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

Unique Protocol ID:	ACH471-201
NCT Number:	NCT03124368
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Date of Protocol:	09 June 2017

Clinical Trial Protocol

ACH471-201

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

Study Number: ACH471-201

Study Phase: 2a

Product Name: ACH-0144471 Tablets

EudraCT Number: 2016-003525-42

Investigators:

Sponsor: Achillion Pharmaceuticals, Inc.

Sponsor Contact: PPD

Medical Monitor: PPD
PPD
PPD

	Date
Original Protocol:	27 January 2017 (Version 1.0)
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Sponsor Signature(s)

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Study Number: ACH471-201

Protocol Version and Date 09 June 2017 (Version 3.0)

This clinical study protocol has been approved by the sponsor.

PPD
PPD
Achillion Pharmaceuticals, Inc.
300 George Street
New Haven, CT 06511

Date

PPD

6/12/2017 | 12:21 PM EDT

Investigator's Signature(s)

Study Title:	A Phase 2a Proof-of-Mechanism, Open-Label Study to Determine the Effect of ACH-0144471 on C3 Levels in Patients with Low C3 Levels Due to Either C3 Glomerulopathy (C3G) or Immune-Complex Membranoproliferative Glomerulonephritis (IC-MPGN)
Study Number:	ACH471-201
Protocol Version and Date	09 June 2017 (Version 3.0)

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. 300 George Street New Haven, CT 06511 Phone: PPD
Name of Finished Product	ACH-0144471 Tablet, 50, 75, and 100 mg
Name of Active Ingredient	ACH-0144471
Name of Inactive Ingredient	CCI CCI
Study Title	A Phase 2a Proof-of-Mechanism, Open-Label Study to Determine the Effect of ACH-0144471 on C3 Levels in Patients with Low C3 Levels Due to Either C3 Glomerulopathy (C3G) or Immune-Complex Membranoproliferative Glomerulonephritis (IC-MPGN)
Study Number	ACH471-201
Study Phase	Phase 2a
Primary Objective	To determine whether the administration of ACH-0144471 can increase C3 levels in patients with low C3 levels due to either C3G or IC-MPGN
Secondary Objective(s)	• To evaluate the safety and tolerability of ACH-0144471 in patients with C3G or IC-MPGN • To evaluate the pharmacokinetic (PK) profile of ACH-0144471 in patients with C3G or IC-MPGN • To evaluate the effect of ACH-0144471 on biomarkers of alternative pathway activity (AP) in patients with C3G or IC-MPGN • To explore the relationship between study drug exposure and changes in C3 levels and other biomarkers of alternative pathway activity
Exploratory Objective(s)	• To explore patients' experience of their disease (C3G or IC-MGPN), its impact, and its management on everyday lives, from first symptoms to definitive diagnosis and beyond • To explore patients' expectations of ACH-0144471 in the treatment of their disease

Study Design	This open-label study will enroll up to 10 patients (between the ages of 16 and 65 years) with biopsy-confirmed C3G or idiopathic IC-MPGN and a low serum C3 level. The trial will evaluate the ability of ACH-0144471 to increase C3 levels via inhibition of factor D (fD) by enrolling patients in two groups. Group 1 will serve as a sentinel group consisting of two patients who will receive ACH-0144471 at a dose of 100 mg three times daily (TID) for 14 days followed by a taper over 7 days. Group 2 will be initiated upon confirmation that dosing was well-tolerated in Group 1 (based on Group 1 safety data through at least Day 28), and may include up to 8 patients. As discussed in Section 3.2.2, the dose for Group 2 will be selected based on the available safety, PK, and PD data from Group 1, but will not exceed 200 mg TID. The 100 mg TID dose level for Group 1 was selected based on safety, PK, and pharmacodynamics (PD) data from the Phase 1 single-ascending dose (SAD) and multiple-ascending dose (MAD) studies (ACH471-001 and ACH471-002), which demonstrated that similar dosing regimens in healthy volunteers were well-tolerated and able to inhibit the alternative pathway of complement. In addition, the relative bioavailability study (ACH471-006) supports transition from the liquid filled capsule (LFC) dosage form used in the SAD and MAD studies to the tablet dosage form to be used in this study. All patients will receive active drug. Patients will receive study drug for 14 days (Treatment Period), followed by a taper over the next 7 days (Taper Period) to minimize the potential adverse effects of a rapid surge in complement activity following drug withdrawal. Patients will have daily clinic visits for the first 3 days of the taper, and then will continue to be followed for 28 days after the last dose of study drug (Follow-Up Period). Long-term follow up visits to allow collection of longitudinal observational data are included, but are not required. During the long-term follow up period, patients will be asked to return for an outpatient clinic visit approximately every 45 days for a maximum of 1 year. If a patient has a C3 level that, at 2 consecutive evaluations, is greater than 125% the upper limit of normal (ULN), or is greater than 3× their baseline and greater than or equal to the lower limit of normal (LLN), then the taper period will be initiated before completion of the 14 days of dosing, as proof-of-mechanism will already be established for that patient. Furthermore, early tapering and possible prevention of supraphysiologic C3 levels may mitigate the theoretical risk for acute precipitation of C3 into the glomerulus upon drug discontinuation. Safety, PK, and PD data will be obtained at multiple time points during the Treatment, Taper and Follow-Up periods. The primary endpoint for the study will be changes in C3 levels. Additional endpoints include the incidence of adverse events (AEs), serious adverse events (SAEs), and discontinuations due to AEs. Clinical measures of renal disease will be monitored (e.g., creatinine, proteinuria, and blood pressure), but are not expected to improve in this short-duration non-therapeutic trial. Additional secondary and exploratory endpoints will include functional assays of complement activity and measurement of selected complement components in blood and urine, as described in Section 6.15. Finally, a PK/PD analysis will be conducted to explore the relationship between study drug exposure and changes in C3 levels and/or other secondary endpoints. Concomitant medications will be considered on a case-by-case basis, and decisions made jointly between the PI and Sponsor, based on knowledge of ACH-0144471 and risks for drug-drug interactions, as well as potential to interfere with interpretation of the study. Based on data from Groups 1 and 2, additional patients may be added to study additional dose levels or regimens (not to exceed 200 mg TID for two weeks, followed by a 7-day taper) or additional C3G or IC-MPGN patients.
Study Population	This study will be conducted in up to 10 patients with low C3 due to either C3G or IC-MPGN

Dosing Regimen	**Group 1:** Treatment Period: 100 mg TID for 14 days (Days 1 – 14) Taper Period: 100 mg twice daily (BID) for 3 days (Days 15, 16, and 17) 50 mg BID for 2 days (Days 18 and 19) 50 mg once daily (QD) for 2 days (Days 20 and 21) **Group 2:** The dose and taper schedule will be determined based on data from Group 1, with a maximum possible dose of 200 mg TID followed by a 7 day taper.
Inclusion Criteria	Each patient must meet all of the following criteria to be enrolled in this study: 1. Must be between the ages of 16 and 65 years, inclusive 2. Must have a clinical diagnosis of C3G (C3 glomerulonephritis [C3GN] or dense deposit disease [DDD], the 2 types of C3G) or idiopathic immune-complex membranoproliferative glomerulonephritis (IC-MPGN) by renal biopsy for at least 3 months prior to dosing, with the pathologic diagnosis verified by review of the renal biopsy by the study central pathologist 3. C3 must be <50% of the lower limit of normal (LLN) 4. C4 must be >90% of the LLN 5. Female patients of childbearing potential must either agree to abstinence or to use two effective methods of contraception as defined in Section 5.5.5 from screening through 3 months after the last dose of ACH-0144471. Females who are of non-childbearing potential as defined in Section 5.5.5 need not employ a method of contraception. 6. Male patients must either agree to abstinence or to use two effective methods of contraception as defined in Section 5.5.5 throughout the dosing period and for at least 3 months after the last dose of ACH-0144471. Males who are surgically sterile need not employ additional contraception. Males must agree to not donate sperm throughout the dosing period and for at least 3 months following the last dose of ACH-0144471. 7. Must be capable of providing written informed consent, must be willing and able to comply with the requirements and restrictions listed in the consent form and with the visit schedule, treatment plan, laboratory tests, pharmacokinetic sampling schedule, and other study procedures, and must be willing and able to return for all study visits 8. Must be up-to-date on routine vaccinations, or be willing to be brought up-to-date, based on local guidelines 9. Must be willing to comply with study-specific vaccination requirements for *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Neisseria meningitidis* strains A, C, W, and Y 10. Must be willing, at all times for the duration of study participation, to have transportation and telephone access, and to be within one hour of an emergency medical center
Exclusion Criteria	Patients who meet any of the following criteria will be excluded from the study: 1. History of a major organ transplant (e.g., heart, lung, kidney, liver) or hematopoietic stem cell/marrow transplant. Individuals receiving renal replacement therapy are also excluded 2. History or presence of any clinically relevant co-morbidities that would make the patient inappropriate for the study (for example, is likely to result in deterioration of the patient's condition, affect the patient's safety during the study, or confound the results of the study), in the opinion of the Principal Investigator 3. Evidence of monoclonal gammopathy of unclear significance (MGUS), infections,

	malignancy, autoimmune diseases, or other conditions to which C3 glomerulopathy or IC-MPGN may be secondary 4. Patients with other renal diseases that would interfere with interpretation of the study 5. Presence or evidence of hepatobiliary cholestasis 6. Known Gilbert's syndrome and/or patients with a history suggestive of Gilbert's syndrome 7. Females who are pregnant, nursing, or planning to become pregnant during the study or within 90 days of study drug administration, or patients with a female partner who is pregnant, nursing, or planning to become pregnant during the study or within 90 days of study drug administration 8. Estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2 at the time of screening or at any time over the preceding four-weeks 9. History of febrile illness, a body temperature >38°C, or other evidence of a clinically significant active infection, within 14 days prior to study drug administration 10. Patients with evidence of human immunodeficiency virus, hepatitis B or hepatitis C infection (positive serology for HIV-1 antibody, positive hepatitis B surface antigen, or positive anti-HCV antibody at Screening or historically) 11. History of meningococcal infection, or a first-degree relative or household contact with a history of meningococcal infection 12. Contraindication to one or more of the required vaccinations 13. 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 14. Participation 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 study drug administration 15. Receipt of eculizumab at any dose or interval within the past 75 days prior to dosing 16. Use of tacrolimus or cyclosporine within 2 weeks of the first dose of ACH-0144471 17. 12-lead electrocardiogram with a QTcF >500 msec or findings which, in the opinion of the PI, could put the patient at undue risk 18. Any of the following laboratory abnormalities at screening: • Alanine transaminase > ULN • Aspartate aminotransferase > ULN • Alkaline phosphatase > ULN • Absolute neutrophil counts <1,000/μL • Total bilirubin >1.5× ULN • Indirect bilirubin > ULN • Any laboratory abnormality that, in the opinion of the PI, would make the patient inappropriate for the study, or put the patient at undue risk 19. Donation of blood or blood products in excess of 500 mL within a 60 day period prior to the first dose of the current study 20. Receipt of blood or blood products within 30 days of screening

	21. Clinically significant history of drug allergy as determined by the Investigator 22. Unwilling or unable to comply with the study protocol for any reason
Primary Endpoints	• Increase in C3 levels relative to baseline
Secondary Endpoints	• The incidence of AEs, SAEs, and discontinuations due to AEs • Time (in days) to achieving peak C3 levels from the first day of dosing • The pharmacokinetic (PK) profiles of ACH-0144471 following the administration of multiple oral doses, and in the setting of dose taper • Changes in biomarkers of alternative pathway activity (AP) relative to baseline • The relationship between ACH-0144471 pharmacokinetics and changes in C3 levels, and inhibition of alternative pathway activity (PK/PD)
Exploratory Endpoints	• Patients' experience of their disease (C3G or IC-MPGN), its impact, and its management on everyday lives, from first symptoms to definitive diagnosis and beyond • Patients' expectations of ACH-0144471 in the treatment of their disease
Group Stopping Rules	Dosing will be terminated if one or more of the following occurs within a dose group: • Two or more patients experience the same or similar study drug-related serious adverse event • Two or more patients experience the same or similar study drug-related Grade 4 or higher adverse events If dosing is terminated in a group, all patients 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 Patients	Any individual patient who meets any of the following criteria will be discontinued from further dosing: • The patient experiences any serious adverse event assessed as related to treatment with ACH-0144471 • The PI believes that patient continuation in the study is not advisable • The patient becomes pregnant 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
Test Product, Dosage Form, and Strength	ACH-0144471, administered orally as 50, 75, or 100 mg tablets
Reference Therapy, Dose, and Mode of Administration	No reference therapy (both groups receiving active ingredient)

Duration of Treatment, Confinement, and Total Study Participation	The maximum screening period is 45 days. Each patient will receive multiple doses of ACH-0144471 for a total of up to 21 days and will be followed for 28 days after the final dose. The maximum duration for patient participation would be 94 days, including screening and follow-up. No overnight stays in the clinic are required; however, there are 2 extended clinic visits of 8 hours each. Patients will be asked to participate in a long-term follow up period in which clinic visits will occur approximately every 45 days for a maximum of 1 year; completion of these visits is not required.
Safety Assessments:	Safety assessments will include assessment of AEs, clinical laboratory tests, physical examination findings, 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:	Serial blood samples will be collected on Days 1 and 7 to determine plasma and/or serum concentrations of ACH-0144471. For each dose group, PK parameters (e.g., C_{max}, t_{max}, $AUC_{0\text{-}tau}$) will be calculated.
Pharmacodynamic and Efficacy Assessments	The primary PD assessment is C3 concentration in blood. A PK/PD analysis will be conducted to explore the relationship between study drug exposure and changes in C3 levels and/or other secondary and/or exploratory endpoints. Additional complement biomarkers to be evaluated for efficacy are: C4, AH50, CH50, AP Wieslab, AP hemolysis, Bb, Ba, factor B (fB), fD, and terminal complement complex sC5b9 (sC5b9). Blood and urine samples will be collected and stored for possible additional exploratory non-genetic complement biomarker testing that includes: iC3b complement cleavage fraction of C3b (iC3b), C3a, C5, C5a, properdin, fH, factor I (fI), autoantibodies to C3 nephritic factor and fH, and C3 convertase activity. These samples may also be used to assess patient response to vaccines. A blood sample will be collected and stored for possible exploratory evaluation of the genetic profile of selected complement components and regulators such as fH, fB, fI, fD, C3, membrane co-factor protein (MCP), complement fH related – 5 gene (CFHR-5), and thrombomodulin (THBD). Note: if historic genetic work-up is not available in dosed patients, genetic profiling may be conducted during the study. Additional serum/plasma/WBCs samples may be collected and retained for possible research use. All biological samples will be stored for a maximum of 3 years after completion of the Clinical Study Report.
Patient-Reported Outcomes Assessments	Patients enrolled in the trial will be interviewed by an independent outcomes researcher chosen by the Sponsor during the Screening period. Each patient will be interviewed once. Interviews will be conducted by phone using a semi-structured study-specific guide, will last approximately 30 minutes, and will be conducted by a trained psychologist/researcher, skilled in qualitative research. Interviews will be audio-recorded, transcribed, and analyzed using validated qualitative software. While completion of the interview is encouraged, it is not required, and eligible patients may participate in all other study activities whether or not they agree to the interview.

Statistical Methods:	Summary statistics will be provided for both original and change from baseline C3 levels at various time points at each dose level / group, during Treatment, Taper, and Follow-Up Periods. Results may be presented by C3G and IC-MPGN if such presentations would be clinically meaningful. The following safety endpoints will be summarized for each dose level: • SAEs • Treatment emergent adverse events (TEAEs) leading to discontinuation of the study medication. • TEAEs (related and regardless of relationship to study medication) • Laboratory abnormalities by toxicity grade PK concentrations at each time points and relevant PK parameters will also be summarized by dose level. Summary statistics will be presented, by dose level / group, for the relevant measurements (markers) from analysis of complement testing results. Time to achieving peak C3 level will be determined for each patient. Descriptive time-to-event analysis techniques may be employed to estimate the time lapse for ACH-0144471 of restoring C3 levels. The relationships between relevant AP component measurements and/or AP function with corresponding plasma concentrations and/or PK parameters will be explored to determine the nature of the correlations if they exist. Graphic presentation techniques will also be employed.

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ACE	Angiotensin converting enzyme
AE	Adverse event
AH50	A method measuring the overall activity of complement alternative pathway
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
CH50	A method measuring the overall activity of complement classical pathway
C_{max}	Maximum plasma concentration
CP	Classical pathway (of complement)
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DDD	Dense deposit disease
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
EM	Electron microscopy
ESRD	End stage renal disease
fB	(Complement) Factor B
fD	(Complement) Factor D
FDA	Food and Drug Administration
fH	(Complement) Factor H
fI	(Complement) Factor I
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	Insurance Portability and Accountability Act of 1996
HIV	Human immunodeficiency virus

Abbreviation	Definition
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
kDa	Kilodalton
LFC	Liquid filled capsule
LLN	Lower limit of normal
MAD	Multiple-ascending dose
MCP	Membrane Co-Factor Protein
MDRD	Modified Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MGUS	Monoclonal gammopathy of unclear significance
MM	Medical monitor
MMF	Mycophenolate mofetil
MPA	Mycophenolic acid
msec	Millisecond
NOAEL	No observed adverse effect level
PAS	Periodic acid-Schiff
PD	Pharmacodynamic(s)
PI	Principal investigator
PK	Pharmacokinetic(s)
PR interval	Period that extends from the beginning of the P wave until the beginning of the QRS complex
PT	Prothrombin time
PTT	Partial thromboplastin time
QRS	Group of electrocardiogram waves comprising the Q, R, and S waves
QTcF	QT interval Fridericia Correction Formula
RBC	Red blood cells
Relative BA	Relative bioavailability study
RR	Respiration rate
SAD	Single-ascending dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
sC5b-9	Soluble terminal complement complex
SD	Standard deviation
TEAE	Treatment-emergent adverse event
THBD	Thrombomodulin
t_{max}	Time after administration of a drug when the maximum plasma concentration is reached
ULN	Upper limit of normal
WBC	White blood cells

1 Introduction

ACH-0144471, a small molecule, orally administered, factor D (fD) inhibitor, is in development by Achillion Pharmaceuticals, Inc. for the treatment of complement-related diseases. Factor D is a serine protease that catalyzes the cleavage of factor B, a rate-limiting step in alternative pathway (AP) activity. By inhibiting fD, ACH-0144471 potently and specifically inhibits AP activity.

Because C3 glomerulopathy (C3G) is a disease of AP over-activity, ACH-0144471 represents an ideal therapeutic approach to C3G, as it has the potential to reverse the underlying pathophysiology of the disease. In addition, other renal diseases, such as IC-MPGN, in which complement likely plays a key role, may also be attractive therapeutic targets.

This protocol is a multiple-center, open-label study in which patients with C3G or idiopathic IC-MPGN will receive ACH-0144471 for 2 weeks, followed by a one week taper. In the preceding single-ascending dose (SAD) and multiple-ascending dose (MAD) 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 patients with C3G or idiopathic IC-MPGN. Doses for this study were selected based on available data from the ongoing SAD, MAD, and relative bioavailability (Relative BA) studies in healthy volunteers.

1.1 Results of Nonclinical Studies

Please refer to the Investigator's Brochure [1] for an overview of the properties of ACH-0144471 and the results of the nonclinical investigations conducted.

1.2 Previous Human Experience with ACH-0144471

1.2.1 Completed Studies

Three clinical studies with ACH-0144471 have been conducted: ACH471-001 (SAD), ACH471-002 (MAD) and ACH471-006 (Rel BA). One hundred and fifteen (115) healthy volunteers have participated in clinical trials with ACH-0144471, of which 87 have received ACH-0144471, and the remaining received placebo. Results from all 3 studies are presented in the Investigator's Brochure [1].

The SAD study was performed to evaluate the safety and tolerability of single ascending doses of ACH-0144471. Healthy volunteers were dosed with ACH-0144471 in five separate groups. Groups 1 through 4 received escalating oral doses in the fasted state of 200, 600, 1200, and 2400 mg, respectively (2400 mg was administered as two divided doses of 1200 mg separated by 12 hours). Group 5 received a 1200 mg oral dose in the fed state. Overall, ACH-0144471 was well-tolerated at all dose levels. There were no drug-related serious adverse events (SAEs), no treatment-emergent adverse events (TEAEs) leading to study discontinuation, and no study-drug related Grade 3 or 4 TEAEs. There were no trends suggesting a drug-related effect on TEAEs, laboratory results, electrocardiogram (ECG) parameters, or vital signs. There were no dose-related trends for infection, and no evidence for drug-induced liver injury.

The MAD study was conducted to evaluate the safety and tolerability of multiple ascending doses of ACH-0144471 and to determine a recommended dose and schedule for treatment of patients in phase 2 studies. Healthy volunteers were dosed with ACH-0144471 in four separate groups. Groups 1 through

3 received multiple daily doses of 200, 500, and 800 mg, respectively, twice daily for 14 days. Group 4 received doses of 75 mg every 8 hours for 7 days. All doses were given in the fasted state. Based on preliminary information, ACH-0144471 administered as 200 mg every 12 hours for 14 days was well-tolerated. CCI [redacted] In Group 4, a dosing regimen of 75 mg administered every 8 hours for 7 days was well-tolerated and resulted in ACH-0144471 trough concentrations that have the potential for efficacy in C3G, IC-MPGN, and other complement-mediated diseases.

The SAD and MAD studies were conducted using liquid-filled capsules (LFC), while studies in patients will be performed using a tablet formulation. A Relative BA study was performed to compare bioavailability of the LFC and the tablet formulations. This was a randomized, crossover, open-label study to assess the relative bioavailability of ACH-0144471 in tablet and softgel capsule formulations relative to the extemporaneously prepared LFC used in the SAD and MAD studies. Based on preliminary information, $AUC_{0-\infty}$ was bioequivalent and C_{max} slightly lower (19%) for ACH-0144471 tablets administered with food relative to the LFC formulation given under fasting conditions as in the SAD and MAD studies. ACH-0144471 was well-tolerated in this study, and there were no SAEs, no discontinuations due to TEAEs, and no drug-related Grade 3 or 4 TEAEs. As discussed in Section 3.2.2, the preliminary data from this study support the transition from the liquid filled capsule (LFC) dosage form used in the SAD and MAD studies to the tablet dosage form to be used in this study.

1.2.2 Ongoing Studies

ACH471-010 is a 3-part study with each part being an open-label, fixed sequence, 2-treatment study in healthy subjects. This study will investigate potential drug-drug interactions between ACH-0144471 and midazolam, between ACH-0144471 and fexofenadine, and between ACH-0144471 and mycophenolate mofetil (MMF). In each part of the study, subjects will receive a single dose of the potentially interacting drug (midazolam, fexofenadine, or MMF) in Period 1, followed by intensive blood sampling. In Period 2, subjects will receive multiple daily doses of ACH-0144471. On Day 4 of Period 2 (after steady-state has been reached for ACH-0144471), subjects will receive a single dose of the potentially interacting drug (midazolam, fexofenadine, or MMF), followed by intensive blood sampling. In both Period 1 and Period 2, the duration of the sampling will vary between parts, depending on the characteristics of the potentially interacting drug. This study is ongoing, and no results are available at this time.

ACH471-100 is a multiple-center, open-label, multiple dose study to evaluate the efficacy of ACH-0144471 in currently untreated paroxysmal nocturnal hemoglobinuria (PNH) patients. Each patient will receive multiple doses of ACH-0144471 for a total of 28 days during Part 1, and may be treated for an additional 8 weeks if they participate in Part 2. Currently, two patients with PNH have been treated with ACH-0144471 at doses ranging from 100 to 150 mg TID. Preliminary data suggest that these doses have an acceptable safety profile, including no evidence of clinically significant ALT elevations. Both patients started the study at a dose of 100 mg TID, and then increased to 150 mg TID based on Day 13 results which demonstrated improvement in, but not optimal control of, hemolysis. Hemolysis was considered improved based on a clinically significant improvement in hemoglobin and a substantial downward trend in lactate dehydrogenase (LDH) in both patients. At 150 mg TID, hemoglobin concentrations were maintained within acceptable ranges, but the LDH response was suboptimal, as levels remained higher than normal. This data demonstrates that although doses of 100 and 150 mg TID inhibit complement and decrease hemolysis in PNH patients, higher doses may be

needed for optimal control. Therefore, after consultation with the PI, PNH experts, and a hepatic safety advisory panel, Achillion has amended this PNH protocol to assess doses as high as 200 mg TID.

1.3 Background

1.3.1 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.

1.3.2 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]. The clinical course is characterized by variable amounts of proteinuria, hematuria, hypertension, and decreased renal function, with approximately 30%-50% of patients reaching end-stage renal disease (ESRD) within 10 years of diagnosis [7, 9, 10, 11]. The diagnosis is based on predominant deposition of C3 in the glomerulus on renal biopsy along with clinical evidence of hyper AP activity. 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 [11].

Unfortunately, no specific therapy has proven effective for the treatment of C3G. Therefore, care is 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. Treatment is otherwise focused on management of hypertension, proteinuria and the manifestations of chronic kidney disease. 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 [11, 12].

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 evidence of 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 [13, 14]. These studies confirmed that removal of fD prevented the renal pathogenesis of C3G in the factor H-deficient mice.

1.3.3 Potential Advantages of ACH-0144471 in the Treatment of C3G

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. Its use has been reported in more than 20 patients with C3G, of whom the majority were reported as individual cases, and only six were reported as part of an open-label proof-of-concept study [12, 15]. Of those presented as case reports, the majority had a successful response. However, this may represent a publication bias, as the results of the open-label trial were less impressive. Specifically, two of the six patients in the open-label trial seemed to have a good response, confirmed by worsening upon discontinuation of eculizumab. Of the remaining four patients, three had an increase in serum creatinine while on treatment. Based on the results of this open-label trial, 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, 11, 12, 15]. 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 [15].

A fD inhibitor like ACH-0144471, which inhibits directly at the level of the AP C3 convertase formation, is expected to provide superior efficacy than eculizumab or complement inhibitors that target the other complement pathways. 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 [13, 14]. 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 [11, 16].

1.3.4 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 idiopathic IC-MPGN. Patients with idiopathic 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 there are current hypotheses suggesting that the majority of IC-MPGN is attributable to overactivity of the classical pathway, those patients with a low C3 and a normal C4 are likely to have significant overactivity of the alternative pathway [17]. Therefore, IC-MPGN patients with a low C3 and a normal C4 may benefit from alternative pathway inhibition.

2 Study Objectives

2.1 Primary Objective(s)

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

2.2 Secondary Objective(s)

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

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

2.3 Other Objective(s)

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

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

3 Investigational Plan

3.1 Overall Study Design and Plan

This open-label study will enroll up to 10 patients (between the ages of 16 and 65 years) with biopsy-confirmed C3G or idiopathic IC-MPGN and a low C3. The trial will evaluate the ability of ACH-0144471 to increase C3 levels via inhibition of fD by enrolling patients in two groups. Group 1 will serve as a sentinel group consisting of two patients who will receive ACH-0144471 at a dose of 100 mg three times daily (TID) for 14 days followed by a taper over 7 days. Group 2 will be initiated upon confirmation that dosing was well-tolerated in Group 1 (based on Group 1 safety data through at least Day 28), and may include up to 8 patients. As discussed in Section 3.2.2, the dose for Group 2 will be selected based on the available safety, PK, and PD data from Group 1, but will not exceed 200 mg TID. The 100 mg TID dose level for Group 1 was selected based on safety, PK, and pharmacodynamics (PD) data from the Phase 1 SAD and MAD studies (ACH471-001 and ACH471-002, respectively), which demonstrated that similar dosing regimens in healthy volunteers were well-tolerated and able to inhibit the alternative pathway of complement. In addition, the relative bioavailability study (ACH471-006) supports transition from the liquid filled capsule (LFC) dosage form used in the SAD and MAD studies to the tablet dosage form to be used in this study. All patients will receive active drug.

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

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

Safety, PK, and pharmacodynamic (PD) data will be obtained at multiple time points during the Treatment, Taper and Follow-Up periods. The primary endpoint for the study will be changes in C3 levels. Additional endpoints include the incidence of AEs, SAEs, and discontinuations due to AEs. Clinical measures of renal disease will be monitored (e.g., creatinine, proteinuria, and blood pressure), but are not expected to improve in this short-duration non-therapeutic trial.

The primary pharmacodynamic assessment is C3 concentration in serum/plasma. In addition, inhibition of AP activity will be evaluated *ex vivo* using serum collected during the study with the AP Wieslab ELISA and AP hemolysis assay. AH50 and CH50 functional assays will be used to qualitatively evaluate the effect of ACH-0144471 on AP and classical pathway (CP) activity. Factor D concentration will be measured at baseline to determine whether it is elevated in the setting of underlying renal disease, as well as over the course of the study to evaluate any changes after dosing with ACH-0144471. Factor Bb concentration will be measured as it is the cleavage product generated by factor D. The

concentrations of additional complement-associated biomarkers will be determined, as described in Section 6.11.2.

Finally, a PK/PD analysis will be conducted to explore the relationship between study drug exposure and changes in C3 levels and/or other secondary and/or exploratory endpoints.

Most concomitant medications will be considered on a case-by-case basis, and decisions made jointly between the principal investigator (PI) and Sponsor, based on knowledge of ACH-0144471 and risks for drug-drug interactions, as well as potential to interfere with interpretation of the study. Further information on concomitant medications is provided in Section 5.5.2.

Based on data from Groups 1 and 2, additional patients may be added to study additional dose levels or regimens (not to exceed 200 mg TID for two weeks, followed by a 7-day taper) or additional C3G or IC-MPGN patients.

Figure 1. Study Schematic

	Screening Period	Treatment Period														Taper Period**						
Day	-45 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Clinic Visits	X	X*	X		X	X		X*	X		X		X		X	X	X	X				X
Dose with ACH-0144471		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Follow-up Period																											
Day	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49
Clinic Visits			X				X							X														X
Dose with ACH-0144471																												

Patients in Group 1 and Group 2 will follow the same schedule.
* Intensive PK days.
** If a patient has a serum C3 level >125% ULN after at least 7 days of treatment, then the taper will be initiated before completion of 14 days of dosing.

3.2 Rationale for Study Design

3.2.1 Justification of Design

This proof-of-mechanism study is an open-label study whose primary objective is to determine whether circulating C3 levels can be increased during two weeks of treatment with ACH-0144471. Restoration of C3 levels to normal would indicate correction of uncontrolled AP activation, the central pathophysiological abnormality in C3G, and likely in some cases of IC-MPGN. The overactive AP leads to excessive consumption of C3, resulting in low levels of C3. As an inhibitor of the AP, ACH-0144471 should mitigate this excessive C3 consumption, and return C3 levels toward normal within a few days. Since the increased C3 consumption results in accumulation of C3 breakdown products in the renal glomerulus and renal damage, prevention of excessive AP activity is predicted to prevent protect the glomerulus from further C3 deposition as well as ameliorate existing C3 deposits, preventing further disease progression and allowing recovery of reversible renal injury. A rise in C3 in this study would demonstrate that ACH-0144471is able to reverse the underlying disease pathophysiologic driver in these diseases. This data would provide a strong justification for proceeding with a trial of therapeutic duration to determine if inhibition of the AP and increases in C3 will translate into improvement in renal manifestations of disease, such as C3 deposition in glomeruli, glomerular inflammation, proteinuria, and estimated glomerular filtration rate (eGFR).

The inclusion and exclusion criteria have been selected to ensure that enrolled patients have one of the relevant diseases (C3G or IC-MPGN), have a low enough C3 to allow an increase to be detected, and to

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. The key criteria that ensure that the patients have C3G, or the relevant subset of IC-MPGN, are the review of historical biopsy by a central study pathologist, demonstrated evidence of alternative pathway over-activation, and lack of evidence of another underlying disease to which the renal disease may be secondary (such as infections, malignancies and autoimmune disorders). In addition, the patient must have had the diagnosis for at least 3 months to avoid inadvertent inclusion of patients with post-infectious glomerulonephritis. The C3 cut-off selected was <50% of the lower limit of normal (LLN), which allows adequate opportunity for improvement in C3 before reaching the normal range. Furthermore, low C3 with normal (or near-normal) C4 is strong evidence for a selective overactivity of the AP. Although available clinical and non-clinical data to date suggests that renal clearance does not play a major role in drug disposition, an eGFR cut-off of 45 mL/min/1.73 m^2 was selected, as factor D levels may be elevated in patients with renal impairment. This eGFR criteria takes into consideration that this is a short duration non-therapeutic trial in which there is no opportunity for dose adjustment and no likely clinical benefit for patients.

In summary, the study is designed with regard to patient inclusion/exclusion, duration of treatment, monitoring, and PK/PD assessments to inform whether ACH-0144471 and fD inhibition can improve and/or normalize C3 levels in patients with C3G or IC-MPGN, while minimizing the risk to patients. A two-week treatment duration was selected as changes in C3 may begin as early as the first 24 hours, but may take several days. With two weeks of treatment, but intensive PK/PD assessments in the first 24 hours, we believe we have maximized our opportunity to characterize the rate of change in C3, and may even have the opportunity to observe the new steady-state levels of C3 in the setting of fD inhibition. The study includes a taper period and daily clinic visits during the first three days of the taper to mitigate any risk of rebound AP activity upon drug discontinuation. In the event that C3 levels rise very quickly, and do not reach a new steady-state before exceeding 125% of the ULN, or 3× the baseline level (provided this is greater than or equal to the LLN), then the taper will begin early.

3.2.2 Justification of Dose

The level of AP inhibition required for efficacy in C3G patients is unknown. Eculizumab, the only commercially available complement inhibitor, is effective in preventing hemolysis in PNH and may benefit some patients with C3G. The pharmacodynamics and potential for clinical efficacy for ACH-0144471 is primarily associated with maintenance of exposure above a target trough level. Exploratory ex vivo AP hemolysis experiments using patient PNH cells showed that ACH-0144471 at concentrations of >20 ng/mL provided protection from hemolysis similar to eculizumab at a concentration of 35 µg/mL (an efficacious eculizumab trough concentration in PNH patients). These data suggested that dosing regimens that provide plasma trough ACH-0144471 concentrations of >20 ng/mL may demonstrate efficacy in PNH patients.

An ACH-0144471 regimen of 200 mg administered every 12 hours for 14 days to healthy volunteers was well tolerated and resulted in a mean plasma trough concentration above 20 ng/mL. PK modeling based on data from the SAD and MAD studies predicts that a dose regimen of 100 mg TID will result in a higher plasma trough ACH-0144471 concentration while producing a lower C_{max} and that ACH-0144471 trough concentrations of >30 and >60 ng/mL can be achieved with doses of 100 and 150 mg 3 times daily (TID), respectively.

Based on the above analysis, the starting dose of ACH-0144471 in the first PNH clinical trial (ACH471-100) was selected to be 100 mg TID. The first two patients in this study both started dosing at 100 mg TID, and were escalated to a dose of 150 mg TID after Day 13. As described in Section 1.2.2, both patients have tolerated the drug well, and no clinically significant increases in ALT have been noted at either dose level. At steady-state on Day 20, mean C_{max}, C_{trough}, and AUC were within the expected exposures based on healthy volunteer PK data. In both patients, hemoglobin concentrations were maintained within acceptable ranges but the LDH response was suboptimal, as levels, although dramatically decreased upon initiation of therapy with ACH-0144471, tended to remain higher than normal even after 28 days of drug treatment, suggesting that higher concentrations are required to maintain the clinical response. Therefore, after consultation with the PI, PNH experts and a CCI Achillion has amended the PNH protocol to assess doses as high as 200 mg TID.

Since it is not known whether the ideal dose for C3G will be the same, higher, or lower than that for PNH, the initial dose for this study will be the same as that initially selected for the first PNH study (ACH471-100), and the two patients in Group 1 will receive a dose of 100 mg TID.

The dose for Group 2 will be selected with the goal of identifying a dose which can return AP function toward normal, as measured by improvement in serum and/or plasma C3 concentration. This dose decision will be informed by the safety, PK, and PD data from Group 1, as well as by emerging data from other clinical and non-clinical studies with ACH-0144471, including the PNH studies. Group 2 will not initiate dosing until it has been confirmed that dosing was well-tolerated in Group 1 (based on safety data through at least Day 28). The dose for Group 2 could be lower, higher or the same as Group 1, but will not exceed 200 mg TID. Of note, a dose of 200 mg TID is likely to be assessed in PNH patients prior to initiation of Group 2.

CCI

CCI

3.2.3 Stopping Criteria

Any decision to terminate drug administration in one or more groups will be made by the Sponsor Medical Monitor (MM) based on ongoing review of safety data from all enrolling sites. 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 a group, the Achillion MM will decide whether or not the taper should be implemented.

The PI may stop dosing in any patient who meets an individual stopping rule (Section 3.2.3.2); however, the Achillion MM should be notified immediately, if possible before dosing is terminated. When dosing is stopped in an individual patient, the PI should consider whether it is in the best interest of the patient to discontinue dosing immediately or to taper (as described in Section 5.2). Whenever possible, this 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 patient should advance to the Taper and/or Follow-Up Periods, as relevant, and complete all activities in these periods as described in Appendix 1.

3.2.3.1 Group Stopping Rules

Dosing will be terminated if one or more of the following occurs within a dose group:

- Two or more patients experience the same or similar study drug-related SAE
- Two or more patients experience the same or similar study drug-related Grade 4 or higher AEs

If dosing is terminated in a group, all patients 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.

3.2.3.2 Stopping Rules for Individual Patients

Any individual patient who meets any of the following criteria will be discontinued from further dosing:

- The patient experiences any SAE assessed as related to treatment with ACH-0144471
- The PI believes that patient continuation in the study is not advisable, or the patient withdraws from the study or meets one of the conditions described in Section 6.20, including, but not limited to:
    - The patient becomes pregnant
    - Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree
    - Patient 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

3.2.4 Safety Considerations

3.2.4.1 Risk of Infection

One of the primary functions of the complement system is to fight infections as part of the innate immune system. As suggested by individual case reports with complement system deficiencies including complement factor D, inhibition of the complement system may result in a lifetime increased

risk of infection, notably with *Neisseria meningitidis (N. meningitidis)* [18,19, 20], and other encapsulated organisms.

Because of this potential risk, special safety precautions will be taken for patients participating in ACH471-201. Patients will be required to be previously vaccinated, or to receive vaccinations for *N. meningitidis* (serogroups A, C, Y and W135), *Streptococcus pneumoniae* (*S. pneumonia*e), and *Haemophilus influenzae* (*H. influenzae*) prior to receiving ACH-0144471 (see Section 6.4).

Throughout the study, including at clinic visits, patients will be monitored for the development of fever. A specific Fever Management Plan (Appendix 3) has been developed for this study.

Patients will also be counseled about behaviors to avoid during the study, and to recognize early and react appropriately to signs and symptoms of infection (Appendix 3).

CCI [redacted]

CCI [redacted]

3.3 Study Duration and Dates

The screening period is up to 45 days. Each patient will receive multiple doses of ACH-0144471 for a total of up to 21 days and will be followed for 28 days after the final dose. The duration for patient participation would be approximately 94 days, including screening and follow-up. No overnight stays in the clinic are required; however, there are 2 extended clinic visits of 8 hours each (Days 1 and 7; see Section 7.2.1). Patients will be asked to participate in a long-term follow up period in which clinic visits will occur approximately every 45 days for a maximum of 1 year; completion of these visits is not required.

4 Study Population Selection

4.1 Study Population

This study will be conducted in up to 10 patients with low C3 due to either C3G or IC-MPGN who meet eligibility criteria.

4.2 Inclusion Criteria

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

1. Must be between the ages of 16 and 65 years, inclusive
2. Must have a clinical diagnosis of C3G (C3 glomerulonephritis [C3GN] or dense deposit disease [DDD], the 2 types of C3G) or idiopathic immune-complex membranoproliferative glomerulonephritis (IC-MPGN) by renal biopsy at least 3 months prior to dosing, with the pathologic diagnosis verified by review of the renal biopsy by the study central pathologist
3. C3 must be <50% of the LLN
4. C4 must be >90% of the LLN
5. Female patients of childbearing potential must either agree to abstinence or to use two effective methods of contraception as defined in Section 5.5.5 from screening through 3 months after the last dose of ACH-0144471. Females, who are of non-childbearing potential as defined in Section 5.5.5 need not employ a method of contraception.
6. Male patients must either agree to abstinence or to use two effective methods of contraception, as defined in Section 5.5.5, throughout the dosing period and for at least 3 months after the last dose of ACH-0144471. Males who are surgically sterile need not employ additional contraception. Males must agree to not donate sperm throughout the dosing period and for at least 3 months following the last dose of ACH-0144471.
7. Must be capable of providing written informed consent, 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
8. Must be up-to-date on routine vaccinations, or willing to be brought up-to-date, based on local guidelines
9. Must be willing to comply with study-specific vaccination requirements for *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Neisseria meningitidis* strains A, C, W, and Y
10. Must be willing, at all times for the duration of study participation, to have transportation and telephone access, and to be within one hour of an emergency medical center

4.3 Exclusion Criteria

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

1. History of a major organ transplant (e.g., heart, lung, kidney, liver) or hematopoietic stem cell/marrow transplant. Individuals receiving renal replacement therapy are also excluded

2. History or presence of any clinically relevant co-morbidities that would make the patient inappropriate for the study (for example, is likely to result in deterioration of the patient's condition, affect the patient's safety during the study, or confound the results of the study), in the opinion of the PI
3. Evidence of monoclonal gammopathy of unclear significance(MGUS), infections, malignancy, autoimmune diseases, or other conditions to which C3G or IC-MPGN may be secondary
4. Patients with other renal diseases that would interfere with interpretation of the study
5. Presence or evidence of hepatobiliary cholestasis
6. Known Gilbert's syndrome and/or patients with a history suggestive of Gilbert's syndrome
7. Females who are pregnant, nursing, or planning to become pregnant during the study or within 90 days of study drug administration or patients with a female partner who is pregnant, nursing, or planning to become pregnant during the study or within 90 days of study drug administration
8. Estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2 at the time of screening or at any time over the preceding four-weeks. Calculation of eGFR will be based on the Modified Diet for Renal Disease (MDRD) equation for patients ≥18 years of age, and will be based on the Schwartz equation for patients <18 years of age
9. History of febrile illness, a body temperature >38°C, or other evidence of a clinically significant active infection, within 14 days prior to study drug administration
10. Patients with evidence of human immunodeficiency virus (HIV), hepatitis B or hepatitis C infection (positive serology for HIV- antibody (HIV Ab), positive hepatitis B surface antigen (HbsAg), or positive anti-HCV antibody (HCV Ab) at Screening or historically)
11. History of meningococcal infection, or a first-degree relative or household contact with a history of meningococcal infection
12. Contraindication to one or more of the required vaccinations
13. 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.
14. Participation 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 study drug administration
15. Receipt of eculizumab at any dose or interval within the past 75 days prior to dosing
16. Use of tacrolimus or cyclosporine within 2 weeks of the first dose of ACH-0144471
17. 12-lead ECG with a QTcF >500 msec or findings which, in the opinion of the PI, could put the patient at undue risk

18. Any of the following laboratory abnormalities at screening:
    - Alanine transaminase (ALT) > ULN
    - Aspartate aminotransferase (AST) > ULN
    - Alkaline phosphatase (ALP) > 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 patient inappropriate for the study
19. Donation of blood or blood products in excess of 500 mL within a 60 day period prior to the first dose of the current study
20. Receipt of blood or blood products within 30 days of screening
21. Clinically significant history of drug allergy as determined by the Investigator
22. 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 as a tablet formulation containing the drug substance, [redacted]

5.2 Treatment(s) Administered

ACH-0144471 tablets will be administered at one of two dose levels as multiple doses over a period of 14 days (Treatment Period), followed by a taper over the next 7 days (Taper Period) to minimize the potential adverse effects of a rapid surge in complement activity following drug withdrawal. If a patient has a serum C3 level that, at 2 consecutive evaluations, is greater than 125% the ULN, or is greater than 3× their baseline (provided this is greater than or equal to the LLN), then the taper period will be initiated before completion of 14 days of dosing. In order to ensure that an early taper is implemented when appropriate, it is important that investigators receive and review C3 levels in a timely fashion.

The dosing regimen for Group 1 is described in Table 1.

Table 1. Dose Levels for Group 1

Study Day	Dose
Treatment Period (Days 1-14)	100 mg TID
Days 15, 16, 17 (Taper Days 1, 2, 3)[1]	100 mg BID
Days 18, 19 (Taper Days 4, 5)	50 mg BID
Days 20, 21 (Taper Days 6, 7)	50 mg QD

1 If the taper is initiated before 14 days of dosing, follow this schedule starting with Taper Day 1 on the first day of the taper.

The dose and taper schedule for Group 2 will be determined based on data from Group 1, with a maximum possible dose of 200 mg TID followed by a 7 day taper.

5.3 Selection of Timing and Dose for Each Patient

Patients will take ACH-0144471 tablets 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. Patients should be instructed to finish a moderate fat meal or snack within 15 minutes prior to dosing with ACH-0144471. 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.

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 patients on how to take their study medication at home between visits. Patients will be instructed to fast for at least 8 hours and to 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. Patients should be instructed to finish a moderate fat meal or snack within 15 minutes prior to dosing with ACH-0144471. Patients will be required to bring back their study drug at each visit so that study site personnel may perform drug accountability.

5.3.2 Home Dose Administration Instructions

Patients should be instructed to finish a moderate fat meal or snack within 15 minutes prior to dosing with ACH-0144471. Patients should also take their medication such that doses are as close as possible to 8 hours apart.

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

5.4 Method of Assigning Patients to Treatment Groups

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

The first two patients will form Group 1, and will receive ACH-0144471 at a dose of 100 mg TID. Group 2 will be initiated upon confirmation that dosing was well-tolerated in Group 1 (based on Group 1 safety data through at least Day 28), and may include up to 8 patients. The dose for Group 2 will be selected based on the data from Group 1, but will not exceed 200 mg TID.

5.5 Restrictions

5.5.1 Prior Therapy

Patients may not have received another investigational agent within 30 days or 5 half-lives of the investigational agent prior to dosing with ACH-0144471, whichever is greater. Patients may not have received eculizumab within 75 days prior to dosing with ACH-0144471. Patients may not have received tacrolimus or cyclosporine within 2 weeks prior to dosing with ACH-0144471.

5.5.2 Concomitant Therapy

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].

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 patient's case report form (CRF). The following are some general guidelines for concomitant medication use based on currently available data:

- Concomitant administration of folic acid, and/or erythropoiesis-stimulating agents is permitted if on stable doses for at least 4 weeks prior to start of study drug.
- 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 steroids is permitted if on stable doses for at least 3 months prior to start of study drug.
- Concomitant administration of mycophenolate mofetil (MMF) may be considered based on emerging data for ACH-0144471, but may require reduction of MMF dose and/or measurement of mycophenolic acid (MPA) levels.
- Oral, injectable, implantable, transdermal, or intravaginal hormonal therapies are allowed for either contraception or hormonal replacement therapy.
- Concomitant administration of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), loop diuretics, and thiazide diuretics should be allowable since these drugs are renally cleared, and it is unlikely that ACH-0144471 will interfere with their pharmacokinetic disposition.
- If it is necessary to treat a fever (see Appendix 3), 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.

5.5.3 Fluid and Food Intake

Patients should be instructed to finish a moderate fat meal (~550 calories with approximately 25% - 35% of the calories from fat that should be entirely consumed within 30 minutes) or snack within 15 minutes prior to dosing with ACH-0144471. Patients should also take their medication such that doses are as close as possible to 8 hours apart.

5.5.4 Patient Activity and Other Restrictions

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

5.5.5 Contraception

All male participants who have not had a vasectomy must use effective contraception from the first day of dosing (Day 1) through at least 3 months after their last dose of study drug. Effective contraception for males is defined as abstinence, or use of a condom plus one of the following for a female partner:

- Intrauterine device or barrier (e.g., occlusive cap)
- Oral, injectable, implantable, transdermal, or intravaginal hormonal contraceptive

Male patients must agree to refrain from sperm donation from the first day of dosing (Day 1) until at least 3 months after their last dose of study drug.

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

- Surgical sterilization by hysterectomy, bilateral salpingo-oophorectomy or oophorectomy, at least 6 months prior to dosing
- Postmenopausal with amenorrhea for at least 1 year prior to dosing and FSH serum levels consistent with postmenopausal status

Female patients of child-bearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline, and must agree to the use of effective contraception from the date of screening to 3 months after their last dose of study drug. Effective contraception for females is defined as abstinence or use of a condom for the male partner plus one of the following:

- Intrauterine device or barrier (e.g., occlusive cap)
- Oral, injectable, implantable, transdermal, or intravaginal hormonal contraceptive
- Bilateral tubal ligation or fallopian tube inserts

5.6 Treatment Compliance

Treatment compliance assessments shall be performed at each visit. Patients will be required to bring their supply of ACH-0144471 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.

Patients will record the time they take each daily dose of ACH-0144471 and will 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 patient directly.

5.7 Packaging and Labeling

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

- 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 Statement 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. Patients should be instructed to keep their study medications at room temperature.

Patients will be required to bring back their study drug at each 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 patient dispensing records and returned or destroyed drug. Dispensing records will document quantities received from Achillion Pharmaceuticals, Inc. (or designee) and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, patient 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, Inc. 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, Inc. requirements for disposal, arrangements will be made between the site and Achillion Pharmaceuticals, Inc. 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

The PI or designee is responsible for administering and obtaining freely given consent, in writing, before entering the patient into the study and performing any study-related procedures. Each patient 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 patients being accepted into the study. Because participation in the patient-reported outcomes interview (Section 6.16) is encouraged but not required, patients will be asked to provide a separate informed consent for this activity.

6.2 Medical History

At Screening, the PI or designee will interview each patient and obtain a complete medical and medication history to determine whether the patient meets the eligibility criteria. The history should include the specific type of C3 glomerulopathy (for C3G patients), date of diagnosis of C3G or IC-MPGN, 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 30 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. The history should also include the results of any genetic testing related to the disease, and a full vaccination history. The medical/medication history will be reviewed at each visit and at the Day 49 follow-up visit, as applicable and as is outlined in the Schedule of Assessments (Appendix 1). The medical history must be recorded in the patient's source documents and in the patient's CRF.

6.3 Review of Historical Renal Biopsy

For each patient, the diagnosis of C3GN, DDD, or IC-MPGN must be confirmed by the study's central pathologist(s). The site will need to obtain renal biopsy slides for each patient, and provide them to the designated central pathology laboratory. Digitally scanned slides are also acceptable if the quality is adequate. Representative diagnostic slides should be provided and should include hematoxylin and eosin (H&E), periodic acid-Schiff (PAS), methenamine silver, and trichrome stains. If immunohistochemistry has been performed on paraffin sections those slides should also be submitted. In addition, electron microscopy (EM) images should be sent and also images of immunofluorescence where available. A copy of the full biopsy report should also be provided. All information should be provided in an anonymized fashion. Detailed instructions will be provided in a separate manual.

6.4 Vaccination

As discussed in Section 6.2, a full vaccination history will be gathered. The need for vaccinations against *Neisseria meningitidis*, serogroups A, C, Y, and W135, *Streptococcus pneumoniae*, and *Haemophilus influenzae* will be evaluated independently, as discussed in the following sections. Any patients who do not have a sufficient history of these particular vaccines will receive their vaccines during the screening period. For any vaccines given as part of this study, full identifying information,

including the brand, should be recorded in the patient's CRF. The vaccination schedule for each is provided in Table 2, Table 3, and Table 4. The brand of vaccine is not specified to allow flexibility based on the available of vaccines in different geographic regions. Note, however, that it is important that the administered meningococcal vaccine is a quadrivalent ACWY conjugate vaccine and not a monovalent serogroup C vaccine, or serogroup B vaccine. In addition, it should be noted that the administered *Streptococcus pneumoniae* vaccine should be the 13-valent vaccine, and not the 23-valent vaccine. Samples will be collected during at the times indicated in the Schedule of Assessments (Appendix 1) to evaluate patient response to the vaccines.

Table 2. Vaccination Schedule for *Neisseria meningitidis*, Serogroups A, C, Y, and W135

	Not vaccinated or vaccination status unknown	**Received 1 dose of vaccine previously**	**Received 2 doses of vaccine >5 years ago**	**Received 2 doses of vaccine <5 years ago**
At least two weeks prior to dosing with ACH-0144471	Administer 1 dose of vaccine	Administer 1 dose of vaccine	Administer 1 dose of vaccine	No action required prior to ACH-0144471 dosing

Table 3. Vaccination Schedule for *Streptococcus pneumoniae*

	Streptococcus pneumoniae				
	Not vaccinated or vaccination status unknown	**Vaccinated >2 years ago with 23-valent conjugate vaccine**	**Vaccinated <2 years ago with 23-valent conjugate vaccine**	**Vaccinated >5 years ago with 13-valent conjugate vaccine**	**Vaccinated <5 years ago with 13-valent conjugate vaccine**
At least two weeks prior to dosing with ACH-0144471	Administer 1 dose of 13-valent conjugate *S. pneumoniae* vaccine	Administer 1 dose of 13-valent conjugate *S. pneumoniae* vaccine	No action required	Administer 1 dose of 13-valent conjugate *S. pneumoniae* vaccine	No action required

Table 4. Vaccination Schedule for *Haemophilus influenzae*

	Not vaccinated or vaccination status unknown	**Vaccinated >5 years ago**	**Vaccinated <5 years ago**
At least two weeks prior to dosing with ACH-0144471	Administer 1 dose of *H. influenzae* vaccine	Administer 1 dose of *H. influenzae* vaccine	No action required

6.5 Physical Examination

A complete physical examination will be conducted by the PI (or designee) at Screening, Day 1, and the Day 49 visit. 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 (height and BMI at Eligibility visit only). Measurements of height and weight should be taken with the patients in light clothing or underwear and without shoes.

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). 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 patient's source documents and in the patient's CRF as an adverse event.

6.6 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. Vital signs may be measured using an automated vital signs monitor, although manual measurements of blood pressure are preferred. All blood pressure measurements should be taken on the same arm throughout the study. Vital sign values, including whether measured manually or via an automated monitor, will be recorded in the patient's source documents and in the patient's CRF.

6.7 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 site will provide each patient with an oral thermometer, and train each patient on its proper use. In addition, the Fever Management Plan (Appendix 3) outlines measures that the site must take to ensure that outside the clinic, the patient will be able to promptly identify a fever, and seek emergency medical attention if needed. Any temperature measurement ≥38.0°C, measured either at the clinic or by the patient outside the clinic, requires action as outlined in the Fever Management Plan (Appendix 3).

6.8 Electrocardiography

The PI or designee will obtain ECG measurements at the times indicated in Appendix 1. All ECG recordings should be 12-lead, and should be performed after the patient has rested quietly for at least 5 minutes in a supine position 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 place 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 6.17.1 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 patient's source documents and in the patient's CRF. Any clinically significant finding must be reported as an adverse event.

6.9 Clinical Laboratory Tests

Blood and urine samples will be collected for safety and pharmacodynamic laboratory evaluation according to Table 5 below, at the times listed in Appendix 1. Patients will be fasted and 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.

Table 5. Clinical Laboratory Tests

Hematology	Chemistry	Urinalysis	Additional Tests at Screening Only	Other Assessments[1]

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)
	Bile Acids[2]
	Bilirubin (fractionated)[3]
	Blood urea nitrogen (BUN)
	Calcium
	Calculated eGFR[4]
	Chloride
	C-reactive protein (CRP)
	Creatine kinase[5]
	Creatinine
	Gamma-glutamyl transferase (GGT)
	Glucose[6]
	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
		Dipstick Analysis including:
		- Bilirubin
		- Color
		- Glucose
		- Ketones
		- Leukocytes
		- Nitrite
		- Occult blood
		- pH
		- Protein
		- Specific gravity
		- Urobilinogen
		Microscopic examination of sediment[7]
		Spot Urine sample, including:
		- Albumin
		- Creatinine
		- Albumin: creatinine ratio
			HCV Ab
			HbsAg
			HIV Ab
			FSH[8]
			Serum Pregnancy test[9]
			Urine drug screen[10]
			Sample for potential genetic biomarker testing (white blood cells)[11]
				Complement Biomarkers:
				- AH50
				- AP Wieslab
				- AP Hemolysis
				- Ba
				- Bb
				- C3
				- C4
				- CH50
				- fB
				- fD
				- sC5b-9
				PT/PTT/INR
				Plasma/Serum/Urine samples for additional potential non-genetic biomarker testing[11]
				Urine pregnancy test[9]
				Samples for assessment of patient response to vaccines

1 Check the Schedule of Assessments (Appendix 1) for specific times when these tests should be done.
2 Days 1, 14, and 49 only.
3 Fractionate and obtain measurements of direct and indirect bilirubin for all patients. If indirect bilirubin levels are > ULN at Screening but ALT and AST are normal, test for Gilbert's syndrome.
4 Provide eGFR based on MDRD equation for patients ≥18 years of age, and based on the Schwartz equation for patients

<18 years of age.
5 Perform at screening, and then subsequently only as a reflex if AST > ULN.
6 If glucose is > ULN, reflexively test HbA1c
7 Only if occult blood, protein, or leukocytes present on dipstick analysis.
8 FSH for postmenopausal women at screening only.
9 Serum pregnancy test at Screening 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.
10 Urine drug screen will be measured at screening. For all patients, the urine drug test should include, at a minimum, cotinine, amphetamines, barbiturates, cocaine metabolites, opiates, benzodiazepines, and cannabinoids.
11 See Section 6.11.2 for a description of tests that may be conducted with these samples.

6.10 Pregnancy Testing

All females of childbearing potential (as determined at screening) will have a serum pregnancy test during screening, and urine pregnancy tests on Day 1 (prior to the start of drug administration) and again every 4 weeks for the duration of the study including follow-up. A final urine pregnancy test will be done at the last study visit. On Day 1, the urine pregnancy test must be done before dosing and be negative to begin dosing.

For female patients of childbearing potential who require vaccinations (see Section 6.4), they must also have a negative urine pregnancy test on the days of vaccination, before any vaccine or booster is administered.

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

6.11 Sample Collection, Storage, and Shipping

6.11.1 Blood Collection for Complement Assays (AH50, AP Wieslab, AP Hemolysis, Ba, Bb, C3, C4, CH50, fB, fD, and sC5b-9)

AH50, AP Wieslab, AP hemolysis, Ba, Bb, C3, C4, CH50, fB, fD, and sC5b-9 assays will be run for all patients at the time points indicated in Appendix 1, Table 7 and Table 8. Depending on the type of complement test, either serum or plasma will be used. 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. Specific instructions for sample collection, processing, and shipping will be provided in a separate laboratory manual.

6.11.2 Blood collection for Genetic and Additional Non-genetic Complement-associated Biomarker Testing

Serum/plasma samples will be collected and stored according to the schedule in Appendix 1 for possible assessment of additional non-genetic complement-associated biomarkers. Specific evaluations that may be conducted with the non-genetic samples include:

- Concentrations of other complement components, their split and terminal products, and complement regulators in serum/plasma: C3a, C5, C5a, fH, factor I (fI), iC3b, and properdin
- C3 convertase activity in serum

- The existence of autoantibodies to complement components and/or regulators: fH and C3 nephritic factor
- Serum samples will be collected to assess patient response to vaccinations at various time points in the study
- Concentrations of additional complement components, their split and terminal products, and complement regulators in blood samples may be measured if deemed necessary
- Western blot or other methods that specifically detect full-length C3

White blood cells will be collected according to the schedule in Appendix 1 and stored for possible assessment of the genetic profiles* of selected complement components and regulators:

- C3
- Complement Factor H Related – 5 gene (CFHR-5)
- fB
- fD
- fH
- fI
- Membrane Co-Factor Protein (MCP)
- Thrombomodulin gene (THBD)

*Note: if historic genetic work-up is not available in dosed patients, genetic profiling may be conducted during the study.

Lastly, serum/plasma/WBCs samples may be collected and retained for possible research use. All genetic samples will be stored for a maximum of 3 years.

Depending on the type of complement test, either serum or plasma will be used. 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. Specific instructions for sample collection, processing, and shipping will be provided in a separate laboratory manual. As an exploratory approach, the level of intact C3 in the blood will be measured through Western blot or other methods that specifically detect full-length C3 in a subject before and during treatment. The data might have an effect on patient selection and efficacy determination.

6.11.3 Urine Collection for Complement Components

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, including:

- Ba, Bb
- C3a

- C5
- C5a
- sC5b-9
- fB
- fD
- fH
- Properdin

Concentrations of additional complement components, their split and terminal products, and complement regulators in urine samples may be measured if deemed necessary. 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).

6.11.4 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.

6.11.5 Blood Volumes

Approximate blood volumes to be drawn are detailed in Table 6 below. The total planned blood volume to be collected per individual is 863.9 mL. This does not include discarded blood from pre-collection used to flush catheters. The discarded volume is not expected to exceed 30 mL. Unanticipated additional blood may be collected throughout the study for such things as safety monitoring and additional PK or PD assessments, should it be necessary.

Table 6. Approximate Total Blood Volumes

TESTS	Screening (mL)	Treatment/Taper (to Day 28) (mL)	Follow-up (Post Day 28) (mL)	Total Volume (mL)
Chemistry	8.5	93.5	85	187
Hematology	2	22	20	44
Coagulation	2.7	13.5	2.7	18.9
Serum C3	2	46	20	68
Plasma C3, fB, fH, properdin, iC3b	2	46	20	68
AP Weislab, AP hemolysis	3.5	66.5	35	105
Bb	2	38	20	60
Ba, sC5b-9	3	33	27	63
C4, AH50, CH50, fD	5	20	45	70
Pt Response to Vaccine	3.5	10.5	3.5	17.5
PK		54	0	54
Ab to fH	2	0	2	4
C3Nefs	3	0	3	6
C5, C5a, C3a		16	4	20
C3 Convertase, fI	3.5	35	31.5	70
Genetic Assessment	8.5	0	0	8.5
TOTALS	**51.2**	**494**	**318.7**	**863.9**

6.12 Dispensing Study Drug

ACH-0144471 will be supplied as 50, 75, and 100 mg tablets. At each visit, the site will dispense study drug as required to provide patients with sufficient study drug for dosing until their next clinic visit.

6.13 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).

6.14 Pharmacokinetic Assessments

Serial blood samples will be collected on Days 1 and 7, at the times indicated in the Schedule of Assessments (Appendix 1) to determine plasma and/or serum concentrations of ACH-0144471. Both free and total drug concentrations will be measured. Concentrations of ACH-0144471 metabolites may also be measured. Multiple-dose PK parameters of ACH-0144471, including t_{max}, C_{max}, and $AUC_{0\text{-}tau}$ will be determined. Single trough PK samples will be taken at other time points.

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 patient and study day.

6.15 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, WBCs, and urine collected

during the study with the assays outlined in Sections 6.11.1, 6.11.2, and 6.11.3. Additional information on sample collection and shipping instructions will be provided in a separate laboratory manual.

The primary pharmacodynamic (PD) assessment is C3 concentration in blood which will be extensively monitored throughout the study. Blockage of C3 convertase formation by inhibition of fD presumably reduces the consumption of C3 in C3G and IC-MPGN patients, resulting in an elevated C3 level from the baseline.

Pharmacodynamics will be evaluated ex vivo using serum collected during the study with the AP Wieslab ELISA and AP hemolysis assay. Additional functional assays are AH50 and CH50 to qualitatively evaluate the effect of ACH-0144471 on AP and CP activity.

Additional exploratory complement biomarkers that might be evaluated are listed in Section 6.11.1.

Blood and urine samples will also be collected and stored for possible additional exploratory non-genetic complement biomarker testing (see Section 6.11.2 and 6.11.3). C3 convertase activity, the presence of autoantibodies to complement components or regulators, and the concentrations of multiple complement components and their split and terminal products in non-genetic serum/plasma 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 6.11.2) for possible exploration of the understanding of the underlining etiology of C3G and IC-MPGN and any correlation with patients' response to ACH-0144471.

6.16 Patient-Reported Outcomes Assessment Interview

Patients enrolled in the trial will be interviewed by an independent outcomes researcher chosen by the Sponsor during the screening period. Each patient will be interviewed once. Interviews will be conducted by phone using a semi-structured study-specific guide. Each interview will last approximately 30 minutes, and will be conducted by a trained psychologist/researcher, skilled in qualitative research. Interviews will be audio-recorded, transcribed, and analyzed using validated qualitative software. In order to collect as much information as possible about the impact of the disease on patients' well-being, participation in the interview will be available to all screened patients, whether or not they qualify or choose to participate in the study. While completion of the interview is encouraged, it is not required, and eligible patients may participate in all other study activities whether or not they agree to the interview.

6.17 Adverse Events Assessments

6.17.1 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.

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 the final follow-up visit will be considered treatment-emergent. 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 6.17.8).
- 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 the following criteria:

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

- Are considered clinically significant by the investigator.

Whenever possible, the etiology of the abnormal findings (rather than the abnormal finding(s) 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 adverse event.

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 adverse events, if the condition(s) was (were) known before the start of the study treatment and documented in the patient's medical record. In the latter case, the condition should be reported as medical history.

All patients 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.

6.17.2 Criteria for Assessing Seriousness

All AEs must be evaluated as potential SAEs. 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 patient 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 adverse event
    - 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 adverse event 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 patient who was exposed to the study drug)
- Is an important medical event or reaction

6.17.3 Documentation and Reporting of Adverse Events

AEs, including TEAEs, may be spontaneously reported by a patient or his/her representative, or elicited during questioning and examination of a patient. 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, intensity, 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 patient's medical record. The relationship to study drug or study procedures should be assessed using the definitions in Section 6.17.7.

6.17.4 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).

6.17.5 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 patient provides informed consent through the 28 days following the patient'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.

6.17.6 Severity and Grading of Adverse Events

The intensity of an adverse event will be graded according to the CTCAE Adverse Event Severity Grading Table (Appendix 2) [21]. 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 patient.

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.

6.17.7 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 adverse event:

- **Unrelated:** In the opinion of the investigator, there is no association between the study drug and the adverse event.
- **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'.

6.17.8 Pregnancy

Any pregnancy, including female partner pregnancies of male patients that occurs or becomes confirmed during a clinical study (time frames outlined in Section 6.17.5) 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 should be followed and discussed with the medical monitor as follows:

- The investigator will follow up with the patient every 3 months throughout the pregnancy and report to Achillion (or designee) using the pregnancy forms.
- Following the estimated date of delivery, the investigator will follow up with the patient and report to Achillion (or designee) using the pregnancy forms.
- The final outcome of the delivery will be reported to Achillion (or designee) using the pregnancy forms.

Any SAEs related to the pregnancy (see below), or occurring during the patient'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.

6.17.9 Reporting Serious Adverse Events

Achillion Pharmaceuticals, Inc. 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 6.17.5).

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

SAE

- Record the SAE on the SAE reporting form provided by Achillion (or designee)
- Send the SAE form to both [redacted] (via fax) AND to Achillion Pharmaceuticals (via email) within 24 hours of becoming aware of the SAE.

Pregnancy

- Record the pregnancy on the pregnancy form provided by Achillion (or designee)
- Send the pregnancy form to both CCI (via fax) AND to Achillion Pharmaceuticals (via email) within one business day of becoming aware of the pregnancy.

All contact information is provided below.

SAE CONTACT
CCI **Pharmacovigilance** **Fax:** PPD **Phone:** PPD SAE Hotline, for questions about completing the forms: Phone: PPD **Achillion Pharmaceuticals** PPD

For fatal or life-threatening events, also fax 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.

Any follow-up information collected on any report of an SAE and/or pregnancy must be reported by the investigator within one business day.

A copy of the submitted SAE form must be retained on file by the investigator. If required, the investigator must submit copies of the SAE forms to the IRB or EC and retain documentation of these submissions in the site study file.

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

6.17.10 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.

6.18 Concomitant Medication Assessments

Details of all prior (within 30 days of the screening evaluation) and concomitant medication use, including all medications administered for the treatment of AEs, will be recorded in the patient's CRF at each study visit.

6.19 Monitoring Patient Safety

The safety of patients will be monitored by Investigators and by a medical monitor (or designee) at Achillion Pharmaceuticals, Inc. on an ongoing basis while patients are receiving ACH-0144471. Additionally, a Fever Management Plan (Appendix 3) has been developed for this study to enable rapid assessment, detection and treatment of any potential serious infection.

6.20 Removal of Patients from the Trial or Study Drug

A patient is free to withdraw from the study at any time without jeopardizing future medical care. In addition, the PI (or designee) may decide, for reasons of medical prudence or patient noncompliance, to discontinue dosing in a patient. The PI should also stop dosing in any patient 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 patient. When dosing is terminated, study participation is not necessarily immediately terminated. Instead, whenever possible, the patient 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 patient 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 patient's best interest to continue the study
- Patient request to discontinue for any reason
- A female patient becomes pregnant or wishes to become pregnant
- Patient noncompliance
- Discontinuation of the study at the request of Achillion Pharmaceuticals, Inc., regulatory agency, or Ethics Committee or IRB
- Any other condition or circumstance that would jeopardize the welfare of the patient if s/he were to continue in the trial

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

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 study period, physical examinations, assessment of vital signs, ECG measurements, all required safety laboratory testing, and collection of blood and urine samples for PK and PD evaluation will be performed at various time points through the study. There will be multiple follow-up visits after the last dose of study drug.

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

- ECG and vital signs prior to blood sampling
- PK samples should be taken at the specified times, within the windows described in Table 8
- 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 patient's CRF.

7.1 Screening Period

7.1.1 Eligibility Visit (Days –45 to -1)

Prospective patients should be screened within 45 days of first administration of study drug. During the screening period, informed consent will be obtained and patient eligibility determined according to the criteria specified in this protocol. The procedures listed in the Schedule of Assessments (Appendix 1) must be performed and documented. 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 patient's medical history should be reviewed as described in Section 6.2, and a complete physical examination should be conducted as described in Section 6.5. In addition, the patient's historical renal biopsy will be reviewed by a central pathologist for confirmation of the diagnosis (see Section 6.3). Patients who meet all eligibility criteria will be educated about the restrictions on concomitant medication usage and other substances.

All evaluations required for eligibility determination must be completed before the patient is accepted into the study for dosing. If the patient is unable to receive study drug within 45 days of screening the patient may be re-screened once.

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, Inc. Medical Monitor (or designee).

Exemptions to inclusion and exclusion criteria are discouraged, but can occasionally be considered at the discretion of Achillion Pharmaceuticals, Inc. Medical Monitor or designee.

Once the patient is entered into the study, all protocol deviations should be reported to Achillion Pharmaceuticals, Inc. for review by the Medical Monitor or designee. The Medical Monitor (or

designee) will assess all protocol deviations. Any protocol deviation which is deemed to impact patient safety or data integrity will be considered a significant protocol deviation. The rationale for considering a protocol deviation significant will be documented.

7.1.2 Vaccination Visit (If Required; Day -14 or Earlier)

As part of the screening process, patients will be evaluated to determine whether vaccination against *N. meningitidis*, *S. pneumoniae*, or *H. influenzae* is required. The criteria for evaluation and the specific timing of any required vaccinations are described in Section 6.4. For patients that require vaccinations, all other screening procedures must be completed, and patients must qualify for the study prior to vaccinations being administered. Female patients of childbearing potential must have a negative urine pregnancy test on the day of vaccination, before any vaccine or booster is administered.

7.1.3 Patient Reported Outcomes Assessment Interview

Each patient will be interviewed once by telephone by an independent outcomes researcher selected by the Sponsor during the Screening period. A Contact Order Form including patient contact details will be completed and sent to a dedicated independent unit in charge of scheduling and setting up the interview. The interview will be conducted by a trained, experienced interviewer in the local language and will last approximately 30 minutes. The interviewer will follow a semi-structured interview guide, specifically developed for the study and the time-point (provided in a separate manual). The guide summarizes the objectives of the study, and the methodology and process of the interview. It contains the themes to be covered during the interview. Amongst those, the main themes that will be explored will include patients' experience of the disease and the disease trajectory, in order to document the symptoms and manifestations, and its impact on everyday lives.

While completion of the interview is encouraged, it is not required, and eligible patients may participate in all other study activities whether or not they agree to the interview.

7.2 Treatment Period

During the Treatment Period, physical examinations, assessment of vital signs, ECG measurements, 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.

Patients should be instructed to fast prior to coming to a clinic visit and to bring their study drug with them for administration at the site.

At clinic visits, patients should be instructed how to take their medication at home and record the time they took it. The first dose of the day should be taken at the same time each morning, the second dose taken approximately 8 hours later, and a third dose 8 hours after the second. Patients should be instructed to finish a moderate fat meal or snack within 15 minutes prior to dosing with ACH-0144471. Dosing should be at the same time(s) each day. Patients should record the time they take their doses at home. 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.

Patients should be instructed to store their study drug at room temperature.

7.2.1 Pharmacokinetic/Pharmacodynamic Sampling Visits (Day 1 and Day 7)

On Day 1 and Day 7, patients should arrive at the clinic in the fasted state at the time designated by site personnel, and will remain at the clinic for intensive PK and PD sampling over 8 hours. The first and second doses of ACH-0144471 should be administered at the clinic. The second dose should be administered approximately 8 hours after the first dose following the completion of the 8-hour blood draws. Patients should take the third dose 8 hours after the second, after discharge from the clinic.

The assessments listed in Table 7 of the Schedule of Assessments (Appendix 1) should be performed prior to the administration of the first daily dose. Following dosing, PK and PD samples should be collected as listed in Table 8 of the Schedule of Assessments (Appendix 1).

7.2.2 Outpatient Clinic Visits

As listed in the Schedule of Assessments (Appendix 1), patients will be evaluated at the clinical site on Days 1, 2, 4, 5, 7, 8, 10, 12, and 14 during the Treatment Period. Patients should arrive at the clinic in the fasted state at the time designated by site personnel. The assessments listed in Table 7 of 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.

7.2.3 Telephone Visits

As listed in the Schedule of Assessments (Appendix 1), patients will be called by the site on the phone on Days 3, 6, 9, 11, and 13 during the Treatment Period. During these phone calls, the investigator should review compliance with the protocol restrictions, remind the patient of their dosing schedule, confirm dose dates and times since the last contact with the patient, collect information about any adverse events, and collect any updates to their concomitant medications. If preferable or more convenient, these activities may take place at the investigator's clinic rather than by phone.

7.3 Taper Period

During the Taper Period, physical examinations, assessment of vital signs, ECG measurements, 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. The taper period will begin after 14 days of dosing unless a patient has a serum C3 level that, at 2 consecutive evaluations, is greater than 125% the ULN, or is greater than 3× their baseline (provided this greater than or equal to the LLN), in which case the taper period will be initiated before completion of 14 days of dosing. As described in Section 5.2, investigators must receive and review C3 levels in a timely manner to ensure that an early taper is implemented when appropriate.

Patients should be instructed how to take their medication at home and record the time they took it. The first dose of the day should be taken at the same time each morning, the second dose taken approximately 8 hours after the first dose, and a third dose 8 hours after the second. Patients should be instructed to finish a moderate fat meal or snack within 15 minutes prior to dosing with ACH-0144471. Dosing should be at the same time(s) each day. Patients should record the time they take their doses at home.

Patients should be instructed to store their study drug at room temperature.

Patients should be instructed to fast prior to coming to a clinic visit and to bring their study drug with them for administration at the site.

Details of the Taper Schedule can be found in Section 5.2.

7.3.1 Outpatient Clinic Visits

As listed in the Schedule of Assessments (Appendix 1), patients will be evaluated at the clinical site on Days 15, 16, 17, and 21 during the Taper Period. Patients should arrive at the clinic at the time designated by site personnel.

The assessments listed in Table 7 of 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.

7.3.2 Telephone Visits

As listed in the Schedule of Assessments (Appendix 1), patients will be called by the site on the phone on Days 18, 19, and 20 during the Taper Period. During these phone calls, the investigator should review compliance with the protocol restrictions, remind the patient of their dosing schedule, confirm dose dates and times since the last contact with the patient, collect information about any adverse events, and collect any updates to their concomitant medications. If preferable or more convenient, these activities may take place at the investigator's clinic rather than by phone.

7.4 Follow-Up Period

During the Follow-Up Period, physical examinations, assessment of vital signs, ECG measurements, 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.

Patients should be instructed to fast prior to coming to a clinic visit.

7.4.1 Outpatient Clinic Visits

As listed in the Schedule of Assessments (Appendix 1), patients will be evaluated at the clinical site on Days 24, 28, and 35 during the Follow-up Period. Patients should arrive at the clinic at the time designated by site personnel. The assessments listed in Table 7 of 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. If necessary, clinic visits during the Follow-Up Period may occur up to 2 days earlier or later than scheduled.

7.4.2 Telephone Visits

As listed in the Schedule of Assessments (Appendix 1), patients will be called by the PI or designee on Days 22, 23, 25, 26, 27, 29, 30, 31, 32, 33, and 34 during the first 2 weeks of the Follow-up Period. In addition, if one of the outpatient clinic visits described in Section 7.4.1 is rescheduled, the patient should be contacted by the PI or designee on the day when the clinic visit was originally scheduled. During these phone calls, the investigator should review compliance with the protocol restrictions, collect

information about any adverse events, and collect any updates to their concomitant medications. If preferable or more convenient, these activities may take place at the investigator's clinic rather than by phone.

7.4.3 Final Visit or Early Termination from the Study

The final visit is scheduled to occur on Day 49. Patients who terminate participation in this study should have the assessments listed for Day 49 in Table 7 of the Schedule of Assessments (Appendix 1). Patients who terminate participation within 7 days of their last dose of ACH-0144471 should also have a blood sample collected for PK evaluation. Of note, a patient who discontinues dosing does not necessarily discontinue from the protocol, and whenever possible, such a patient should continue with follow-up visits as per the protocol.

7.5 Long-Term Follow-Up Visits

Long-term follow up visits to allow collection of longitudinal observational data are included, but are not required. During the long-term follow up period, patients will be asked to return for an outpatient clinic visit approximately every 45 days for a maximum of 1 year. Patients participating in this portion of the study should have the assessments listed for Long-Term Follow-up (LTF) in Table 7 of the Schedule of Assessments (Appendix 1).

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 patient'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 subjects 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, subject 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

Due to the small sample size, only descriptive and exploratory statistical methods will be utilized to present results from data analysis.

Patient listings will be provided for all efficacy (including PK and PD) and safety parameters. Summary statistics will be computed, by dose level and all dose levels combined, for selected efficacy and safety parameters so that meaningful clinical interpretations can be made. Results may be presented by C3G and IC-MPGN if such presentations would be clinically meaningful. Graphic presentations will also be produced for selected efficacy and safety parameters.

No summary tables will be provided for long-term follow-up observational data since patients are not required complete the visits.

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

9.2 Determination of Sample Size

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

9.3 Analysis Populations

All patients receiving at least one dose of ACH-0144471 will be included in the efficacy, safety, pharmacokinetic, and pharmacodynamic analyses.

9.4 Demographics and Baseline Characteristics

Demographic parameters (age, gender, race, weight, BMI) and baseline C3G or IC-MPGN disease characteristics will be summarized, by dose level and all dose levels combined, to provide an overall description of study population.

9.5 Efficacy Analysis – Complement C3 Measurements

The primary efficacy endpoint will be an increase in blood C3 levels relative to baseline during the 14-day Treatment Period.

Summary statistics will be provided for both original and change from baseline C3 levels at various time points, including Treatment, Taper, and Follow-up periods, at each dose level and all dose levels combined. Time (in days) to peak C3 level for each patient will be estimated and summarized. Descriptive time-to-event analysis techniques may be employed to estimate the time lapse for ACH-0144471 of restoring C3 levels.

C3 levels, both original and changes from baseline, will be plotted against time.

Inferential statistical methods, e.g., confidence interval procedures, time-to-event techniques, etc., may also be utilized if available data deem such analyses being feasible and meaningful.

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 patient. Descriptive summary statistics may be provided for selected lab tests.

Data on physical exam, vital signs, and ECG will be examined either through patient 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.

9.7 Pharmacokinetic (PK) Analysis

Pharmacokinetic analysis will be done using a validated computer program for the PK concentrations. For each patient, the PK characteristics of ACH-0144471, including, but not limited to, the standard PK parameters outlined in the table below, will be derived from the individual concentration time data following intensive PK sampling on study Days 1 and 7. Descriptive statistics (number of patients, arithmetic mean / geometric mean, SD, median, minimum, and maximum) will be used to summarize the calculated PK parameters for Day 1 and Day 7.

AUC	Area under the curve
C_{max}	Maximum plasma concentration
t_{max}	Time after administration of a drug when the maximum plasma concentration is reached

Trough plasma concentrations will be listed and summarized to assess the amounts of ACH-0144471 in the body at steady state prior to daily dose. Graphic presentations will also be provided to depict PK profiles of ACH-0144471 from C3G and IC-MPGN patients.

9.8 Pharmacodynamic (PD) Analysis

As described in Section 6.15, PD markers include selected laboratory tests to assess the effects of ACH-0144471 on complement alternative and classical pathways.

Except for the alternative pathway functional assay result AH50 and results from AP Wieslab assay, change from baseline values at various time points will be computed for selected PD markers; summary statistics may be provided for these selected markers if they are deemed clinically meaningful.

The derivation from the raw data of AP Wieslab assay to the reported percentages will be presented in the SAP. The two reported measures (in unit of %), along with complement Bb, are central for assessing the inhibitory effect of ACH-0144471 on the complement alternative pathway activity.

Concentration versus time graphic presentations may be utilized for selected markers.

9.9 PK/PD Assessments

The relationships between C3 levels and selected AP component measurements, e.g., AP Wieslab reported percentages, etc. with corresponding plasma concentrations and/or PK parameters may be explored if available data deem such assessment being clinically meaningful.

9.10 Patient-Reported Outcome Measures Assessments

De-identified transcripts of the patients' interviews will be qualitatively analyzed following a thematic analysis. The analysis of patient interviews will be based on the grounded theory approach, allowing the voice of the patient to be heard rather than apply a priori concepts or hypotheses [22]. A validated software package will be used to facilitate the storage, coding, analysis, and retrieval of qualitative data.

The interviews will be conducted prior to initiation of study treatment and will be analyzed cross-sectionnally, on all the patients interviewed. Concepts relevant in the disease and important to the patients will be elicited. Based on findings collected a conceptual model will be developed to obtain comprehensive pictures of C3G and IC-MPGN, the signs and symptoms, their impact on patients' lives, their diagnosis, and their management from the perspective of the patients.

A separate report may be provided for the patient interview data if deemed feasible and clinically appropriate.

10 Administrative Considerations

10.1 Investigators and Study Administrative Structure

The PI must maintain a screening log of all patients seen and considered for the study. For those patients 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, patient information and consent form, the Investigator Brochure, available safety information, patient recruitment procedures (e.g., advertisements), information about payments and compensation available to the patients 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 patient 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 patient'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 Patient Information and Consent

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirements and should adhere to ICH GCP (E6). Each patient 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 at any time without affecting their medical care. If important new information is incorporated in the ICF and approved by the EC, all patients still actively participating in the study must be re-consented.

Written informed consent should be documented by the patient's personally dated signature and the personally dated signature of the investigator or designee who conducted the informed consent discussion. The investigator or designee should supply all enrolled patients with a copy of their signed informed consent. The monitor will inspect the original consent form for all patients.

10.5 Patient Confidentiality

The investigators and Sponsor and its designees will preserve the confidentiality of all patients 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 patient's notes, confidentiality of all patient identities will be maintained. Only patient initials, date of birth, and study number will be used on the CRF and in all study correspondence, as permitted. No material bearing a patient's name will be kept on file by the Sponsor.

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 patient 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, Inc. 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, Inc. Medical Monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Achillion Pharmaceuticals, Inc. 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, patient-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 patient 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 patient status throughout the course of the study. CRFs will be completed within 5 days of the last patient visit.

10.7.2 Source Documentation and Medical/Study Records

The patient's number and date of entry into the study, along with the study code, should be recorded in the patient'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 patient'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 Data Monitoring Committee

There will be no formal data monitoring committee.

10.9 Protocol Deviations

Protocol deviations will be assessed on a case-by-case basis. Significant protocol deviations will be reported to the Ethics Committee or IRB according to local regulations.

10.10 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, patient 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.

Patients will have access to safety laboratory results upon request at any time during the study. PK levels will not be available until after all study analysis is completed.

10.11 Data Generation and Analysis

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

10.12 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
- Patient 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.

Patient 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, patient 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, Inc. The investigator (or designee) must contact Achillion Pharmaceuticals prior to destroying any records associated with the study. Achillion Pharmaceuticals, Inc. 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, Inc. 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, Inc. 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 patient, appropriate copies should be made for storage outside of the site.

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, Inc. may use data derived from this trial for the purpose of research and development. The data may be disclosed by Achillion Pharmaceuticals, Inc. 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, Inc. approval. To gain

approval, a copy of the manuscript for review must, therefore, be sent to Achillion Pharmaceuticals, Inc. 60 days before submission for publication.

It is the intent of Achillion Pharmaceuticals, Inc. to present the results of this study at future scientific meetings. Additionally, it is the intent of Achillion Pharmaceuticals, Inc. 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, Inc. Achillion Pharmaceuticals, Inc. will determine additional authors. Presentations and manuscripts will be provided and agreed to by the authors and Achillion Pharmaceuticals, Inc.

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12 Appendices

Appendix 1. Schedule of Assessments

Table 7. Schedule of Assessments

	Screening Day -45 to Day -1		Visit Day(s)[1]																								LTF[4]
			Treatment														Taper			Follow-Up[2]								
	Elig	Vacc[3]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15-17	18-20	21	22-23	24	25-27	28	29-34	35	49	
Drug Administration[5]			X	X	X	X	X	X	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]								
Outpatient Clinic Visit[6]	X	X	X	X		X	X		X	X		X		X		X	X		X		X		X		X	X	X
Telephone Visit					X			X			X		X		X			X		X		X		X				
Dosing Reminder					X			X			X		X		X			X										
Screening Assessments																												
Informed Consent	X																											
Inclusion/ Exclusion Criteria	X																											
Protocol Restrictions	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Demographics	X																											
Medical History	X		X																									
Central review of historical renal biopsy	X																											
FSH[7]	X																											
Pregnancy Test[8]	X	X[9]	X[10]																				X			X		
Urine drug screen[11]	X																											
Patient-Reported Outcomes Assessment Interview	X																											
Vaccinations[12]		X																										

	Screening Day -45 to Day -1		Visit Day(s)[1]																								LTF[4]
			Treatment														Taper			Follow-Up[2]								
	Elig	Vacc[3]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15-17	18-20	21	22-23	24	25-27	28	29-34	35	49	
Clinical Assessment																											
Physical Exam & Vital Signs[13]	X		X			X			X			X				X	X		X		X		X		X	X	X
Body Temperature[14]	X		X			X			X			X				X	X		X		X		X		X	X	
12-Lead ECGs (single)	X		X			X			X			X				X	X		X		X		X		X	X	
AE/SAE	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments																											
PK samples[15]			X[10,16]			X			X[16]			X				X	X		X		X		X				
Hematology, Chemistry, and Urinalysis[17]	X		X[10]			X[10]			X[10]			X[10]				X[10]	X[10]		X[10]		X		X		X	X	X
PT, PTT, and INR	X		X[10]						X[10]							X[10]			X[10]				X			X	
Complement biomarkers																											
AP Wieslab, AP Hemolysis, Bb (serum/plasma)	X		X[10,16]			X[10]			X[16]			X[10]				X[10]	X[10]		X[10]		X		X		X	X	X
C3 (serum and plasma)	X		X[10,16]	X[10]		X[10]	X[10]		X[16]	X[10]		X[10]		X[10]		X[10]	X[10]		X[10]		X		X		X	X	X
Ba, sC5b-9 (plasma)	X		X[10]			X[10]			X[10]			X[10]				X[10]	X[10]		X[10]		X		X			X	X
C4, AH50, CH50, fD (serum)	X		X[10]						X[10]							X[10]			X[10]							X	X
fB (plasma)			X[10]						X[10]							X[10]			X[10]							X	X
Sample for assessment of patient response to vaccines	X		X[10]						X[18]																	X	

	Screening Day -45 to Day -1		Visit Day(s)[1]																								LTF[4]
			Treatment														Taper			Follow-Up[2]								
	Elig	Vacc[3]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15-17	18-20	21	22-23	24	25-27	28	29-34	35	49	
Samples for potential assessment of additional non-genetic biomarkers																											
Auto-antibodies to fH and C3 nephritic factor (plasma/serum)	X																									X	
C5, C5a, fH, fI, properdin, C3a (plasma/serum)			X[10]						X[10]							X[10]			X[10]						X		
C3 convertase activity (serum)	X		X[10]	X[10]		X[10]	X[10]		X[10]	X[10]		X[10]		X[10]		X[10]			X[10]						X		X
iC3b (plasma)	X		X[10]			X[10]			X[10]			X[10]				X[10]	X[10]		X[10]		X		X			X	X
Urine complement components	X		X[10]			X[10]			X[10]			X[10]				X[10]	X[10]		X[10]		X		X			X	X
Sample for potential genetic assessment of complement genes	X																										

AE = Adverse event; AH50 = 50% hemolytic activity of complement alternative pathway; AP = Alternative pathway; BMI = Body mass index; ECG = Electrocardiogram; Elig = Eligibility evaluation; fD = Factor D; LTF = Long-Term Follow-Up visits; PK = Pharmacokinetic; SAE = Serious adverse event; Unsch = Unscheduled visit; Vacc = Vaccination visit

1 Where Visit Day is a range, the specified activities should take place on each day of the range.

2 If necessary, clinic visits during the Follow-Up Period may occur up to 2 days earlier or later than scheduled. If a visit is rescheduled, a telephone visit should be conducted on the day when the clinic visit was originally scheduled.

3 If required, vaccinations must be at least 2 weeks prior to dosing with ACH-0144471. With the exception of the historical biopsy review, patients should be confirmed to be eligible based on all other inclusion and exclusion criteria before being vaccinated.

4 Long-term follow-up visits should be every 45 days, ±15 days, for a maximum of one year. Patients are not required to complete these visits.

5 If a patient has a serum C3 level that, at 2 consecutive evaluations, is greater than 125% the ULN, or is greater than 3× their baseline (provided this is greater than or equal to the LLN), then the taper period will be initiated before completion of the 14 days of dosing. In this instance, skip to Day 15 of the study schedule on the first day of the taper.

6 Patients will be offered the opportunity to stay within the inpatient clinical research unit and/or offered local overnight accommodations for the two extended clinic visit days (Day 1 and Day 7), and during the period of daily outpatient visits.

	Screening Day -45 to Day -1		Visit Day(s)[1]																								LTF[4]
			Treatment														Taper			Follow-Up[2]							
	Elig	Vacc[3]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15-17	18-20	21	22-23	24	25-27	28	29-34	35	49	

7 FSH for postmenopausal women at screening only.

8 Serum pregnancy test at Screening and urine pregnancy tests at other time points for women of childbearing potential only. On Day 1, urine pregnancy test must be done pre-dose and be negative to continue. Any positive urine pregnancy test will be confirmed by a serum pregnancy test.

9 Female patients of childbearing potential who require vaccinations (see Section 6.4) must have a negative urine pregnancy test on the day of vaccination, before any vaccine or booster is administered.

10 Blood draws and urine collection should be done pre-dose.

11 Urine drug screen should include, at a minimum, cotinine, amphetamines, barbiturates, cotinine, cocaine metabolites, opiates, benzodiazepines, and cannabinoids. All analytes can be evaluated in a single urine sample.

12 If needed, per the guidance in Section 6.4.

13 Full physical exam and vital signs, including height, weight, and BMI at screening. Full physical exam and vital signs, including weight on Day 1 and Day 49 visit. Brief physical exam and vital signs for all other visits, per Section 6.5 and Section 6.6. Vital signs may be measured using an automated vital signs monitor, although manual measurements of blood pressure are preferred.

14 Oral temperature, per Section 6.7.

15 Except on Days 1 and 7, collect only one sample prior to dose administration (trough sample).

16 For PK and PD sampling schedule on Days 1 and 7, refer to Table 8.

17 Hematology, Chemistry, and Urinalysis tests as listed in Section 6.9, Table 5.

18 Collect samples at Hour 0 (before dosing) and Hour°2 of Day 7, as indicated in Table 8.

Table 8. PK and PD Sampling on Days 1 and 7

	Time After Dosing (hr)								
Hour[a]	**0[b]**	**1**	**1.5**	**2**	**2.5**	**3**	**4**	**6**	**8**
PK plasma samples	X	X	X	X	X	X	X	X	X
C3 (serum and plasma)	X			X			X	X	X
AP Wieslab (serum)	X			X			X	X	X
Bb (plasma)	X			X			X	X	X
AP Hemolysis (serum)	X			X			X	X	X
Sample for assessment of patient response to vaccines	X[c]			X[c]					

a Samples at 0, 1, 1.5, 2, and 2.5 hours should be drawn at ± 5 min of the scheduled time. Later samples should be drawn at ± 10 min of the scheduled time.

b Prior to dosing

c Day 7 only

Appendix 2. Grading the Severity of Adult Adverse Events

Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, Published: May 28, 2009 (v4.03: June 14, 2010)

To view or print the table, go to:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Appendix 3. 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 subjects 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 patient; instead, they are intended to facilitate rapid initiation of assessment and management of fever.

A. General Management for outpatients

All patients in this study 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 patients 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. They will be advised not to wait for site staff to return their phone call before seeking emergency medical attention. They should go to the nearest emergency 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 and telephone, and be within one hour of an emergency medical center
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

B. General Management for Any Fever Detected in the Clinic

For Any fever, the site needs to:

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

Intravenous (IV) antibiotics should be given as soon as meningococcal disease is suspected. The choice of antibiotics should be selected to provide adequate coverage for *N. meningitidis* - suggestions are 2 g of ceftriaxone IV after basic blood draws for CBC and blood culture are completed, or 2 g Meropenem IV every 8 hours. Cefotaxime IV may be used as well. If unavailable, penicillin G IV could be used (the recommended dose in persons with normal renal function is 2 million units every 2 h, or 4 million units every 4 hours (24 million units/day). As far as possible, 2 sets of blood cultures should be collected prior to antibiotic administration. Other investigations should not delay antimicrobial therapy.

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.