment.
- **Definite:** In the opinion of the investigator, it is definite that the study drug caused or contributed to an AE, and other conditions (e.g., concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not explain the event.

For the purposes of determining expedited reporting status to Health Authorities, Achillion considers the assessments of 'unrelated' and 'unlikely' as unrelated to study drug and 'possible', 'probable', and 'definite' as related to study drug.

In addition, for any analyses of AE data in which only two categories of 'related' and 'unrelated' are used, the assessments of 'unrelated' and 'unlikely' will be combined into the category of 'unrelated', and the assessments of 'possible' and 'probable' and 'definite' will be combined into the category of 'related'.

6.19.8. Pregnancy

Any pregnancy, including in a female partner of a male participant, that occurs or becomes confirmed during a clinical study (time frames outlined in Section 6.19.5) must be reported to Achillion (or designee) within one business day of first knowledge of the pregnancy. The report should be provided on the pregnancy form. While pregnancy itself is not considered an AE, for the purposes of tracking, it should be captured as an AE as well as reported on the pregnancy forms.

All pregnancies temporally related to study drug should be followed and discussed with the medical monitor as follows:

- The investigator will follow up with the participant or the participant's female partner approximately every 3 months throughout the pregnancy and report to Achillion (or designee) using the pregnancy forms. Generally, follow-up will not be required for longer than 6-8 weeks beyond the estimated delivery date.
- The investigator will report any information on the status of the pregnancy to Achillion (or designee) using the pregnancy forms.
- The outcome of the pregnancy will be reported to Achillion (or designee) using the pregnancy forms. Any termination of pregnancy will be reported, regardless of fetal status (i.e., presence or absence of anomalies) or indication for the procedure.

Any SAEs related to the pregnancy (see below), or occurring during the participant's pregnancy, or after delivery, must be documented and reported to Achillion (or designee) on both the SAE Form and the pregnancy forms. SAEs occurring in the child (e.g., congenital anomalies or other conditions present at birth, whether genetically inherited or occurring in utero) must also be documented on both the SAE form and the pregnancy forms.

Reportable SAEs associated with pregnancy include, but are not limited to:

- Pregnancy losses (e.g., spontaneous abortion, late fetal death, elective termination)
- Life-threatening developments (e.g., placental abruption, fetal distress)
- Congenital anomalies
- Neonatal or maternal death, or
- Any event resulting in maternal or neonatal hospitalization/prolonged hospitalization.

6.19.9. Reporting Serious Adverse Events

Achillion Pharmaceuticals has requirements for the expedited reporting of safety events meeting specific requirements to worldwide regulatory authorities; therefore, Achillion Pharmaceuticals must be notified immediately regarding the occurrence of any SAE and/or pregnancy that occurs during the study (time frames outlined in Section 6.19.5).

The procedures for reporting all SAEs and/or pregnancies, regardless of causal relationship, are as follows:

SAE

- Record the SAE within 24 hours of becoming aware of the event by
- Logging into the EDC system CCI and completing an initial SAE report.

This will trigger an email notification to the CCI Achillion Pharmaceuticals distribution

Pregnancy

- Record the pregnancy into the EDC system CCI form
- This will trigger an email notification to the CCI Achillion Pharmaceuticals distribution lists.

Contact information is provided below.

SAE CONTACT
SAE Telephone Number: In the event of System failure, or for questions about completing the forms in EDC: CCI PPD PPD

For fatal or life-threatening events, provide copies of hospital discharge reports, autopsy reports, and other documents, as applicable. Achillion Pharmaceuticals may request additional information from the PI to ensure the timely completion of accurate safety reports.

In the case of a medical emergency, please use the contact provided on the title page of the protocol.

6.19.10. Investigator Reporting Requirements for SAEs

Achillion is responsible for ensuring that Investigators and central ECs/IRBs are notified of all AEs that are serious, unexpected and considered related, probably related, or possibly related to the investigational product. A CRO may be designated to perform this notification. This notification will be in the form of a MedWatch/CIOMS report. The PI will notify the local ECs or IRBs as per EC or IRB requirements. Upon receiving such notices, the PI must review and retain the notice. The Sponsor, investigator, and EC or IRB will determine if the informed consent requires revision. The PI should also comply with EC or IRB procedures for reporting any other safety information.

6.20. Concomitant Medication Assessments

Details of all prior (within 90 days of the screening evaluation) and concomitant medication use, including all medications administered for the treatment of AEs as well as prior administration of ACH-0144471 in study ACH471-201, will be recorded in the participant's CRF at each study visit.

6.21. Monitoring Participant Safety

The safety of participants will be monitored by Investigators and by a medical monitor (or designee) at Achillion Pharmaceuticals on an ongoing basis while participants are receiving

ACH-0144471. Additionally, a Fever Management Plan (Appendix 2) has been developed for this study to enable rapid assessment, detection and treatment of any potential serious infection.

6.22. Removal of Participants from the Trial or Study Drug

A participant is free to withdraw from the study at any time without jeopardizing future medical care. The PI (or designee) may decide, for reasons of medical prudence or participant noncompliance, to discontinue dosing in a participant. The PI should also stop dosing in any participant who meets an individual stopping rule (Section 3.2.3.2). In either case, whenever possible, the Achillion MM should be notified immediately, and if possible, before dosing is terminated.

If dosing is to be terminated, it may be done so immediately, or a taper can be implemented as described in Section 5.2, whichever is considered to be in the best interest of the participant. When dosing is terminated, study participation is not necessarily immediately terminated. Instead, whenever possible, the participant should complete all activities in the Taper and Follow-Up periods (if tapered) or in the Follow-Up period (if discontinued immediately), as described in Appendix 1.

Reasons for participant withdrawal include (but are not limited to):

- One or more of the stopping criteria described in Section 3.2.3 is met
- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree
- Unacceptable toxicity (including a clinically significant laboratory abnormality) necessitating discontinuation of study or that, in the judgment of the investigator, compromises the ability to continue study-specific procedures, or it is considered not to be in the participant's best interest to continue the study
- Participant request to discontinue for any reason
- A female participant becomes pregnant or wishes to become pregnant
- Participant noncompliance
- Discontinuation of the study at the request of Achillion Pharmaceuticals, regulatory agency, or Ethics Committee or IRB
- Any other condition or circumstance that would jeopardize the welfare of the participant if s/he were to continue in the trial

The reason for any participant's discontinuation and the date of withdrawal will be recorded in the participant's CRF. The participant's CRF, which will be completed up to the point of withdrawal, will be retained for the Sponsor.

6.23. Study Assessments When Clinic Visits are Not Possible due to the COVID-19 Pandemic

If a study participant is unable to get to a clinic visit, study data collection may still occur:

Option 1 (preferred option)

- **Home Healthcare Visits**: At these home visits, nurses may collect 24-hour urine, first morning urine, and safety labs, including pregnancy testing, for shipment to the central laboratory. Serum/plasma biomarker laboratory assessments, and serum C3 and C4 assessments cannot be collected at home visits, due to the stringent storage and handling requirements of these specimens. Other assessments will include adverse events, vital signs, concomitant medications, and study drug accountability. Physical examinations, weights, and patient-reported outcomes will not be collected at home health visits.

Option 2 (if Option 1 is not possible)

- **Telephone visits**: If home visits are not possible, participants may have telephone visits with the PI or designee. Data collection should include adverse events and concomitant medications. Physical examinations cannot be performed during a telephone visit. Patients will be asked about study drug compliance.
    - **Local Laboratories**: If home visits are not possible, the participant should go to a local laboratory to drop off 24-hour urine collections, and for safety laboratory testing, including pregnancy testing (if applicable), to be performed.

6.24. Study Drug Compliance and Supply When Clinic Visits are Not Possible

If a study participant is unable to get to a clinic visit during the COVID-19 global pandemic, study drug may be shipped to the participant's home.

Treatment compliance assessments shall be made at each home visit or telephone visit. Participants will be asked about their supply of study drug so that drug accountability may be assessed. Study staff will address any non-compliance issues with the participant.

6.25. Renal Biopsies When Clinic Visits are Not Possible

If a study participant is unable to get to a clinic visit during the COVID-19 global pandemic, optional renal biopsies at Week 52 and Week 104 should be performed when possible, even if the biopsy is done outside the visit window of ± 7 days. In addition, an unscheduled 24-hour urine collection should be obtained at the same time as the optional renal biopsies at Week 52 and Week 104. If the collection of 24-hour urine is to occur after a renal biopsy, it must be done at least 7 days after the biopsy procedure.

7. STUDY ACTIVITIES

Activities for each visit are provided in the Schedule of Assessments (Appendix 1). Additional details for the various activities are provided in Section 6.

During the periods when multiple assessments occur at the same time, they should be conducted in the following order:

- Vital signs prior to blood sampling
- PK samples should be taken before the first daily dose
- Blood for laboratory safety test may be collected prior to PK sampling, provided that PK sampling times are not affected

The actual times of procedures and sample collections will be recorded in the participant's CRF.

7.1. Screening Period (Days –75 to -1)

For each participant, informed consent or assent will be obtained as described in Section 6.1 before the participant enters into the study and any study-related procedures are performed, and participant eligibility will be determined according to the criteria specified in this protocol. All screening eligibility assessments listed in the Schedule of Assessments (Appendix 1) should be performed and documented prior to dosing. This should include a review of the inclusion and exclusion criteria, and a review of the study restrictions, as defined in Section 5.5. The participant's medical history should be reviewed as described in Section 6.2, and a complete physical examination should be conducted as described in Section 6.7. A 24-hour urine sample should be collected as described in Section 6.6.1 and a first morning urine sample should be collected as described in Section 6.6.2; participants may be provided with collection containers and bring their samples to the clinic prior to dosing.

If the participant remains eligible, then arrangements can be made for any required vaccinations (see Section 6.4). If required, vaccinations should be at least 2 weeks before the start of dosing with ACH-0144471, unless otherwise recommended by national and/or local guidelines or local clinical practice. Participants who meet all eligibility criteria will be educated about the restrictions on concomitant medication usage and other substances.

Each adult participant will complete the KDQOL-SF v1.3, FACIT-Fatigue, and EQ-5D-3L questionnaires and each adolescent participant will complete the Peds-FACIT-F and EQ-5D-Y questionnaires during the screening period, prior to study treatment administration.

All evaluations required for determination of eligibility must be completed before the participant is accepted into the study for dosing.

If the participant is unable to receive study drug within 75 days of screening the participant may be re-screened once (for all assessments except the renal biopsy).

The repeating of individual screening laboratory results that fall outside the protocol-required range may be permitted on a case-by-case basis with the written pre-approval of the Achillion Pharmaceuticals Medical Monitor (or designee).

7.1.1. Screening or Pre-Treatment Renal Biopsy

If necessary to confirm eligibility (as discussed in Section 6.3.1) or as a pre-treatment biopsy for the renal biopsy sub-study, a renal biopsy should be performed during screening according to the procedures described in Section 6.3. When obtained to confirm eligibility, the results must be available and reviewed prior to dosing. Given that the renal biopsy is an invasive procedure, a participant should be confirmed as eligible by all other criteria before the renal biopsy is performed.

Biopsies will not be obtained from participants less than 18 years of age (unless they are determined to be clinically indicated by the treating provider), or from participants for whom a biopsy is contraindicated.

7.1.2. Vaccination

As part of the screening process, participants will be evaluated to determine whether vaccination against *N. meningitidis*, *S. pneumoniae*, or *H. influenzae* is to be performed, as described in Section 6.4. Female participants of childbearing potential must have a negative urine pregnancy test on the day of vaccination, before any vaccine or booster is administered.

7.2. Treatment Period

During the Treatment Period, physical examinations, assessment of vital signs, all required safety laboratory testing, and collection of blood and urine samples for PK and PD evaluation will be performed at various time points as specified in Appendix 1.

Participants should be instructed to fast prior to coming to a clinic visit; however, they may drink water or other non-alcoholic beverages. Participants should be instructed to bring their study drug with them for administration at the site.

At clinic visits, participants should be instructed how to take their medication at home, as described in Section 5.3, and record the time they took it.

Participants should be instructed to store their study drug at room temperature, as described in Section 5.8.

Patient visits will be scheduled as listed in the Schedule of Assessments (Appendix 1). The final treatment period visit will be at Week 169. Participants should arrive at the clinic at the time designated by site personnel. The assessments listed in the Schedule of Assessments (Appendix 1), including collection of blood for determination of trough levels of study drug and measurement of the listed complement markers should be performed prior to the administration of the first daily dose of ACH-0144471.

Each adult participant will be asked to complete the KDQOL-SF v1.3 questionnaire, EQ-5D-3L and the FACIT-Fatigue scale and adolescent participants will be asked to complete the Peds-FACIT-F and EQ-5D-Y at the visits specified in the Schedule of Assessments (Appendix 1).

7.3. Taper Period

It is recommended that participants who discontinue ACH-0144471 have study drug tapered over 6 days, as described in Section 5.2. If a participant meets an Individual Stopping Rule

(Section 3.2.3.2) and dosing is stopped, the PI should consider whether it is in the best interest of the participant to discontinue dosing immediately or to taper (as described in Section 5.2). Whenever possible, the taper decision should also be discussed with the Achillion MM prior to dosing termination. If a Group Stopping Rule is met and dosing is terminated in the study, the Achillion MM in consultation with the PI will decide whether or not the taper should be implemented. When dosing is terminated, study participation is not necessarily immediately terminated. Instead, whenever possible, the participant should advance to the Taper and/or Follow-Up Periods, as relevant, and complete all activities in those periods as described in Appendix 1. Participants who are completing the taper will have assessments indicated in Appendix 1 performed on Days 3 (T3) and 6 (T6) of the taper period.

Participants will be instructed to bring their study drug with them for administration at the site. Participants will continue taking their medication at home in the same way as previously described (see Section 5.2).

Participants will be instructed to store their study drug at room temperature, as described in Section 5.8.

Participants should be instructed how to take their medication at home, as described in Section 5.3.2, and record the time they took it.

7.4. Follow-Up Period

During the Follow-Up Period, physical examinations, assessment of vital signs, all required safety laboratory testing, and collection of blood and urine samples for PD evaluation will be performed at various time points as specified in Appendix 1.

As listed in the Schedule of Assessments (Appendix 1), participants will be evaluated at the clinical site 2 weeks after the last dose of study drug, and again 4 weeks after the last dose of study drug during the Follow-up Period. Participants should arrive at the clinic at the time designated by site personnel. If necessary, clinic visits during the Follow-Up Period may occur up to 2 days earlier or later than scheduled.

7.5. Early Termination from the Study

A participant who discontinues dosing does not necessarily discontinue from the protocol, and whenever possible, should have the assessments listed for Follow-up Visit 2 in the Schedule of Assessments (Appendix 1) and should continue with the Taper and/or Follow-Up Periods, as relevant, and complete all activities in those periods as described in Appendix 1. If this is not possible, a participant who withdraws from this study should at a minimum have the assessments listed for the second follow up visit in the Schedule of Assessments (Appendix 1). If withdrawal from the study occurs within 7 days of the last dose of ACH-0144471, a blood sample should also be collected for PK evaluation.

7.6. Unscheduled Visits

Additional clinic visits may be added if deemed necessary by the Investigator. Activities at these visits will be directed by the circumstances, but should include at a minimum:

- Assess for compliance with protocol restrictions
- Assess for AEs and SAEs
- Record concomitant medications
- Measure body temperature
- Additional tests or procedures as appropriate

The reason for the visit and the results of any tests or procedures must be recorded in the participant's CRF.

8. QUALITY CONTROL AND ASSURANCE

8.1. Routine Monitoring

The PI is responsible for the validity of all data collected at the clinical site and must accept the various monitoring procedures employed by the Sponsor. The purpose of monitoring is to verify that the rights and well-being of human participants are protected; that trial data are accurate, complete, and verifiable with source data; that the trial is conducted in compliance with the protocol, GCP, and the applicable regulatory requirements.

A monitor assigned by the Sponsor will conduct regular site visits for the purpose of monitoring various aspects of the study. Visits will take place usually within a predetermined interval, but this may vary during the course of the study. The PI must agree to allow the study monitor and authorized representatives of the Sponsor to inspect all CRFs and corresponding source documents, e.g., original medical records, participant records and laboratory raw data, access to the clinical supplies, dispensing, and storage areas and agree to assist with their activities if requested. The PI should provide adequate time and space for monitoring visits.

The monitor will query any missing or spurious data with the PI (or designee), which should be resolved in a timely manner. A monitoring log will be maintained recording each visit, the reason for the visit, the monitor's signature, and PI or designee's confirmation signature.

8.2. Site Audits

For the purpose of compliance with GCP and regulatory agency guidelines, it may be necessary for Sponsor authorized Quality Assurance personnel and/or authorized personnel from an external regulatory agency to conduct an audit/inspection of an investigational site. The purpose of an audit is to assess the quality of data with regard to accuracy, adequacy, and consistency, and to assure that studies are in accordance with GCP, and Regulatory Agency guidelines. Having the highest quality data from studies is an essential aspect of drug development.

The PI will be given sufficient notice to prepare for such visits, which are planned to take usually between one and two days and may be conducted at any stage during the study. The audit will involve the review of all study related documentation, which is required by GCP to be maintained by each site, review of drug storage, dispensing, and return, review of all study related supplies and review of source documents against the CRFs to assure the adequacy and accuracy of the information that has been recorded, including the verification of any AEs that have occurred.

In the event of the site being notified of a regulatory inspection, the Sponsor will help with the preparation and it is essential that they be notified of the inspection as soon as possible.

9. PLANNED STATISTICAL METHODS

9.1. General Considerations

Summary statistics will be provided for efficacy and safety parameters.

To summarize continuous data, descriptive statistics will include: number of participants, mean, standard deviation, median, minimum, and maximum. To summarize categorical data, frequency counts and percentages will be presented.

Longitudinal summaries of efficacy and safety parameters use pre-defined visit week as described in Appendix 1, Schedule of Assessments. Laboratory measures will be summarized using US standard values and units.

Participant listings will be provided for all efficacy (including PK and PD) and safety parameters.

Subgroup analysis may be performed if data deem such analysis feasible. The grouping criteria could be disease type (C3G or IC-MPGN) or prior study status (ACH471-201 or none) or other clinically relevant demographic and baseline characteristics.

A statistical analysis plan (SAP) will be developed to provide details of the data analysis procedures and presentations, including relevant subgroup analysis.

Note that analysis procedures for addressing exploratory objectives, except for patient-reported outcomes (PRO) interviews, will also be included in the SAP which will be finalized prior to database lock.

9.2. Determination of Sample Size

The sample size is determined based on limited clinical cases of C3G and IC-MPGN. Note that the sample of 20 participants include those who completed study ACH471-201.

9.3. Analysis Populations

All participants receiving at least one dose of ACH-0144471 will be included in the efficacy, safety, pharmacokinetic (PK), and pharmacodynamics (PD) analyses.

9.4. Demographics and Baseline Characteristics

The following will be summarized for treated participants:

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

Additional baseline characteristics may also be summarized as clinically indicated.

9.5. Efficacy, including Pharmacodynamics Analysis

The primary efficacy endpoint is:

- Change from baseline in biopsy, based on a score incorporating changes in both the activity index and C3 staining at the end of 12 months of treatment.
- Number and percent of participants with reduction in proteinuria relative to baseline at the end of 12 months of treatment

The secondary efficacy endpoints include:

Number and proportion of participants with significant (≥25%) increase in eGFR relative to baseline at the end of 12 months of treatment

- Change and percent change from baseline in proteinuria and eGFR over 12 months of treatment period for all participants
- Change and percent change from baseline in eGFR over 12 months of treatment for participants meeting eGFR inclusion criterion at study entry
- Descriptive analysis of slope of GFR over the treatment period of ACH-0144471 therapy

Calculation of eGFR will be based on the following formulas:

- For participants 19 years old and older the CKD-EPI creatinine equation (2009) will be used for inclusion/exclusion and primary endpoint analysis. However, cystatin C will also be measured and as exploratory analysis, eGFR will be calculated by the CKD-EPI creatinine-cystatin equation (2012), the CKD-EPI cystatin C equation (2012), and the MDRD equation. Cystatin C will be measured to allow use of formulas requiring this parameter.
- For participants <19 years old the creatinine-based "Bedside Schwartz" equation (2009) will be used for inclusion/exclusion and primary endpoint analysis. However, cystatin C will also be measured and as exploratory analyses, eGFR will be calculated by the cystatin C-based equation (2012) and the creatinine-cystatin C-based CKiD equation (2012). Cystatin C will be measured to allow use of formulas requiring this parameter.

The calculation of eGFR will be described in detail in the laboratory manual.

When possible, proteinuria will be evaluated in 24-hour urine collections, but if a 24-hour urine is not available, a calculated equivalent will be derived from albumin:creatinine and/or total protein: creatinine ratios, obtained from spot urine samples. The process for deriving this calculated equivalent will be described in detail in the laboratory manual.

Ninety-five percent (95%) confidence intervals will be constructed for mean change and mean percent change at the end of 12 months of treatment.

In addition to the calculation of eGFR, some investigators may choose to measure GFR based on iohexol clearance. Change and percent change from baseline in measured GFR over the 12 months of treatment will be calculated for participants for whom this data is available.

9.6. Safety Analysis

Treatment-emergent AEs (TEAEs) will be summarized and listed by system-organ-class and preferred term using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA®). All SAEs and discontinuation due to AEs will be listed in tabulated format.

All clinical laboratory data (hematology, serum chemistry, and urinalysis) with normal ranges, out-of-range flags, and toxicity grades will be listed by participant. Descriptive summary statistics may be provided for selected lab tests.

Data on physical exam and vital signs will be examined either through participant listings or by summary statistics of selected parameters.

Other exploratory techniques, e.g., graphic presentations, may also be employed to facilitate clinical interpretations of the safety results.

10. ADMINISTRATIVE CONSIDERATIONS

10.1. Investigators and Study Administrative Structure

The PI must maintain a screening log of all participants seen and considered for the study. For those participants who are not eligible to participate in the study, the reason for their exclusion should be recorded.

10.2. Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and Regulatory Approval

10.2.1. Ethical Approval

The study protocol, participant information, and consent and assent forms, the Investigator Brochure, available safety information, participant recruitment procedures (e.g., advertisements), information about payments and compensation available to the participants and documentation evidencing the investigator's qualifications should be submitted by the investigator to the EC or IRB for ethical review and approval according to local regulations, prior to the start of the study. The written approval should identify all documents reviewed by name, version, and the date on which the committee met and granted the approval.

Any modifications to EC or IRB approved documents must also be submitted to the EC or IRB for approval before implementation.

10.2.2. Regulatory Approval

As required by local regulations, the Sponsor's (or designee's) Regulatory Affairs group will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to study initiation.

10.2.3. Amendments

Any change to the protocol will be effected by means of a protocol amendment. Any changes, which affect participant safety or welfare, will be submitted to the EC or IRB and regulatory authority (where applicable) for approval prior to implementation. The investigator, EC, and Sponsor must agree on all amendments. No amendment will be implemented until it is approved and signed by the investigator and Sponsor. Exceptions to this are when the investigator considers that the participant's safety is compromised. Protocol amendments detailing minor administrative changes should be submitted by the investigator (or designee) to the EC or IRB for notification.

10.3. Ethical Conduct of the Study

This study will be performed in accordance with: 1) the principles of ICH Guideline E6 for Good Clinical Practice (CPMP/ICH/135/95 January 1997); 2) European Directive 2001/20/EC, 3) standard operating procedures and/or guidelines, 4) the U.S. Food and Drug Administration (FDA) regulations, 5) the Declaration of Helsinki, and 6) all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

10.4. Participant Information and Consent

In obtaining and documenting informed consent or assent, the investigator should comply with the applicable regulatory requirements and should adhere to ICH GCP (E6). Each participant must be adequately informed in a language that they can understand and read of the aims, methods, anticipated benefits, potential hazards and the discomfort the study may entail, as well as their right to abstain from participating in the study and to withdraw their consent/assent at any time without affecting their medical care. If important new information is incorporated in the ICF and approved by the EC, all participants still actively participating in the study must be re-consented.

Written informed consent for adult participants should be documented by the participant's personally dated signature and the personally dated signature of the investigator or designee who conducted the informed consent discussion. Written assent for adolescent participants should be documented by the participant's personally dated signature and the personally dated signature of the investigator or designee who conducted the assent discussion, and by the personally dated signature of the participant's parent or guardian. The investigator or designee should supply all enrolled participants with a copy of their signed informed consent or assent. The monitor will inspect the original forms for all participants.

10.5. Participant Confidentiality

The investigators and Sponsor and its designees will preserve the confidentiality of all participants taking part in the study, in accordance with GCP, local regulations and, to the extent applicable, the Health Insurance Portability and Accountability Act of 1996 ("HIPAA"). Subject to the requirement for source data verification by the study personnel by reference to the participant's notes, confidentiality of all participant identities will be maintained. Only participant initials, date of birth, and study number will be used on the CRF and in all study correspondence, as permitted. No material bearing a participant's name will be kept on file by the Sponsor.

Audio files of the interviews will be transcribed and de-identified (any identifying information such as dates, names, locations will be removed). The de-identified transcripts will be delivered for analysis and a single audio file will be kept as a source document in the Trial Master File. Any copies of the audio file will be destroyed immediately upon confirmation of receipt of the transcript.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing participant contact details and data. Participants will be informed accordingly and will be requested to give their consent on contact details data handling procedures in accordance with national regulations. In order to secure data privacy protection, participant contact details will be sent to a dedicated unit in charge of scheduling and setting up the interviews independently from study sponsor, monitor, data management and data analysis structures and other study stakeholders. The specific information about participant contact details management will be provided on a Contact Order Form to be completed by Investigator and participant, signed by the participant and sent to the unit in charge of scheduling and setting up the interviews. This form will not include health data.

10.6. Study Monitoring

10.6.1. Access to Information for Monitoring

In accordance with ICH-GCP guidelines, the Study Monitor must have direct access to the investigator's source documentation in order to verify the consistency of the data recorded in the CRFs.

The Study Monitor is responsible for routine review of the CRFs at regular intervals throughout the study, to verify adherence to the protocol, and the completeness, consistency, and accuracy of the data being entered. The Study monitor should have access to any participant records needed to verify the entries on the CRFs. The investigator agrees to cooperate with the Study Monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

10.6.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or Achillion Pharmaceuticals may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the Achillion Pharmaceuticals Medical Monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Achillion Pharmaceuticals access to records, facilities, and personnel for the effective conduct of any inspection or audit.

10.7. Case Report Forms and Study Records

10.7.1. Recording of Data

All data collected during the study will be recorded in individual, participant-specific electronic case report forms (eCRFs). All eCRFs should be completed by the investigator (or designee), who should be identified and agreed upon with the Sponsor before the start of the study. A signature log identifying personnel who can enter data and/or sign off an eCRF will be maintained. Instructions for data entry will be provided.

A CRF must be completed for each participant who signs a consent form and is admitted to the study. Corrections to the data on the CRF will only be made by the investigator (or designee).

CRFs should be kept current to enable the study monitor to review the participant status throughout the course of the study. CRFs will be completed within 5 days of the last participant visit.

10.7.2. Source Documentation and Medical/Study Records

The participant's number and date of entry into the study, along with the study code, should be recorded in the participant's medical/study records by the investigator (or designee). The investigator (or designee) should also record, in the medical/study records, confirmation of written and oral consent, the participant's clinical status/disease being treated, date of every study visit, date study drug started and stopped, concomitant medications, copies of all relevant reports and laboratory tests, comments on results and reference to any AEs.

10.8. Protocol Deviations

Protocol deviations will be assessed on a case-by-case basis. Withdrawal of consent for one or more activities within the protocol will not necessarily be considered to be a protocol deviation, and will not necessarily result in the removal of the participant from further study activities. The available data from any such participants will be included in analyses as appropriate. Significant protocol deviations will be reported to the Ethics Committee or IRB according to local regulations.

10.9. Access to Source Documentation

The investigator and staff must agree to allow the study monitor and authorized representatives of the Sponsor to inspect all eCRFs and corresponding source documents, e.g., original medical records, participant records, and laboratory raw data; to have access to the clinical supplies, and dispensing and storage areas; and to agree to assist with their activities if requested. The investigator and staff should provide adequate time and space for monitoring visits.

Participants will have access to safety laboratory results upon request but should be aware that these typically are not immediately available. The results of the baseline biopsy evaluation can be provided to the investigator, who may share them with the participant. PK levels will not be available until after all study analysis is completed.

10.10. Data Generation and Analysis

Data generation and analysis will be specified and detailed in the SAP.

10.11. Retention of Data

The investigator (or designee) must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least two separate categories as follows:

- Investigator study file, and
- Participant clinical source documents

The investigator study file will contain the protocol/amendments, CRF and query forms, EC or IRB and governmental approval with correspondence, informed consent, drug records, staff *curricula vitae* and authorization forms, and other appropriate documents and correspondence.

Participant clinical source documents (usually defined by the protocol-specified procedures and data collection requirements in advance to record key efficacy/safety parameters independent of the CRFs) include, but are not limited to, participant hospital/clinic records, physician and nurse notes, appointment book, original laboratory reports, ECG and/or EEG tracings, pathology and special assessment reports, consultant letters, screening and enrollment logs.

All clinical study documents must be retained by the investigator for at least 2 years after the last approval of a marketing application in an ICH region (i.e., United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be

required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with Achillion Pharmaceuticals. The investigator (or designee) must contact Achillion Pharmaceuticals prior to destroying any records associated with the study. Achillion Pharmaceuticals will notify the PI when the trial records are no longer needed.

If the investigator withdraws from the study (e.g., relocates, retires, or dies), the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, EC). Notice of such transfer will be given in writing to Achillion Pharmaceuticals. If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangement must be made between the PI and Achillion Pharmaceuticals to store these in sealed containers outside of the site, so that they can be returned sealed to the PI in case of a regulatory audit. Where source documents are required for the continued care of the participant, appropriate copies should be made for storage outside of the site.

The interviews will be audio recorded in a de-identified way. The audio files will serve as source documents and will be archived in Trial Master File. Any additional copy of audio recordings temporarily retained by interviewers and / or transcription unit will be destroyed after transcription process completion. The audio recordings will be transcribed word by word for the analysis.

10.12. Study and Site Closure

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.13. Final Report, Publication and Disclosure Policy

All information contained in this protocol and the trial results are considered to be confidential. The investigator agrees to use this information for purposes of conducting this trial. It is understood that Achillion Pharmaceuticals may use data derived from this trial for the purpose of research and development. The data may be disclosed by Achillion Pharmaceuticals. to other investigators, the FDA, other government agencies, or foreign drug regulatory authorities, or to the public. No publication of trial design or results is permitted without specific Achillion Pharmaceuticals approval. To gain approval, a copy of the manuscript for review must, therefore, be sent to Achillion Pharmaceuticals 60 days before submission for publication.

It is the intent of Achillion Pharmaceuticals to present the results of this study at future scientific meetings. Additionally, it is the intent of Achillion Pharmaceuticals to publish the results of this study in leading scientific journals. The investigator of each investigative site will be invited to be an author in conjunction with the investigator(s) from Achillion Pharmaceuticals. Achillion Pharmaceutical will determine additional authors. Presentations and manuscripts will be provided and agreed to by the authors and Achillion Pharmaceuticals.

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12. APPENDICES

Appendix 1. Schedule of Assessments

Table 4. Schedule of Assessments – Screening through Week 12

Study Period	**Screening**[1]		**Treatment**[2]										
Study Week			**Wk 1**			**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 7**	**Wk 8**	**Wk 10**	**Wk 12**
Study Day	**Day -75 to Day -1**		**1**	**3**	**7**	**14**	**21**	**28**	**35**	**49**	**56**	**70**	**84**
Required Clinic Visit	**X**	**X**	**X**	**X**	**X**	**X**		**X**			**X**		**X**
Phone Visit							**X**		**X**	**X**		**X**	
Screening Assessments													
Informed Consent	X												
Inclusion/ Exclusion Criteria[3]	X												
Demographics	X												
Medical History	X		X										
FSH	X												
Urine Drug screen	X												
Vaccinations		X[4]											
Sample for potential genetic assessment of complement genes	X												
12-Lead ECG (single)	X												
Study Drug Dispensing			X			X		X			X		X
AE/SAE/Protocol Restrictions/Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient-Reported Outcomes Assessments													
FACIT-Fatigue OR Peds-FACIT-F	X												
KDQOL (Adults only)	X												
EQ-5D-3L OR EQ-5D-Y	X												

Table 4 Schedule of Assessments – Screening through Week 12(Continued)

Study Period	Screening[1]		Treatment[2]										
Study Week			Wk 1			Wk 2	Wk 3	Wk 4	Wk 5	Wk 7	Wk 8	Wk 10	Wk 12
Study Day	Day -75 to Day -1		1	3	7	14	21	28	35	49	56	70	84
Required Clinic Visit	X	X	X	X	X	X		X			X		X
Phone Visit							X		X	X		X	
Clinical Assessments													
Complete Physical Exam	X		X										
Brief Physical Exam[4]				X	X	X		X			X		X
Weight	X	X	X[4]	X[4]	X[4]	X[4]		X[4]			X[4]		X[4]
Vital Signs[4]	X	X	X	X	X	X		X			X		X
Other Assessments													
Renal Biopsy		X[5]											
Standard Laboratory Assessments[6]													
PK samples[7]				X		X							X
Safety Labs													
Chemistry	X		X	X	X	X		X			X		X
Hematology	X		X	X	X	X		X			X		X
Coagulation (PT/PTT/INR)	X												
Serum C3 and C4	X		X			X							X
First Morning urine sample[8]	X		X	X	X	X		X			X		X
24-Hour Urine Collection[9]		X											X
Pregnancy Test[10]	X	X	X			X		X			X		X
Complement Biomarkers[6]	X		X		X	X		X			X		X

AE = Adverse event; Con Meds = concomitant medications; ECG = Electrocardiogram; PK = Pharmacokinetic; SAE = Serious adverse event

1. Screening assessments do not need to occur on the same day.
2. Visits may be ± 2 days after Week 4. Unless the PI feels a clinic visit is required, the visits on Weeks 3, 5, 6, 7 and 10 should be conducted by phone.
3. Patients should be confirmed to be eligible based on all other inclusion and exclusion criteria, except the renal biopsy, before being vaccinated.
4. Prior to dosing
5. If obtained during screening to confirm eligibility, the results must be available and reviewed prior to dosing.
6. During the treatment period, blood draws and urine collection should be done prior to dosing
7. Collect only one sample prior to dose administration (trough sample).
8. If the first morning urine collection coincides with a renal biopsy, collection must be completed before or at least 7 days after the biopsy procedure.
9. The 24-hour urine collection period may be at any time during screening, but if it is to occur at least 7 days after the biopsy procedure.
10. Serum pregnancy test at the initial screening visit and urine pregnancy tests at other time points for women of childbearing potential only.

Table 5. Schedule of Assessments – Week 16 through Week 52

Study Period	**Treatment**[1]												
Study Week	**Wk 16**	**Wk 18**	**Wk 20**	**Wk 22**	**Wk 24**	**Wk 26**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 52**
Study Day	**112**	**126**	**140**	**154**	**168**	**182**	**196**	**224**	**252**	**280**	**308**	**336**	**364**
Clinic Visit[1]	**X**		**X**				**X**		**X**		**X**		**X**
Phone Visit		**X**		**X**	**X**	**X**		**X**		**X**		**X**	
Study Drug Dispensing			X				X		X		X		X
AE/SAE/Protocol Restrictions/Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient-Reported Outcomes Assessments													
FACIT-Fatigue OR Peds-FACIT-F							X						X
KDQOL (Adults only)							X						X
EQ-5D-3L OR EQ-5D-Y							X						X
Clinical Assessments													
Brief Physical Exam[2]	X		X				X		X		X		X
Weight	X[3]		X[3]				X[3]		X[3]		X[3]		X[3]
Vital Signs[4]	X		X				X		X		X		X
Biopsy Assessments													
Renal Biopsy							X[5]						X
Standard Laboratory Assessments[6]													
PK samples[7]							X						
Safety labs													
Chemistry[6]	X		X				X		X		X		X
Hematology[6]			X				X		X		X		X

Table 5. Schedule of Assessments – Week 16 through Week 52 (Continued)

Study Period	Treatment[1]												
Study Week	**Wk 16**	**Wk 18**	**Wk 20**	**Wk 22**	**Wk 24**	**Wk 26**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 52**
Study Day	**112**	**126**	**140**	**154**	**168**	**182**	**196**	**224**	**252**	**280**	**308**	**336**	**364**
Clinic Visit[1]	**X**		**X**				**X**		**X**		**X**		**X**
Phone Visit		**X**		**X**	**X**	**X**		**X**		**X**		**X**	
Serum C3 and C4	X		X				X		X		X		X
First Morning urine sample[8]	X		X				X		X		X		X
24-Hour urine collection[9]							X						X
Pregnancy Test[10]	X		X				X		X		X		X
Complement Biomarkers[6]	X		X		X		X		X		X		X

AE = Adverse event; Con Med = concomitant medications; PK = Pharmacokinetic; SAE = Serious adverse event

1 Clinic visits may be ± 2 days. Starting with the Week 28 visit, visits may be ± 1 week. Unless the PI feels a clinic visit is required, the visits on Weeks 18, 22, 24, 26, 32, 40, 48, should be conducted by phone. If a patient is unable to get to a clinic visit during the COVID-19 global pandemic (Section 6.23), study data collection should still occur. The preferred option is **home healthcare visits**; nurses may collect 24-hour urine, first morning urine, and safety labs, including pregnancy testing. Additional assessments should include AEs, vital signs, and concomitant medications. Nurses will perform study drug accountability. If a home healthcare visit is not possible, patients may have **telephone visits** with the PI or designee. Data collection will include AEs and concomitant medications, and patients will be asked about study drug compliance.

2 Conduct as described in Section 6.7; during the treatment period exam should be prior to dosing. Assessment of edema is part of the brief physical exam.

3 Prior to dosing

4 Vital signs include body temperature, blood pressure in triplicate, heart rate and respiratory rate. During the treatment period, assessments should be done prior to dosing.

5 For all subjects, a biopsy should be obtained at Week 52. If clinic visits are not possible during the COVID-19 global pandemic, the Week 52 biopsy should be done when safely possible, even if the biopsy is unable to be done within 7 days of the target date. In addition, an unscheduled 24-hour urine collection should be obtained at the same time as the Week 52 renal biopsy. If the collection of 24-hour urine is to occur after a renal biopsy, it must be done at least 7 days after the biopsy procedure. Subjects in the renal biopsy sub-study, will have biopsies obtained after approximately 6 months and/or at the end of dosing. The end of treatment renal biopsy can occur anytime between the Week 91 visit and the Week 104 visit but should be prior to the last dose.

6 During the treatment period, blood draws and urine collection should be done prior to dosing. Collected as described in the laboratory manual. Blood collection for biomarkers will not be done at home health visits or at local laboratories. If a home visit occurs but laboratory samples cannot be shipped to the central laboratory by the nurse conducting home visits, the nurse should go to a local laboratory to drop off all laboratory samples, including 24-hour urine collections and safety labs. If home visits are not possible, the participant should go to a local laboratory to drop off 24-hour urine collections and for safety laboratory testing, including pregnancy testing (if applicable), to be performed.

7 Collect one sample prior to dose administration (trough sample)

8 If the first morning urine collection coincides with a renal biopsy, collection should be completed before or at least 7 days after the biopsy procedure.

9 The 24-hour urine collection period is to occur after a renal biopsy, it must be at least 7 days after the biopsy procedure.

10 Urine pregnancy tests for women of childbearing potential only. Any positive urine pregnancy test will be confirmed by a serum pregnancy test. Pregnancy tests should be done monthly.

Table 6. Schedule of Assessments – 27 Month Long Term Follow-up, with Taper and Follow-up

Study Period	Long Term Follow-up[1]				Taper[2]		Follow-up[3]	
Study Week	Wk 65 Wk 117 Wk 156	Wk 78 Wk 130 Wk 169	Wk 91 Wk 143	Wk 104	T3	T6	F/U 1	F/U 2
Clinic Visits[1]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Phone Call								
Study Drug Dispensing	X	X	X	X	X			
AE/SAE/Protocol Restrictions/Con Meds	X	X	X	X	X	X	X	X
Patient-Reported Outcomes Assessments								
FACIT-Fatigue OR Peds-FACIT-F				X			X	
KDQOL (Adults only)				X			X	
EQ-5D-3L OR EQ-5D-Y				X			X	
Clinical Assessments								
Complete Physical Exam[4]				X				
Brief Physical Exam[4]		X			X	X	X	
Weight	X	X	X	X	X	X	X	
Vital Signs[4]	X	X	X	X	X	X	X	
Histology								
Renal Biopsy[5]				X				
Standard Laboratory Assessments[6]								
Safety labs: Chemistry	X	X	X	X	X	X	X	X
Safety labs: Hematology			X	X		X		X
Coagulation (PT/PTT/INR)								
Serum C3 and C4		X		X	X		X	
First Morning Urine[7]	X	X	X	X	X	X	X	X
24-Hour Urine[8]								
Pregnancy Test[9]		X		X	X		X	X
Complement Biomarkers[10]	X	X	X	X	X	X	X	X

AE = Adverse Event; F/U = Follow-up Visit; SAE = Serious Adverse Event; T3 = Day 3 of the taper; T6 = Day 6 of the taper; Wk = Weeks

1. Clinic visits may take place within a window of ±7 days relative to the specified day for week 65 to week 104, except as noted for the Taper, Follow-Up, and Dose Escalation visits. If clinic visits are not possible during the COVID-19 global pandemic, home visits or telephone visits may be done. If a patient is unable to get to a clinic visit (Section 6.23), study data collection may still occur. The preferred option is **home healthcare visits**; nurses may collect 24-hour urine, first morning urine, and safety labs, including pregnancy testing. Additional assessments should include AEs, vital signs, and concomitant medications. Nurses will perform study drug accountability. If a home healthcare visit is not possible, patients may have **telephone** visits with the PI or designee. Data collection will include AEs and concomitant medications, and patients will be asked about study drug compliance.

If a home healthcare visit is not possible or specimens cannot be shipped to the central laboratory, a patient may go to a **local laboratory** to drop off 24-hour urine collections, and for safety lab and pregnancy testing.

2. Participants should gradually decrease the daily total dose of ACH 0144471 during the taper. Visits should be on the 3rd (T3) and 6th (T6) day of the taper.
3. Follow-up visits should be conducted 2 and 4 weeks after the last dose of ACH 0144471 (including the taper, if applicable), within a window of ±2 days.
4. During the treatment periods, exam should be prior to dosing.
5. The end of treatment renal biopsy can occur anytime between the Week 91 and the Week 104 visit, but should be prior to the last dose
6. If a home visit occurs but laboratory samples cannot be shipped to the central laboratory by the nurse conducting home visits, the nurse should go to a local laboratory to drop off all laboratory samples, including 24-hour urine collections and safety labs. If home visits are not possible, the participant should go to a local laboratory to drop off 24-hour urine collections and for safety laboratory testing, including pregnancy testing (if applicable), to be performed.
7. If the first morning urine collection coincides with a renal biopsy, collection should be completed before or at least 7 days after the biopsy procedure.
8. The 24-hour urine collection should be within a window of ± 1 week. The 24-hour urine collection period must be at least 7 days after the biopsy procedure. If a clinic visit is not possible during the COVID-19 global pandemic and a home healthcare visit is done, the home healthcare nurse will collect the 24-hour urine sample. If a telephone visit is done instead, the patient should take the 24-hour urine to the local laboratory, if possible.
9. Urine pregnancy tests for women of childbearing potential only. Any positive urine pregnancy test will be confirmed by a serum pregnancy test.
10. Blood collection for biomarkers will not be done at home health visits or at local laboratories.

Appendix 2. Fever Management Plan

Treatment with complement inhibitors may lead to an increased lifetime risk of acute meningococcal disease, or other encapsulated bacterial infection. Because of this risk, it is essential to monitor participants for signs and symptoms of infection.

Minimum Requirements

The points mentioned below are to be considered as a minimum diagnostic and management procedure. These are not meant to replace or bypass a systematic and thorough assessment of the participant; instead, they are intended to facilitate rapid initiation of assessment and management of fever.

A General Management for Any Fever Detected in the Clinic

For any fever, the site must:

1. Assess for symptoms - consider meningococcal disease as a diagnosis. When meningococcal disease is suspected, early treatment is critical
2. Repeat and confirm all temperature measurements >38.0°C
3. Notify the PI and Sponsor for all confirmed temperature measurements >38.0°C
4. Consider if referring to an emergency medical facility is appropriate. If so, refer. Otherwise:

a. PI or designee to perform a complete physical examination (including assessing if fever is accompanied by a severe headache, stiff neck, or other signs of meningeal irritation, shortness of breath, skin rashes, or other unusual signs or symptoms), document a plan based on her/his clinical judgment, and possibly an ID consult depending on assessment
b. CBC (if not done in the last 12 hours) and blood culture
c. Treat any suspicion of meningococcal infection aggressively; consider initiation of empirical antimicrobial therapy (assuming there are no other obvious sources of fever) at least until culture results become available and/or an alternative etiology is found
d. Infectious disease consult is required once the PI or designee initiates empiric antibiotic treatment
e. Measure temperature hourly until <38.0°C
f. All cases of fever will be assessed by the Investigator, regardless of apparent causality from use of the study treatment(s)
g. All activities performed as part of the Fever Management Plan should be documented

Acute Meningococcal Disease

If acute meningococcal disease is diagnosed, immediate medical and antibiotic management by local physician must be initiated documented and reported to the sponsor's medical monitor immediately, but not more than 24 hours from diagnosis.

Normal body temperature varies over the course of the day. The normal daily temperature variation is typically 0.5°C (0.9°F). During a febrile illness, daily low and high temperature readings are maintained but at higher levels. However, this daily variation can be as high as 1.0°C in some individuals recovering from a febrile illness.