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

Unique Protocol ID:	ACH471-100
NCT Number:	NCT03053102
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Date of Protocol:	13 March 2018

Clinical Trial Protocol

ACH471-100

Study Title:	A Phase 2 Open-Label Proof of Concept Study to Assess the Efficacy, Safety, and Pharmacokinetics of ACH-0144471 in Untreated Patients With Paroxysmal Nocturnal Hemoglobinuria (PNH)
Study Number:	ACH471-100
Study Phase:	2
Product Name:	ACH-0144471 Tablets
EudraCT Number:	2016-002652-25
Universal Trial Number (UTN):	U1111-1190-3490
Indication:	Paroxysmal Nocturnal Hemoglobinuria (PNH)
Investigators:	Multi-center
Sponsor:	Achillion Pharmaceuticals, Inc.
Sponsor Contact:	PPD
Medical Monitor:	PPD

	Approval Date
Original Protocol:	22 November 2016 (Version 1.0)
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Amendment 6	21 December 2017 (Version 7.0)
Amendment 7	13 March 2018 (Version 8.0)

Confidentiality Statement

Sponsor Signature(s)

Study Title:	A Phase 2 Open-Label Proof of Concept Study to Assess the Efficacy, Safety, and Pharmacokinetics of ACH-0144471 in Untreated Patients With Paroxysmal Nocturnal Hemoglobinuria (PNH)
Study Number:	ACH471-100
Protocol Version and Date	Protocol ACH471-100, Amendment 7 13 March 2018 (Version 8.0)

This clinical study protocol has been approved by the sponsor.

PPD

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

Date

PPD

3/13/2018 | 6:04 PM EDT

Investigator's Signature(s)

Study Title:	A Phase 2 Open-Label Proof of Concept Study to Assess the Efficacy, Safety, and Pharmacokinetics of ACH-0144471 in Untreated Patients With Paroxysmal Nocturnal Hemoglobinuria (PNH)
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I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

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

Synopsis

Sponsor:	Achillion Pharmaceuticals, Inc. 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:	ACH-0144471 Tablet: Lactose, Microcrystalline Cellulose, Croscarmellose Sodium, Sodium Lauryl Sulphate, Magnesium Stearate, Colloidal Silicon Dioxide and Hypromellose Acetate Succinate. The coating components are: polyvinyl alcohol, titanium dioxide, macrogol/polyethylene glycol and talc
Study Title:	A Phase 2 Open-Label Proof of Concept Study to Assess the Efficacy, Safety, and Pharmacokinetics of ACH-0144471 in Untreated Patients With Paroxysmal Nocturnal Hemoglobinuria (PNH)
Study Number:	ACH471-100
Study Phase:	Phase 2
Primary Objective:	To evaluate the efficacy of 28 days of oral dosing with ACH-0144471 in currently untreated PNH patients, based on decreases in lactate dehydrogenase (LDH)
Secondary Objectives:	• To evaluate the efficacy of 28 and 84 days of oral dosing with ACH-0144471 in currently untreated PNH patients, based on increases in hemoglobin (Hgb) levels • To evaluate the safety and tolerability of ACH-0144471 in currently untreated PNH patients receiving daily oral dosing by assessing SAEs, AEs ≥ Grade 3, and laboratory abnormalities ≥ Grade 3, and events leading to discontinuation of study drug • To evaluate the pharmacokinetic (PK) and pharmacodynamics (PD) profile of ACH-0144471 in currently untreated PNH patients receiving daily oral dosing for 28 days
Exploratory Objectives:	• To evaluate the relationship between ACH-0144471 multiple-dose pharmacokinetics and pharmacodynamics biomarkers through inhibition of complement alternative pathway (AP) activity (PK/PD) • To evaluate health-related quality of life measures in patients with PNH based on patient-reported outcome instruments and their evolution over the course of ACH-0144471 treatment • To explore the benefits of ACH-0144471 treatment as perceived by patients with PNH, by: o Exploring patients' experiences of PNH, its impact on everyday lives and the disease trajectory, from first symptoms to definitive diagnosis and beyond o Documenting the evolution of PNH over the course of ACH-0144471 treatment from a patient's perspective • To explore patients' expectations towards ACH-0144471 treatment

Study Design:	This is a multiple-center, open-label, multiple dose study. Patients may be enrolled in a pretreatment screening protocol to establish baseline values for the PD, efficacy and safety parameters evaluated in this study, or may be directly enrolled into this study. During the screening period, patients will be evaluated for eligibility criteria and have screening assessments performed. Screening procedures may be spread over more than one visit. Once patients have been confirmed as eligible, they will be evaluated for history of vaccination against *Neisseria meningitidis* (*N. meningitidis*), *Haemophilus influenzae (H. influenza*e), and *Streptococcus pneumoniae* (*S. pneumoniae*). Those who have not been vaccinated will receive vaccinations during this study, as described in Section 6.3. Those who have been previously vaccinated will receive recommended boosters as described in Section 6.3. After screening (including vaccinations, when applicable), patients will enter the treatment portion of the study which will be conducted in 2 parts. In Part 1, each participant will receive daily oral doses of ACH-0144471 for 28 days. Based on data from the Phase 1 single-ascending dose (SAD), multiple-ascending dose (MAD), and Relative Bioavailability (Rel BA) studies, and emerging data from the first two patients in this study, the starting dose will be 150 mg TID and the maximum dose will be 250 mg TID. Patients will begin dosing on Day 1. Patients will return to the clinic on Days 6, 13, and 20 for additional intensive PK sampling and other assessments, and will be evaluated for potential dose escalations after review of Days 6 and 13 safety and LDH values. Patients will continue dosing until Day 28 for continued collection of safety information. Dosing for patients not continuing to Part 2 will then be tapered over 6 days, as described in Section 5.2.1. The primary efficacy endpoint will be the relative decrease in LDH from baseline after 28 days of dosing. Based on a review of safety and efficacy data through Day 20 for each individual, patients with reductions in LDH meeting specified criteria will be offered continued dosing beyond Day 28 for up to 8 additional weeks (Part 2). Patients who do not meet the criteria may be offered participation in Part 2 if there has been clinically significant improvement during Part 1 (see Section 3.2.3). Participation in Part 2 will be based on Day 20 data to allow adequate time for review and decision making prior to the scheduled end of dosing in Part 1 on Day 28. Patients participating in Part 2 of the study will continue to receive daily oral doses of ACH-0144471, and will return for additional visits on Days 42, 56, 70, and 84. After Day 84, dosing will then be tapered over 6 days, as described in Section 5.2.1. For all patients, a final follow-up visit will be conducted approximately 14 days after the last dose. Considering PNH is a serious life threatening disease, a long-term extension study, beyond the 3 months of dosing included in this study, may be offered to patients, if supported by clinical and nonclinical data. Pending regulatory and ethics committee approval of such a study, patients who, in the opinion of the Principal Investigator (PI), are receiving benefit from ACH-0144471 may be enrolled directly into that study without interruption from this study, and will continue to receive daily treatment with ACH-0144471 and safety and efficacy monitoring. Any patients so enrolled will not require a dosing taper or the follow-up visits described in this protocol.
Treatment Groups:	A single treatment group is planned. ACH-0144471 will be administered as multiple doses over a period of at least 28 days, followed by a taper over 6 days.
Study Population:	Currently untreated PNH patients meeting eligibility criteria.
Number of Patients	A total of approximately 4 to 12 patients are planned.

Inclusion Criteria:	1. Currently untreated PNH patients with PNH Type III erythrocyte and/or granulocyte clone size ≥10% and anemia (Hgb <12 g/dL) with adequate reticulocytosis (as determined by the investigator) 2. LDH ≥1.5× upper limit of normal (ULN) 3. Platelet count ≥50,000/μL without the need for platelet transfusions 4. Documentation of vaccination for *N. meningitidis*, *H. influenzae,* and *S. pneumoniae*, or willingness to receive vaccinations as described in Section 6.3 5. Age ≥18 years (or ≥ minimum adult age in accordance with local legal requirements) 6. Female participants of childbearing potential must agree to use an acceptable method of contraception (as defined in Section 5.5.5) from the date of signing the informed consent to the first day of dosing (Day 1), and must agree to use a highly effective method of contraception (as defined in Section 5.5.5) from the first day of dosing to 30 days after their last dose of study drug. Female participants of childbearing potential must also have a negative serum pregnancy test during Screening and negative urine pregnancy test on Day 1. Female participants of non-childbearing potential need not employ a method of contraception. 7. Non-sterile male participants must agree to use a highly effective method of contraception (as defined in Section 5.5.5) with their partner(s) of childbearing potential from the first day of dosing to 90 days after their last dose of study drug. Males who are surgically sterile need not employ additional contraception. Males must agree not to donate sperm while enrolled in this study and for 90 days after their last dose of study drug. 8. Must agree to provide written informed consent 9. Must be willing, at all times, to have transportation and telephone access, and to be within one hour of an emergency medical center
Exclusion Criteria	1. History of a major organ transplant (e.g., heart, lung, kidney, liver) or hematopoietic stem cell/marrow transplant 2. History of dosing with another investigational agent within 30 days or 5 half-lives of the investigational agent prior to study drug administration, whichever is greater 3. History of dosing with eculizumab at any dose or interval within the past 75 days before study drug administration 4. Known or suspected complement deficiency 5. Contraindication to one or more of the required vaccinations 6. Active bacterial infection or clinically significant active viral infection, a body temperature >38°C, or other evidence of infection on Day 1, or history of febrile illness within 14 days prior to first study drug administration 7. History of meningococcal infection, or a first-degree relative or household contact with a history of meningococcal infection 8. History of hypersensitivity reactions to commonly used antibacterial agents, including beta-lactams, penicillin, aminopenicillins, fluoroquinolones (specifically including ciprofloxacin), cephalosporins, and carbapenems, which in the opinion of the investigator would make it difficult to properly provide either empiric antibiotic therapy or treat an active infection

	9. 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) 10. Laboratory abnormalities at screening, including: • Alkaline phosphatase (ALP) >1.5× upper limit of normal (ULN) • Absolute neutrophil count (ANC) <1,000/μL • Alanine aminotransferase (ALT) > ULN • Any other clinically significant laboratory abnormality that, in the opinion of the Primary Investigator (PI), would make the patient inappropriate for the study or put the patient at undue risk 11. 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 12. Prior history or current evidence of biliary cholestasis 13. Gilbert's syndrome Patients with history or family history suggestive of Gilbert's syndrome should be tested and excluded from study if positive for UGT1A1 genotyping polymorphism or missense change 14. Evidence of human immunodeficiency virus (HIV), hepatitis B or hepatitis C infection (positive serology for HIV-1 antibody (HIV Ab), positive hepatitis B surface antigen (HbsAg), or positive anti-HCV antibody (HCV Ab) at Screening or historically)
Criteria to Escalate to a Higher Dose	Decisions to dose escalate or change the dosing regimen will be made by the site PI. The Sponsor will be notified of dose escalation/regimen changes and any study termination decisions. **1st Dose Escalation Point (Day 7)** On a patient-by-patient basis, if the starting dose of 150 mg TID is well tolerated and the available safety data are satisfactory, a patient may be escalated to 175 mg TID if his/her Day 6 LDH level, as measured locally, is still greater than 50% of his/her baseline value, unless the patient has achieved <1× ULN for LDH. Depending on when these data are received and reviewed, if the patient is going to dose escalate, the site should contact the patient as soon as possible (Days 6-8) to provide new dosing instructions. If necessary, the patient may be asked to return to the clinic for new drug supplies. **2nd Dose Escalation Point (Day 14)** On a patient-by-patient basis, if the patient was not dose escalated at Day 7, the 150 mg TID dose is well tolerated, and the available safety data are satisfactory, a patient may be escalated to 175 mg TID if his/her Day 13 LDH level, as measured locally, is still greater than 20% of his/her baseline value, unless the patient has achieved <1× ULN for LDH. Depending on when these data are received and reviewed, if the patient is going to dose escalate, the site should contact the patient as soon as possible (Days 13-15) to provide new dosing instructions. If necessary, the patient may be asked to return to the clinic for new drug supplies. In addition to the dose escalation evaluations defined above, the PI, in consultation with the Sponsor, may escalate dosing in increments of 25 mg to a maximum of 250 mg TID after

	evaluating the clinical benefit and the available safety, PK, and PD data (including laboratory test results) in order to improve control of hemolysis. The dose will not be escalated for a patient if one or more of the following occurs: • Patient experiences a study drug-related Grade 4 adverse event (AE) • It is determined that the limit of safety and/or tolerability has been reached. This decision will be made following discussions between the sponsor's Medical Monitor and the site PI • The maximum allowed dose of 250 mg TID has already been reached • LDH level, as measured locally, is reduced to ≤50% relative to baseline by Day 6, or to ≤20% relative to baseline by Day 13 If a patient has been dose escalated, patients may be dose reduced to a lower dose for safety or tolerability reasons following consultation between the investigator and the Achillion medical monitor. Based on Day 20 LDH results, if a patient's LDH level is still less than or equal to 20% of his/her baseline value and remains <1.5× ULN for LDH, then the patient will be permitted to continue dosing after Day 28 by entering Part 2 of the study without further approval from the sponsor. For patients who do not meet the preceding definition, the investigator will discuss with the sponsor about progressing the patient to Part 2 of the study if they believe that there has been clinically significant improvement in Part 1. This discussion and the resulting decision and rationale will be documented in the site file.
Individual Stopping Criteria:	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 (exceptions may be considered at the request of the investigator if the event can be managed by dose reduction or interruption); • 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 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 clinically significant elevation in Total Bilirubin* relative to baseline * Because patients may have ongoing hemolysis which may result in increased bilirubin and AST, increases in bilirubin and/or AST during the study must be evaluated in the context of any continuing hemolysis. The PI should evaluate LDH and Hgb levels as well as baseline bilirubin and AST levels to determine if the increases observed are due to an effect on liver function or are secondary to hemolysis.
Test Product; Dosage Form; and Strength:	ACH-0144471, administered orally as 50, 75, or 100 mg tablets

Mode of Administration:	Oral
Duration of Treatment, Confinement, and Total Study Participation	Each patient will receive multiple doses of ACH-0144471 tablets for a total of 28 days during Part 1, and may be treated for an additional 8 weeks if they participate in Part 2. Additionally, there will be a 6-day taper at the end of treatment, for a total treatment duration of up to 90 days. Including the taper, the total study duration for patients who complete Part 1 but do not participate in Part 2 will be 48 days, not including screening. For patients who participate in both Part 1 and Part 2, the total study duration will be up to 104 days, not including screening. There are no overnight stays in the clinic. The maximum screening period is up to 60 days.
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 the Schedule of Assessments. Due to the increased risk of infection from treatment with complement inhibitors, patients in this study will receive vaccinations and will be carefully monitored for the development of fever.
Pharmacokinetic Assessments:	Blood samples will be collected as described in Section 6.14, at the times indicated in the schedule of assessments in Appendix 1, to determine plasma concentrations of ACH-0144471. Multiple-dose PK parameters of ACH-0144471, including t_{max}, C_{max} and $AUC_{0\text{-}tau}$ will be determined at each dose level using validated bioanalytical methods. Single trough PK samples will be taken at other time points.
Pharmacodynamic and Efficacy Assessments	Pharmacodynamics will be evaluated as described in Section 6.15, using serum, plasma, or whole blood collected during the study. Samples will be collected and retained for non-genetic complement-associated biomarker testing and potentially may also be retained for genetic complement-associated biomarker testing, as discussed in Section 6.11.2. Efficacy will be assessed using LDH and hemoglobin levels and other measures of hemolysis, as well as RBC transfusion requirements.
Patient-reported Outcomes Assessments	Quality of Life (QoL) assessments will be conducted at various time points as specified in schedule of assessment in Appendix 1 using the tools in Appendix 2. The FACIT Fatigue scale (Version 4) questionnaire and the EORTC-QLQ-C30 scale will be administered to patients to collect patients' health-related QoL at baseline and after treatment with ACH-0144471, respectively. In addition, interviews by independent outcomes researchers chosen by the Sponsor will be conducted with patients prior to initiation of study treatment (during the screening period) to collect patients' experience of PNH, its impact on everyday lives and the disease trajectory. For patients enrolled in the Screening Study (ACH471-102), the interview conducted as part of that study will replace the screening interview in the current study. At the end of Part 1 (Day 28 ± 1 week), phone interviews will be conducted with all patients to collect patients' experience of ACH-0144471 treatment and their perception of the evolution of their condition. Patients continuing in Part 2 will also be interviewed at the end of Part 2 (Day 84 ± 1 week). The interviews will be conducted over the phone by a trained, experienced interviewer and will last approximately 30 minutes. For patients who terminate early, a follow-up interview will be obtained at the time of termination.

Statistical Methods:	Summary statistics will be provided for the following efficacy, safety, PK, and PD parameters: • Efficacy parameters: o Primary: Change in LDH level relative to baseline at Day 28 o Secondary: ▪ Change in Hgb level at Day 28 relative to baseline ▪ Change in Hgb level relative to baseline at Day 84 ▪ Change in LDH level relative to baseline at Day 84 • Safety parameters: o SAEs o AEs leading to discontinuation of the study medication o AEs (related and regardless of relationship to study medication) o Laboratory abnormalities by toxicity grade • PK, PD, and biomarker parameters: o Selected chemistry and hematology measures o PK parameters at various time points o PD markers/assays to assess the biological effect of ACH-0144471 on the classical and alternative pathways of complement • Patient-reported outcomes o FACIT Fatigue scale (Version 4) o EORTC QLQ-C30 All continuous variables will be summarized using descriptive statistics including number of observations, number of missing data, mean, standard deviation (SD), minimum (min), median (med), and maximum (max). All categorical variables will be summarized using frequency counts and percentages.

Table of Contents

List of Tables

List of Figures

List of Appendices

List of Abbreviations and Definitions of Terms

Abbreviation	Definition
1A1	Cytochrome P450 family 1 subfamily A member 1
ACIP	Advisory Committee on Immunization Practices
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AP	Alternative Pathway (of complement)
AST	Aspartate aminotransferase
AUC	Area under the curve
BA	Bioavailability
Bb	Bb fragment of complement factor B
BID	"bis in die" or twice daily
BP	Blood pressure
BMI	Body mass index
°C	Degrees Celsius
C3	C3 complement protein
C5	C5 complement protein
CH50	a measurement of general function of complement classical pathway
CK	Creatine kinase
C_{max}	Maximum plasma concentration
CRF	Case report form
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
fB	Complement Factor B
fD	Complement Factor D
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GPI	glycosylphosphatidylinositol
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
Hct	Hematocrit
Hgb	Hemoglobin
HCV	Hepatitis C virus
HIPAA	Insurance Portability and Accountability Act of 1996
HIV	Human immunodeficiency virus
HR	Heart rate
HSCT	Hematopoietic stem cell transplantation
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional review board
IV	Intravenous
kDa	Kilodalton
LDH	Lactate dehydrogenase
LFC	Liquid-filled capsule
LLN	Lower limit of normal

Abbreviation	Definition
MAC	Membrane attack complex
MAD	Multiple-ascending dose
max	Maximum
MDRD	Modification of Diet in Renal Disease equation
med	Median
MedDRA	Medical Dictionary for Regulatory Activities
min	Minimum
NOAEL	No observed adverse effect level
NOEL	No observable effect level
PD	Pharmacodynamic(s)
PI	Principal investigator
PIGA	Phosphatidylinositol N-acetylglucosaminyltransferase subunit A
PK	Pharmacokinetic(s)
PNH	Paroxysmal Nocturnal Hemoglobinuria
PR	PR interval
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
QoL	Quality of Life
QRS	Group of electrocardiogram waves comprising the Q, R, and S waves
QT	QT interval
QTc	Corrected QT
QTcF	QT interval Fridericia Correction Formula
RBC	Red blood cells
Rel BA	Relative bioavailability study
RR	Respiration rate
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
TE	Treatment-emergent
TEAE	Treatment-emergent adverse event
TID	"ter in die" or three times daily
t_{max}	Time after administration of a drug when the maximum plasma concentration is reached
UGT1A1	Uridine diphosphate glucuronosyltransferase family 1 member A1
ULN	Upper limit of normal
µM	Micromolar
WBC	White blood cells

1 Introduction

This is a multiple-center, open-label, multiple dose study, and will be the first study in which ACH-0144471 is administered to patients with paroxysmal nocturnal hemoglobinuria (PNH). Dosing has been determined based on data from the first-in-human single-ascending dose (SAD), multiple ascending dose (MAD), and Relative Bioavailability (Rel BA) studies in healthy volunteers.

Many inflammatory, autoimmune, neurodegenerative and age-related diseases, including PNH, are associated with either normal complement system activity acting on cells which are missing complement regulatory proteins, or alterations of complement regulation itself [1]. ACH-0144471 is a small molecule, orally administered complement factor D (fD) inhibitor being developed by Achillion Pharmaceuticals, Inc. for the treatment of patients with PNH to reduce hemolysis and other complement-mediated diseases. ACH-0144471 could potentially represent an important advance for the treatment of several complement-mediated diseases as it targets complement fD, the control point for the complement amplification loop [2] as well as providing the convenience of oral dosing.

1.1 Results of Nonclinical Studies

Please refer to the Investigator's Brochure (IB) [3] 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

Three clinical studies with ACH-0144471 have been conducted: ACH471-001 Single Ascending Dose Study (SAD), ACH471-002 Multiple Ascending Dose Study (MAD) and ACH471-006 Relative Bioavailability Study (Rel BA). One hundred and fifteen (115) healthy volunteers have participated in clinical studies with ACH-0144471, of which 87 have received ACH-0144471, and the remaining received placebo. Preliminary results from all 3 studies are presented in the IB [3].

The SAD study was performed to evaluate the safety and tolerability of single ascending doses of ACH-0144471. Healthy volunteers were dosed with ACH-1044471 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 with PNH in phase 2 studies. Healthy volunteers were dosed with ACH-1044471 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. The higher doses studied (500 and 800 mg administered every 12 hours for 14 days) were associated with elevations in alanine aminotransferase (ALT) levels in some patients. 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 PNH and other complement-mediated diseases.

The pharmacodynamics (PD) and potential for clinical efficacy for ACH-0144471 is primarily associated with maintenance of exposure above a target trough level. Exploratory ex vivo alternative pathway (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) [4]. Pharmacokinetic modeling, based on data from the SAD and MAD studies, predicts that plasma trough ACH-0144471 concentrations can be increased substantially with minimal increase C_{max} or AUC, 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 these analyses and additional emerging data from the first 2 patients enrolled in this study (see Section 3.2.2), 150 mg TID is expected to provide clinical efficacy, and is selected as the starting dose for this study. All patients enrolled in ACH471-100 to date have dose escalated to 200 mg TID with no clinically significant alterations in liver enzymes.

The SAD and MAD studies were conducted using liquid-filled capsules (LFC). Studies in PNH 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-1044471 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.

Another study in patients with C3 Glomerulopathy (C3G) or Immune-Complex Membranoproliferative Glomerulonephritis (IC-MPGN), ACH471-201, is ongoing. The trial will evaluate the ability of ACH-0144471, given for 14 days, to increase C3 levels via inhibition of fD.

1.3 Rationale

1.3.1 Complement Factor D

Factor D (fD) is one of nine serine proteases in the complement system. It is a highly specific enzyme with only one known substrate, factor B (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, 5]. 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, 5]. 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 [6, 7]. 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 such as PNH.

1.3.2 Paroxysmal Nocturnal Hemoglobinuria (PNH)

PNH is a rare disease of unknown frequency both in the United States and worldwide. One small study conducted in Great Britain and France, reported in 1995, provided an incidence rate of approximately 1.3 cases/1 million inhabitants. Attempts to get a more accurate incidence and to learn more about its natural course are currently under way under the auspices of the PNH Registry [8].

PNH may occur at any age; it has been reported in children as young as 2 years to adults as old as 83 years, but it is most frequently diagnosed in adults, with a median age at diagnosis of approximately 40 years. Men and women are affected equally, and no familial tendencies exist. It has been suggested that PNH, like aplastic anemia, with which it is associated, may be more frequent in Southeast Asia and in the Far East.

PNH is caused by a somatic mutation in the PIGA gene in hematopoietic stem cells, resulting in the loss of glycosylphosphatidylinositol (GPI) anchored proteins, including the complement regulatory proteins CD55 and CD59, from the surface of mutant red blood cells (RBCs). This leaves these mutant RBCs vulnerable to intravascular hemolysis mediated by the membrane attack complex (MAC) of complement and to extravascular hemolysis presumably mediated by C3 fragment opsonization primarily due to constitutive activation of the complement alternative pathway via tickover mechanism [9]. In addition to anemia that requires frequent RBC transfusions, there are other serious sequelae related to the liberation of intracellular hemoglobin and its consequent derangement of nitric oxide levels in the vasculature. These effects include an increased risk of thrombotic events as well as painful vascular crises.

The only curative treatment for PNH is hematopoietic stem cell transplantation (HSCT) using allogeneic donors. Given the high transplant-related mortality, especially when using unrelated or mismatched donors, HSCT is generally not offered as initial therapy for most patients with classic PNH. The only drug approved to treat PNH is eculizumab, a monoclonal antibody directed against complement C5, which prevents intravascular hemolysis by inhibiting formation of the terminal complement complex. Other supportive therapies include: recombinant erythropoietin, corticosteroids, and androgens to stimulate erythropoiesis; anticoagulants to treat thrombotic complications; and immunosuppressive agents to stimulate hematopoiesis in the aplastic phase.

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

PNH is a serious life threatening disease and there are unmet needs in this population that are not addressed by eculizumab that could potentially be addressed by an effective oral fD inhibitor. Three groups of patients who are not adequately served by eculizumab and could receive benefit from ACH-0144471 can be identified:

- Patients who have a suboptimal response to eculizumab (approximately 25% - 30%), presumably largely due to extravascular hemolysis that is mediated by C3 opsonization. Eculizumab treatment spares the hemolytic destruction of PNH erythrocytes by the MAC (terminal stage of the complement pathway); however, it does not prevent deposition of C3 fragments on PNH erythrocyte membranes which can direct their extravascular hemolysis [10]. ACH-0144471 has a potential

mechanistic advantage since it acts upstream of C3 cleavage and has been shown to block C3 fragment deposition.

- Patients who respond partially to eculizumab due to a genetic polymorphism in CR1 (e.g., HindIII H/L and L/L genotypes [11]), which has been postulated to result in an increased proportion of C3-opsonized RBCs, may have an improved treatment response with ACH-0144471.
- Rare patients (~1%) with no response to eculizumab due to mutations in C5 (e.g., Arg885His) [12] could also benefit from ACH-0144471 because ACH-0144471 acts at a different target in the complement cascade and should be unaffected by a mutation in C5.

Additionally, oral administration of ACH-0144471 would be an advantage compared to systemic intravenous administration of eculizumab which is given weekly in the initial phase of treatment and then every two weeks as maintenance therapy.

1.3.4 Safety Considerations

1.3.4.1 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 fD, inhibition of the complement system may result in a lifetime increased risk of infection, notably with *Neisseria meningitidis (N. meningitidis)* [13, 14, 15], and other encapsulated organisms.

Because of this potential risk, special safety precautions will be taken for patients participating in ACH471-100. Patients will be required to be previously vaccinated, or to receive vaccinations for *N. meningitidis*, *Streptococcus pneumoniae* (*S. pneumonia*e), and *Haemophilus influenzae* (*H. influenzae*) (see Section 6.3).

During clinic visits, patients will be monitored for the development of fever. A specific Fever Management Plan (Appendix 4) has been developed for this study. Patients will also be counseled about behaviors to avoid and also be asked to monitor themselves between clinic visits (Appendix 4).

1.3.4.2 Hepatic Injury

In humans, elevations in ALT levels have been observed in some healthy volunteers with doses of 500 mg twice daily and 800 mg twice daily for 14 days, doses higher than the currently anticipated clinical dose. The ALT elevations were not associated with signs or symptoms of hepatic failure, occurred after completion of dosing, and were self-limited.

Additionally, DILIsym simulations indicate maximal loss of hepatocytes that occurred at the high doses in the MAD study would not have a significant effect on liver function [16]. Simulated dosing at 250, 300, and 325 mg TID for up to 1 year predicted minor, clinically insignificant (<1× ULN) ALT increases 17].

In nonclinical studies, hepatobiliary cholestasis has been observed in the dog toxicology studies at exposures higher than those intended for clinical use. Therefore, alkaline phosphatase, gamma-glutamyl transferase (GGT), total/direct/indirect bilirubin, aspartate aminotransferase (AST), and ALT will be closely monitored in all clinical studies with ACH-0144471.

2 Study Objectives

2.1 Primary Objective

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

2.2 Secondary Objectives

The secondary objectives of this study are:

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

2.3 Exploratory Objectives

The exploratory objectives of this study are:

- To evaluate the relationship between ACH-0144471 multiple-dose pharmacokinetics and pharmacodynamic biomarkers through inhibition of AP activity (PK/PD)
- To evaluate health-related QoL based on patient-reported outcome (PRO) instruments and its evolution over the course of ACH-0144471 treatment
- To explore the benefits of ACH-0144471 treatment as perceived by patients with PNH, by:
  - Exploring patients' experiences of PNH, its impact on everyday lives and the disease trajectory, from first symptoms to definitive diagnosis and beyond
  - Documenting the evolution of PNH over the course of ACH-0144471 treatment from a patient's perspective
- To explore patients' expectations towards ACH-0144471 treatment

3 Investigational Plan

3.1 Overall Study Design and Plan

This is a multiple-center, open-label, multiple dose study. Screening data may be collected during the Screening Phase of this study or if the patient has been previously enrolled in Study ACH471-102, during that study. Baseline values for the PD and safety parameters will be evaluated during screening.

During screening, patients will be evaluated for eligibility criteria and have screening assessments performed. Screening procedures may be spread over more than one visit. A window of up to 60 days is permitted to allow screening followed by any required vaccinations; if a patient is participating in the preliminary screening study (ACH471-102), vaccinations may already have been administered, and tests performed as part of that study within 30 days of first administration of study drug and may fulfill screening requirements for this study. Once patients have been confirmed as eligible, they will be evaluated for history of vaccination against *N. meningitidis*, *H. influenzae*, and *S. pneumoniae*. Those who have not been vaccinated will receive vaccinations during this study according to the schedule described in Section 6.3. Those who have been previously vaccinated will receive recommended boosters as described in Section 6.3. After screening and any vaccination procedures occurring before dosing, patients will enter the treatment portion of the study which will be conducted in 2 parts (Figure 1). In Part 1, each participant will receive daily oral doses of ACH-0144471 for 28 days. In Part 2, patients may continue dosing for an additional 8 weeks (56 days).

Patients will begin dosing on Day 1. Patients will return to the clinic on Days 6, 13, and 20 for additional intensive PK sampling and other assessments, and will be evaluated for dose escalation as described in Section 3.2.2. Patients will continue dosing until Day 28 for continued collection of safety information. Dosing for patients not continuing to Part 2 will then be tapered over 6 days, as described in Section 5.2.1.

Based on a review of safety and efficacy data through Day 20 for each individual, patients with reductions in LDH meeting the criteria specified in Section 3.2.3 will be offered continued dosing beyond Day 28 for an additional 8 weeks (Part 2). Patients who do not meet the criteria may be offered participation in Part 2 if there has been clinically significant improvement during Part 1, as described in Section 3.2.3. Participation in Part 2 will be based on Day 20 data to allow adequate time for review and decision making prior to the scheduled end of dosing in Part 1 on Day 28. Patients participating in Part 2 of the study will continue to receive daily oral doses of ACH-0144471, and will return for follow-up visits on Days 42, 56, 70, and 84. On Days 35, 49, 63, and 77 patients will have local safety labs drawn. After Day 84, dosing will then be tapered over 6 days, as described in Section 5.2.1. For all patients, a final follow-up visit will be conducted approximately 14 days after the last dose.

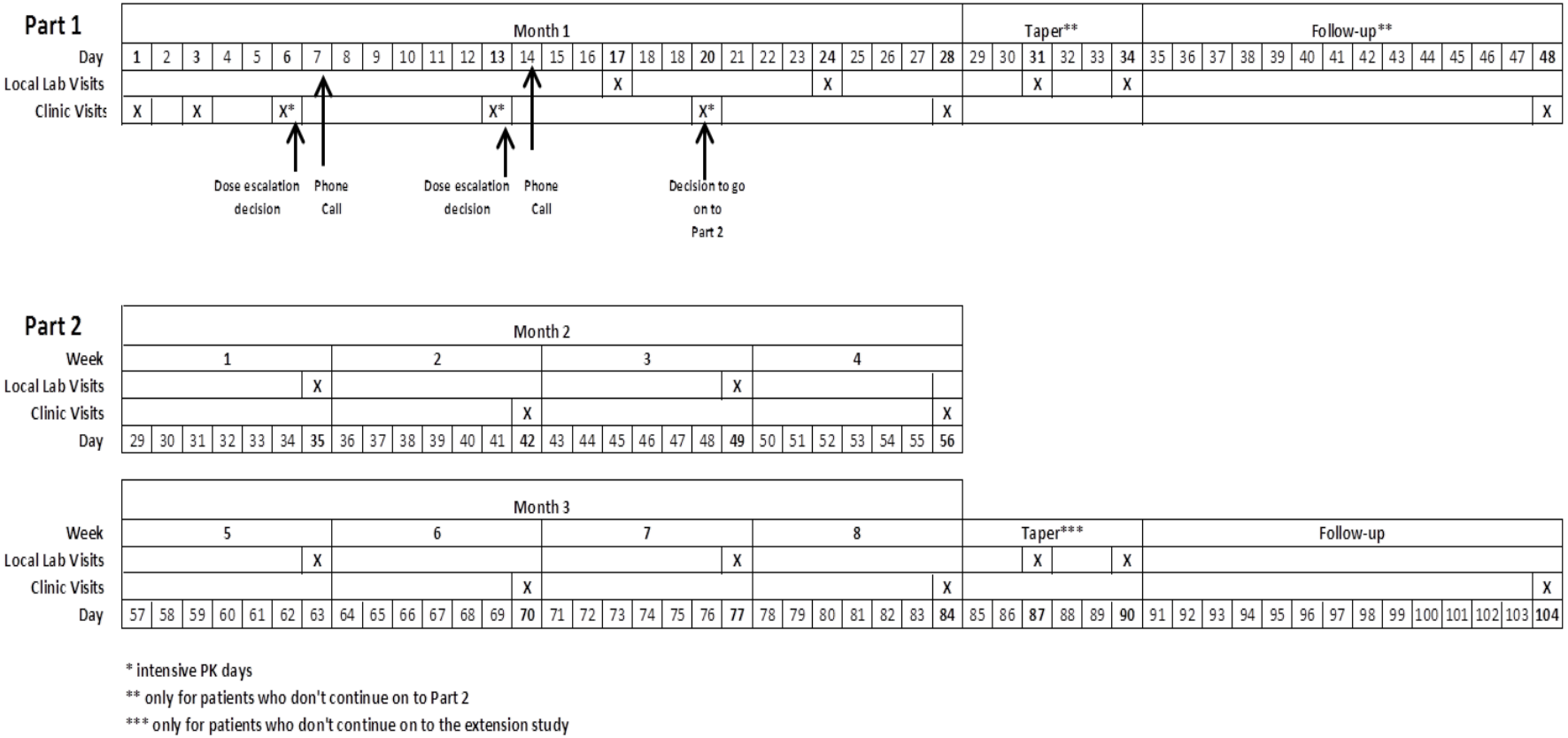
The FACIT Fatigue Scale (Version 4) questionnaire and the EORTC-QLQ-C30 (Version 3) will be administered to patients at the schedule indicated in Appendix 1 using the tools provided in Appendix 2, to collect patients' health-related quality of life at baseline and after treatment with ACH-0144471.

In addition, patients will be interviewed by an independent outcomes researcher chosen by the Sponsor to collect their experience of PNH, its impact on everyday lives and the disease trajectory, and, following treatment, to collect patients' experience of ACH-0144471 treatment and their perception of the evolution of their condition. The interviews will be conducted over the phone by a trained, experienced interviewer and will last approximately 30 minutes.

Patients who have not been included in the Screening Study (protocol ACH471-102) will be interviewed during the screening period (prior to study initiation). Interviews for all patients will be conducted at the end of Part 1 (Day 28 ± 1 week). Patients continuing in Part 2 will also be interviewed at the end of Part 2 (Day 84 ± 1 week). For patients who terminate early, a follow-up interview will be obtained at the time of termination.

Considering PNH is a serious life threatening disease, a long-term extension study beyond the 3 months of dosing included in this study may be offered to patients, if supported by clinical and nonclinical data. Pending regulatory and ethics committee approval of such a study, patients who, in the opinion of the PI, are receiving benefit from ACH-0144471 may be enrolled directly into that study without interruption from this study, and will continue to receive daily treatment with ACH-0144471 and safety and efficacy monitoring. Any patients so enrolled will not require a dosing taper or the follow-up visits described in this protocol.

Figure 1. Study Schematic



* intensive PK days

** only for patients who don't continue on to Part 2

*** only for patients who don't continue on to the extension study

3.2 Rationale for Study Design

3.2.1 Justification of Design

This will be the first study of ACH-0144471 in patients diagnosed with PNH. The study design therefore includes careful patient safety monitoring, and extensive laboratory, PK, and PD marker monitoring during Part 1 of the study. At each of two protocol-defined dose escalation time points, the individual patient's safety data and LDH values will be reviewed to determine if dose escalation is warranted. In addition, the PI, in consultation with the Sponsor, may escalate dosing in increments of 25 mg to a maximum of 250 mg TID after evaluating the clinical benefit and the available safety, PK, and PD data (including laboratory test results) in order to improve control of hemolysis, as discussed in Section 3.2.3.

LDH has long been accepted as a marker for RBC hemolysis, as reported in prior studies of hemolytic anemia and in studies of patients with PNH. Therefore, a reduction in LDH relative to baseline, reflecting a reduction in intravascular hemolysis, will be the primary endpoint.

3.2.2 Justification of Dose

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 suggest 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 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 plasma trough ACH-0144471 concentrations can be increased substantially with minimal increase C_{max} or AUC, 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. The starting dose in this study will therefore be 150 mg TID, which is expected to provide clinical efficacy.

All patients enrolled in this study to date have dose escalated to 200 mg TID with no clinically significant alterations in liver enzymes, but the available data suggests that some patients may receive additional clinical benefit from further dose escalation. If necessary to achieve an improved reduction in hemolysis, as measured by correction of serum LDH, dose escalation will be permitted in increments of 25 mg to a maximum of 250 mg TID after evaluating the clinical benefit and the available safety, PK, and PD data (including laboratory test results).

3.2.3 Criteria to Escalate to a Higher Dose or Change the Dosing Regimen

Decisions to dose escalate or change the dosing regimen will be made by the site PI. The Sponsor will be notified of dose escalation/regimen changes and any study termination decisions.

1st Dose Escalation Point (Day 7)

On a patient-by-patient basis, if the starting dose of 150 mg TID is well tolerated and the available safety data are satisfactory, a patient may be escalated to 175 mg TID if his/her Day 6 LDH level, as measured locally, is still greater than 50% of his/her baseline value, unless the patient has achieved <1× ULN for LDH. Depending on when these data are received and reviewed, if the PI plans to dose escalate the patient, the site should contact the patient as soon as possible (Days 6-8) to provide new dosing instructions. If necessary, the patient may be asked to return to the clinic for new drug supplies.

2nd Dose Escalation Point (Day 14)

On a patient-by-patient basis, if the patient was not dose escalated at Day 7, the 150 mg TID dose is well tolerated, and the available safety data are satisfactory, a patient may be escalated to 175 mg TID if his/her Day 13 LDH level, as measured locally, is still greater than 20% of his/her baseline value, unless the patient has achieved <1× ULN for LDH. Depending on when these data are received and reviewed, if the PI plans to dose escalate the patient, the site should contact the patient as soon as possible (Days 13-15) to provide new dosing instructions. If necessary, the patient may be asked to return to the clinic for new drug supplies.

Following the dose escalation evaluations defined above, the PI, in consultation with the Sponsor, may escalate dosing in increments of 25 mg to a maximum of 250 mg TID after evaluating the clinical benefit and the available safety, PK, and PD data (including laboratory test results). Patients should have blood drawn (locally or at the clinic) 72 to 84 hours after starting the new dose for measurement of LDH and liver function tests (ALT, AST, GGT, and ALP).

Dosing will not be escalated for a patient if one or more of the following occurs:

- Patient experiences a study drug-related Grade 4 AE
- It is determined that the limit of safety and/or tolerability has been reached. This decision will be made following discussions between the sponsor Medical Monitor and the site PI
- The maximum allowed dose of 250 mg TID has already been reached
- LDH level, as measured locally, is reduced to ≤50% relative to baseline by Day 6, or to ≤20% relative to baseline by Day 13

If a patient has been dose escalated, he/she may be dose reduced to a lower dose for safety or tolerability reasons following consultation between the investigator and the with Achillion medical monitor.

Based on Day 20 LDH results, if a patient's LDH level is less than or equal to 20% of his/her baseline value and remains <1.5× ULN for LDH, then the patient will be permitted to continue dosing after Day 28 by entering Part 2 of the study without further approval from the sponsor.

For patients who do not meet the preceding definition, the investigator will discuss with the sponsor about progressing the patient to Part 2 of the study if they believe that there has been clinically significant improvement in Part 1. This discussion and the resulting decision and rationale will be documented in the site file.

3.2.4 Individual Stopping Criteria

The PI may stop dosing in any patient who meets one of the stopping criteria described below; however, the Achillion medical monitor should be notified immediately and if possible, before dosing is terminated. If dosing is to be terminated for any reason other than safety, it is recommended that a taper be implemented as described in Section 5.2.1. If dosing is terminated for safety-related reasons, the PI may discontinue dosing immediately if they feel it is in the best interest of the patient. Whenever possible, this decision should be discussed with the Achillion medical monitor prior to dosing termination.

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 (exceptions may be considered at the request of the investigator if the event can be managed by dose reduction or interruption);
- 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:

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 clinically significant elevation in Total Bilirubin* relative to baseline

* Because patients may have ongoing hemolysis which may result in increased bilirubin and AST, increases in bilirubin and/or AST during the study must be evaluated in the context of any continuing hemolysis. The PI should evaluate LDH and Hgb levels as well as baseline bilirubin and AST levels to determine if the increases observed are due to an effect on liver function or are secondary to hemolysis.

In addition to the individual stopping criteria described above, the sponsor reserves the right to close any study site or terminate the study at any time for any reason at the sole discretion of the sponsor.

3.3 Study Duration and Dates

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. Additionally, there will be a 6-day taper at the end of treatment, for a total treatment duration of up to 90 days. Including the taper, the total study duration for patients who complete Part 1 but do not participate in Part 2 will be 48 days, not including screening. For patients who participate in both Part 1 and Part 2, the total study duration will be up to 104 days, not including screening. There are no overnight stays in this study. The maximum screening period is up to 60 days.

4 Study Population Selection

4.1 Study Population

This study will be conducted in currently untreated PNH patients meeting eligibility criteria.

4.2 Inclusion Criteria

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

1. Currently untreated PNH patients with PNH Type III erythrocyte and/or granulocyte clone size ≥10% and anemia (Hgb <12 g/dL) with adequate reticulocytosis (as determined by the investigator)
2. LDH ≥1.5× upper limit of normal (ULN)
3. Platelet count ≥50,000/µL in the absence of platelet transfusion
4. Documentation of vaccination for *Neisseria meningitidis*, *Haemophilus influenzae*, and *Streptococcus pneumoniae*, or willingness to receive vaccinations as described in Section 6.3
5. Age ≥18 years (or ≥ minimum adult age in accordance with local legal requirements)
6. Female participants of childbearing potential must agree to use an acceptable method of contraception (as defined in Section 5.5.5) from the date of signing the informed consent to the first day of dosing (Day 1), and must agree to use a highly effective method of contraception (as defined in Section 5.5.5) from the first day of dosing to 30 days after their last dose of study drug. Female participants of childbearing potential must also have a negative serum pregnancy test during Screening and negative urine pregnancy test on Day 1.

   Female participants of non-childbearing potential need not employ a method of contraception.
7. Non-sterile male participants must agree to use a highly effective method of contraception (as defined in Section 5.5.5) with their partner(s) of childbearing potential from the first day of dosing to 90 days after their last dose of study drug.

   Males who are surgically sterile need not employ additional contraception.

   Males must agree not to donate sperm while enrolled in this study and for 90 days after their last dose of study drug.
8. Must agree to provide written informed consent
9. Must be willing, at all times, 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 hematopoetic stem cell/marrow transplant

2. History of dosing with another investigational agent within 30 days or 5 half-lives of the investigational agent prior to study entry, whichever is greater
3. History of dosing with eculizumab at any dose or interval within the past 75 days before study drug administration
4. Known or suspected complement deficiency
5. Contraindication to one or more of the required vaccinations
6. Active bacterial infection or clinically significant active viral infection, a body temperature >38°C, or other evidence of infection on Day 1, or with a history of febrile illness within 14 days prior to first study drug administration
7. History of meningococcal infection, or a first-degree relative or household contact with a history of meningococcal infection
8. History of hypersensitivity reactions to commonly used antibacterial agents, including beta-lactams, penicillin, aminopenicillins, fluoroquinolones (specifically including ciprofloxacin), cephalosporins, and carbapenems, which in the opinion of the investigator would make it difficult to properly provide either empiric antibiotic therapy or treat an active infection
9. 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)
10. Laboratory abnormalities at screening, including:
    - Alkaline phosphatase (ALP) >1.5× ULN
    - Absolute neutrophil count (ANC) <1,000/μL
    - Alanine aminotransferase (ALT) > ULN
    - Any other clinically significant laboratory abnormality that, in the opinion of the PI, would make the patient inappropriate for the study or put the patient at undue risk
11. 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
12. Prior history or current evidence of biliary cholestasis
13. Gilbert's syndrome

    Patients with history or family history suggestive of Gilbert's syndrome should be tested and excluded from study if positive for UGT1A genotyping polymorphism or missense change
14. Evidence of human immunodeficiency virus (HIV), hepatitis B or hepatitis C infection (positive serology for HIV-1 antibody (HIV Ab), positive hepatitis B surface antigen (HbsAg), or positive anti-HCV antibody (HCV Ab) at Screening or historically

5 Study Treatment(s)

5.1 Study Drug

ACH-0144471 will be dosed as a tablet formulation containing the drug substance, lactose, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulphate, magnesium stearate, colloidal silicon dioxide and hypromellose acetate succinate. The coating components are: polyvinyl alcohol, titanium dioxide, macrogol/polyethylene glycol and talc.

5.2 Treatment(s) Administered

5.2.1 ACH-0144471

A single treatment group is planned. The expected enrollment is approximately 4 to 12 patients. ACH-0144471 will be administered as multiple doses over a period of at least 28 days. The starting dose, dosing interval and maximum dose is based on data from the Phase 1 SAD, MAD, Rel BA studies, and emerging data from the first two patients in this study. The starting dose will be 150 mg TID, and the maximum dose will be 250 mg TID.

If patients do not go on to an extension study, it is recommended that a taper of ACH-0144471 be implemented, according to the schedule in Table 1. If dosing is terminated for safety-related reasons, the PI may discontinue dosing immediately if they feel it in the best interest of the patient. Whenever possible, this decision should be discussed with the Achillion medical monitor prior to dosing termination.

Table 1. Dosing Taper Schedule

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

5.2.2 Vaccines

Depending on the patient's vaccination history, the vaccines described in Section 6.3 may need to be administered to patients according to the schedule described. Since these are commercially available products, information about the specific vaccines can be found on the package inserts/product labels for those products.

5.3 Selection of Timing and Dose for Each Patient

Patients will be dosed three times daily (TID) (a dose in the morning, a second dose approximately 8 hours later, and a third dose approximately 8 hours after the second dose). Doses should be taken at approximately the same time each day and as close as possible to 8 hours apart. All doses should be taken approximately 15-30 minutes after completion of a meal or snack. 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. For Clinic Visit days, patients should be instructed 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. In addition, patients should be instructed to fast for at least 8 hours prior to coming to the clinic on Days 1, 13, and 28. Patients will be required to bring their study drug at each visit so that study site personnel may perform drug accountability.

5.3.2 Home Dose Administration Instructions

Patients will take ACH-0144471 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. All doses should be taken approximately 15-30 minutes after completion of a meal or snack. 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 keep their study medications at room temperature.

5.4 Method of Assigning Patients to Treatment Groups

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

5.5 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 study drug administration, whichever is greater. Patients must not have received eculizumab at any dose or interval within the past 75 days before study drug administration.

5.5.2 Concomitant Therapy

Based on in vitro data, ACH-0144471 has the potential to inhibit several cytochrome (CYP) enzymes as well as some transporters. In contrast, the PK profile of ACH-0144471 is not likely to be affected by other drugs. Specific in vitro results for various CYP enzymes and transporters are described in the IB [3].

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. 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 steroids or other immunosuppressants is permitted if the dosage regimen is stable for at least 3 months before Day 1.
- Oral, injectable, implantable, transdermal, or intravaginal hormonal therapies are allowed for either contraception or hormonal replacement therapy.
- If it is necessary to treat a fever (see Appendix 4), 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.
- Administration of eculizumab or any other complement inhibitor is not permitted during this study.

The use of concomitant medications during the trial should be assessed at each visit, as indicated in the Schedule of Assessments (Appendix 1).

5.5.3 Fluid and Food Intake

Patients should be instructed to take each dose of ACH-0144471 with food. All doses should be taken approximately 15-30 minutes after completion of a meal or snack. Patients should be instructed to fast for at least 8 hours prior to coming to the clinic on Days 1, 13, and 28, and before the local safety lab sample collections on Days 49 and 77 to allow collection of fasting samples for determination of bile acids as described in Table 2.

5.5.4 Patient Activity and Other Restrictions

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

While the consumption of alcohol is not prohibited, patients should be counseled to avoid the consumption of alcohol while participating in this study.

5.5.5 Contraception

5.5.5.1 Contraception for Male Participants

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

Sterile is defined as having bilateral orchiectomy.

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

- Vasectomy with confirmed medical assessment of surgical success
- Condom plus use of one of the following by partner(s) of child-bearing potential:

- Oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
- Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation
- Intrauterine device (IUD) or Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion

- Sexual abstinence, defined as refraining from heterosexual intercourse during the entire period from the first day of dosing (Day 1) through 90 days after their last dose of study drug. Periodic abstinence (e.g., calendar, symptothermal, post-ovulation methods) is not an acceptable method of contraception. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. If a participant is usually not sexually active but becomes active, they, with their partner(s), must comply with the contraceptive requirements described in this section.

Male participants must agree to refrain from sperm donation while enrolled in this study and for 90 days after their last dose of study drug

5.5.5.2 Contraception for Female Participants

Female participants of childbearing potential must use an acceptable method of contraception from the date of signing the informed consent to the first day of dosing (Day 1), and must use a highly effective method of contraception from the first day of dosing (Day 1) through 30 days after their last dose of study drug.

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

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

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

- Any of the methods of highly effective contraception listed above
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide. Combinations of a male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.
- Cap, diaphragm or sponge with spermicide

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

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

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

5.6 Treatment Compliance

Treatment compliance assessments shall be performed at each visit. Patients will be required to bring their ACH-0144471 drug supply at 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 receive automated reminders (e.g., via SMS text or phone call) and must respond to record the time they take each daily dose of ACH-0144471 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:

- 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
- 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 in the original container at room temperature.

Patients will be required to bring 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 the 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.

6.2 Medical History

At Screening, the PI or designee will interview each patient and obtain a complete medical and medication history, including information related to the diagnosis, disease history, and management of the patient's PNH, to determine whether the patient meets the eligibility criteria. The history should include 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), and any prior use of alcohol, illicit drugs and/or controlled substances. The history should also include a full vaccination history. Patients must not require any treatment or medication for concurrent illnesses as specified by the inclusion and exclusion criteria or anticipate the need for any excluded concomitant medications. The history should also include up to 3 years of transfusion history, if available. The medical/medication history will be reviewed at each visit and at the final 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 Vaccination

Inhibition by ACH-4471 of factor D, and of the complement alternative pathway, may be associated with an increased risk of infection by *N. meningitidis*, *H. influenza*, and *S. pneumoniae*. Vaccination is an important means to mitigate this theoretical risk. Additional information regarding the risk of infection can be found in Section 6.5.1 of the Investigator's Brochure.

As discussed in Section 6.2, a full vaccination history will be gathered. Based on the vaccination history, the need for vaccinations against *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* in this study will be evaluated according to national and/or local guidelines. If local and/or national guidelines do not exist or do not fully address vaccination against these organisms, investigators should consider consulting the Advisory Committee on Immunization Practices (ACIP) guidelines (available at https://www.cdc.gov/vaccines/acip/index.html). Based on the available guidelines and each subject's vaccination history, the Investigator will assess the need for vaccinations against each organism and/or serotype. Study participants who do not have a sufficient history for some or all of these vaccines should be vaccinated or provided boosters as recommended in the applicable guidelines.

For any vaccines given as part of this study, full identifying information, including the brand, will be recorded in the participant's CRF. Samples will be collected from participants at the times indicated in the Schedule of Assessments (Table 5) for possible evaluation of response to vaccines.

6.4 Prophylactic Antibiotics

Antibiotic prophylaxis is allowed if deemed appropriate by local clinical practice and/or guidelines for treatment with a complement inhibitor. For example, if the vaccination series for *N. meningitidis* has not been completed at least 2 weeks prior to dosing with ACH-0144471, antibiotic prophylaxis with oral penicillin or an appropriate alternative (as described in Appendix 4) could be implemented in accordance with local practice on prevention of meningococcal infection. In such instances, consider continuing prophylaxis until at least two weeks after completion of the vaccination series.

6.5 Physical Examination

A complete physical examination will be conducted by the PI (or designee) at Screening and Day 1. This will include an examination of all major body/organ systems (including skin, head, eyes, ears, nose, throat, neck, thyroid, lungs, heart, abdomen, lymph nodes, and extremities), height, weight and calculation for BMI (height and BMI at Screening 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/skin, and additional organs or systems targeted to any new signs or symptoms, will be performed by the PI (or designee) at the times specified in the Schedule of Assessments (Appendix 1) or at the discretion of the Investigator or designee, and/or when patients present with AEs. 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. All vital sign measurements for an individual should be taken on the dominant arm (if possible) throughout the study. Vital signs may be measured using an automated vital signs machine. Vital sign values 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 4) 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 4).

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 by the PI or designee.

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

All ECGs must be read by the PI or designee. The PI/designee needs to evaluate the finding of ECG abnormalities promptly (refer to Section 6.17.1 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 Measurements

Blood and urine samples will be collected according to Table 2, at times listed in Appendix 1.

Patients will be in a seated or supine position during the blood collection. Specific instructions for sample collection, processing, and shipping will be provided in a separate laboratory manual.

Table 2. Clinical Laboratory Tests

Hematology	Chemistry	Urinalysis	Additional Screening Tests	Other Assessments[11]
Complete blood count (CBC), including: - Red blood cell (RBC) count - White blood cell (WBC) count - WBC differential (absolute and percent): - neutrophils - lymphocytes - monocytes - eosinophils - basophils - Hematocrit (Hct) - Hemoglobin (Hgb) - Mean corpuscular volume (MCV) - Mean corpuscular hemoglobin (MCH) - Mean corpuscular hemoglobin concentration (MCHC) - Mean platelet volume (MPV) - Platelet count - Red cell distribution width (RDW) - Reticulocyte count	Alanine aminotransferase (ALT) Albumin Alkaline phosphatase Aspartate aminotransferase (AST) Bicarbonate (HCO_3) Bilirubin (fractionated)[1] Bile Acids[2] Blood urea nitrogen (BUN) Calcium Calculated eGFR[3] Chloride Creatine kinase[4] Creatinine C-reactive protein (CRP) Gamma-glutamyl transferase (GGT) Glucose[5] Lactate dehydrogenase (LDH) 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) Potassium Sodium Total protein Uric acid	Bilirubin Color Glucose Ketones Hemosiderin Leukocytes Microscopic examination of sediment[6] Nitrite Occult blood pH Protein Specific gravity Urobilinogen	Erythropoietin FSH[7] HCV Ab HBsAg HIV Ab Sample for genetic biomarker testing (white blood cells)[8] Serum Pregnancy test[9] Urine drug screen[10]	AP Wieslab Bb C3 CH50 C3fragment deposition D-dimer Direct Coombs Factor D Free hemoglobin Haptoglobin Plasma/Serum samples for additional non-genetic biomarker testing[8] PNH Clone Size PT/PTT/INR Urine pregnancy test[9] Samples for assessment of patient response to vaccines

All tests to be performed as per the schedule outlined in Appendix 1.

1 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

2 Days 1, 13, 28, 49, and 77 only; samples must collected under fasting conditions on these days

3 Provide estimated Glomerular Filtration Rate (eGFR) based on Modification of Diet in Renal Disease (MDRD) equation

4 Perform at Screening and Day 1, and then subsequently only as a reflex if AST > ULN

5 If glucose is > ULN, reflexively test HbA1c

6 Only if occult blood, protein, or leukocytes present on dipstick analysis

7 For postmenopausal women

8 See Section 6.11.2

9 Serum pregnancy test at Screening and urine pregnancy tests as per the schedule in Appendix 1 for women of childbearing potential only. See Section 6.10.

10 Urine drug screen will be measured at screening. For all patients, test should include, at a minimum, amphetamines, barbiturates, cotinine, cocaine metabolites, opiates, benzodiazepines, and cannabinoids

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

6.10 Pregnancy Testing

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

Female patients of childbearing potential who require vaccinations (see Section 6.3) 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 (AP Wieslab, CH50, C3, Bb, and fD)

Depending on the type of complement test, either serum or plasma will be used. It is important that serum 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 PD Samples for Genetic and Additional Non-genetic Complement-associated Biomarker Testing, and for Determination of Vaccine Response

Samples will be collected and retained for potential assessment of non-genetic complement-associated biomarkers as per the schedule in Appendix 1 including: hemolysis assay, and the plasma concentrations of fB, Ba, iC3b, C5a, and soluble C5b-9. Subject to patient consent, a sample will also be collected at screening for potential genetic analysis. Genetic analyses may be conducted if a patient does not respond to the investigative drug, if a patient experiences drug-related toxicity, or to further characterize the underlying disease. Serum samples will be collected to assess patient response to vaccinations at various time points in the study.

Samples used for PD analyses will be stored from the beginning of this clinical study to one year after the clinical study report is finished.

6.11.3 PK Plasma Samples

For samples collected for pharmacokinetic analysis, whole blood (2 mL) will be collected into 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 in a laboratory manual.

6.11.4 Blood Volumes

Approximate blood volumes for each cohort are detailed in Table 3 below. The total planned blood volume to be collected per individual is approximately 776.9 mL over 3 months. 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. Please refer to the laboratory manual for specific instructions regarding blood and urine volume, collection, processing and handling.

Table 3. Approximate Total Blood Volumes

Test	Volume/ Test (mL)	Screening		Part 1		Part 2 (Including Taper and Follow-up)		Total	
		Tests	Blood Drawn (mL)	Tests	Blood Drawn (mL)	Tests	Blood Drawn (mL)	Tests	Blood Drawn (mL)
Screening Visit Labs (chemistry, LDH, erythropoietin, hematology, serum pregnancy, FSH, Serology [HIV, HBsAg, HCV Ab]	14.0	1	14.0	0	0	0	0	1	14.0
Clinical Labs (chemistry [including LDH & haptoglobin] & hematology)	10.5	0	0	8	84	11	115.5	19	199.5
PT/PTT/INR	2.7	1	2.7	2	5.4	1	2.7	4	10.8
Free Hemoglobin	6.0	1	6.0	5	30.0	5	30.0	11	66.0
LDH (Local)	3.5	0	0	2	7.0	2	7.0	4	14.0
D-dimer[a]	2.7	0	0	2	5.4	1	2.7	3	8.1
Direct Coombs	2.0	1	2.0	1	2.0	2	4.0	4	8.0
Flow Cytometry: Clone Size	2.0	1	2.0	1	2.0	4	8.0	6	12.0
Flow Cytometry: C3 Fragment Deposition	4.0	0	0	2	8.0	3	12.0	5	20.0
AP Wieslab	3.5	0	0	20	70	5	17.5	25	87.5
Bb	2.0	0	0	20	40.0	5	10.0	25	50.0
CH50, C3, fD	7.5	0	0	3	22.5	3	22.5	6	45.0
Samples for non-genetic biomarkers	5.5	0	0	20	110.0	3	16.5	23	126.5
Sample for genetic biomarker testing	8.5	1	8.5	0	0	0	0	1	8.5
Sample for assessment of patient response to vaccines	7.0	1	7.0	3	21.0	1	7.0	5	35.0
PK samples	2.0	0	0.0	31	62.0	5	10.0	36	72.0
Total Volume			**42.2**		**469.3[b]**		**265.4**		**776.9**

For each test, the number of tests is the maximum described in the Schedule of Assessments (Appendix 1).

a Shared sample with PT/PTT/INR when appropriate; only D-dimer-specific samples listed

b Drawn over 1 month

c Drawn over 3 months

6.12 Dispensing Study Drug

ACH-0144471 will be supplied as tablets. The site will dispense study drug as required to provide patients with sufficient study drug to last until the next visit. If the information necessary to support a dose escalation decision is not available during the time the patient is in the clinic, the patient may be required to return for new drug supplies following dose escalation.

6.13 Safety Assessments

Safety will be evaluated by monitoring and assessment of AEs, clinical laboratory tests, ECG findings, 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 6, 13, and 20, at the times indicated in the Schedule of Assessments (Appendix 1) to determine plasma and/or serum concentrations of ACH-0144471. 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 and Efficacy Assessments

Pharmacodynamics will be evaluated using serum, plasma, and whole blood collected during the study with the assays outlined in Table 4 and the Schedule of Assessments (Appendix 1). Additional information on sample collection and shipping instructions will be provided in a separate laboratory manual.

Table 4. Pharmacodynamic Markers

Assay Identifier*	Assay Descriptions
LDH	Blood test
CBC components	Blood test
Free hemoglobin	Blood test
Haptoglobin	Blood test
D-dimer	Blood test
PNH clone size	Flow cytometry
C3	ELISA
CH50	MAC-mediated lysis of the anti-body sensitized target; serial diluted serum
AP Wieslab assay	ELISA; LPS as activator; measurement of TCC
fD	ELISA
Bb	ELISA
C3 fragment deposition	Flow cytometry
Direct Coombs test	Blood test
Additional complement-associated biomarkers	ELISA or other

*The schedule for when these tests are to be done can be found in Appendix 1

Samples will also be collected and retained for genetic and non-genetic complement-associated biomarker testing, as described in Section 6.11.2.

While multiple tests of the complement system will be performed to assess effect of ACH-0144471 on complement activity, clinical efficacy will be assessed using changes in LDH and Hgb levels and other measures of hemolysis, as well as RBC transfusion requirements.

6.16 Patient-Reported Outcomes Assessments

The FACIT Fatigue scale and the EORTC-QLQ-C30 will be administered to patients at the schedule indicated in Appendix 1 using the tools provided in Appendix 2 to collect patients' health-related quality of life at baseline and after treatment with ACH-0144471, respectively.

In addition, patients will be interviewed by an outcomes researcher chosen by the Sponsor to collect their experience of PNH, its impact on everyday lives and the disease trajectory, and, following treatment, to collect patients' experience of ACH-0144471 treatment and their perception of the evolution of their condition. The interviews will be conducted over the phone by a trained, experienced interviewer and will last approximately 30 minutes.

Patients who have not been included in the prescreening study (protocol ACH471-102) will be interviewed during the screening period (no more than 1 week prior to the first dose of ACH-0144471). At the end of Part 1 (Day 28 ± 1 week), follow-up phone interviews will be conducted with all patients to collect patients' experience of ACH-0144471 treatment and their perception of the evolution of their condition. Patients continuing in Part 2 will also be interviewed at the end of Part 2 (Day 84 ± 1 week). Patients who terminate early may be interviewed at the time of termination.[a]

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.

[a] If interviews are not permitted by local regulations or EC requirements, the PI may administer these as questionnaires. If this is necessary, the questionnaires will be provided by Achillion

- 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.); or,

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
- 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). Achillion Pharmaceuticals may request that certain AEs be followed until resolution or stabilization.

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 Common Terminology Criteria for Adverse Events (CTCAE) Adverse Event Severity Grading Table (Appendix 3) [18]. 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 (via email) to both CCI AND to Achillion Pharmaceuticals 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 (via email) to both CCI AND to Achillion Pharmaceuticals within one business day of becoming aware of the pregnancy

Contact information is provided below. Local telephone contact numbers will be provided in the SAE Reporting Form Completion Guidelines.

SAE CONTACT

CCI **Pharmacovigilance**

SAE Reporting email Addresses:

PPD

SAE Telephone Numbers:

In the event of email failure, report by telephone via the Safety Hotline: PPD

Achillion Pharmaceuticals

PPD

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

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 IRB 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 4) 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

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 3.2.4). In either case, whenever possible, the Achillion medical monitor should be notified immediately, and if possible, before dosing is terminated. When dosing is terminated, study participation is not necessarily also terminated. Instead, whenever possible, the patient should complete all the activities for the Day 84 or Early Termination Visit as described in Appendix 1, complete a dosing taper as described in Section 5.2.1, and return for a Follow-up visit two weeks after the last dose of study drug.

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

- 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 (see Section 3.2.4 for individual patient stopping rules)
- Patient request to discontinue for any reason
- A female patient becomes pregnant or wishes to become pregnant, or the female partner of a male 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 efficacy, PK, and PD evaluation will be performed at various time points throughout the study. There will be a follow-up visit approximately 2 weeks after the last dose of study drug.

Dosing should be at approximately the same time(s) each day.

Transfusion history should be collected at every visit.

During the treatment 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 precisely at the specified times
- 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 Activities

7.1.1 Screening Visit (Days –60 to -1)

Prospective patients should be screened within 60 days of first administration of study drug. A window of up to 60 days is permitted to allow screening followed by any required vaccinations; if a patient is participating in the preliminary screening study (ACH471-102), vaccinations may already have been administered, and tests performed as part of that study within 30 days of first administration of study drug may fulfill screening requirements for this study. During the screening period, informed consent will be obtained and patient eligibility determined according to the criteria specified in this protocol. The screening clinic and laboratory 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. A urine drug screen will be performed during screening, and must be negative to allow dosing. The urine drug screen should include, at a minimum, amphetamines, barbiturates, cotinine, cocaine metabolites, opiates, benzodiazepines, and cannabinoids. For women of childbearing potential, a serum pregnancy test will be done during screening and must be negative to be eligible for the study.

If screening laboratory assessments show elevated indirect bilirubin levels in conjunction with normal liver function tests (AST, ALT, Alkaline phosphatase), or if the patient has a history of unexplained

jaundice, unexplained high bilirubin levels, or a history of dark urine, the patient should be tested for Gilbert's syndrome.

Screening procedures may be spread over more than one visit. All evaluations must be completed before the patient is accepted into the study.

If the patient is unable to receive study drug within 60 days of screening, the patient may be re-screened once. The repeating of individual screening laboratory results that fall outside the reported normal 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.

Patients who meet all eligibility criteria will be educated about the restrictions on concomitant medication usage and other substances.

Once the patient is entered into the study, all protocol deviations should be reported to the Achillion Pharmaceuticals, Inc. Medical Monitor or designee. The Medical Monitor (or designee) will assess all protocol deviations to determine if any impacted patient safety or data integrity. Any protocol deviation which is deemed to impact patient safety or data integrity will be considered a significant protocol deviation, and the rationale for considering a protocol deviation significant will be documented.

7.1.2 Vaccination Visit(s) (Days -42 to Day -14, if required)

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 6.3. All other screening procedures must be completed, and patients must qualify for the study prior to any vaccinations being administered. Female patients of childbearing potential who require vaccinations (see Section 6.3) must also have a negative urine pregnancy test on the days of vaccination, before any vaccine or booster is administered.

7.1.3 Patient Reported Outcomes Interview - Screening

Patients who did not participate in the prescreening study (protocol ACH471-102) will be interviewed as part of quality of life assessments during the screening period, no more than 1 week prior to the first dose of ACH-0144471 (see Section 6.16). Patients must pass all other screening tests and be considered eligible for the study prior to being scheduled for their interview. Patients who participated in ACH471-102 will have had this first interview during that study and do not need to repeat this activity.

7.2 On-Study Activities

7.2.1 Clinic Visits

During the study period, physical examinations, assessment of vital signs, ECG measurements, all required safety laboratory testing, pregnancy testing for women of child-bearing potential, and collection of blood and urine samples for PK and PD evaluation will be performed at various time points between as specified in Appendix 1. On days when patients will remain at the clinic for intensive PK sampling (Days 6, 13, and 20), all doses of ACH-0144471 should be administered at the clinic.

At clinic visits, patients should be instructed how to take their medication at home, as described in Section 5.3.

During Part 1 (Days 1 to 28), all visits should occur on the specified day. During Part 2 (Days 29 through the end of follow-up), visits may take place within a window of ±1 day relative to the specified day.

7.2.2 Safety Follow up at Local Laboratory

On the days indicated in Appendix 1 (Schedule of Assessments) the patients will have blood drawn for safety assessments at their local laboratories. Patients should be instructed to fast for at least 8 hours prior to the local safety lab sample collections on Days 49 and 77 to allow collection of fasting samples for determination of bile acids as described in Table 2.

7.2.3 Safety Follow up After Escalation

As described in Section 3.2.3, the PI, in consultation with the Sponsor, may escalate dosing at times other than the dose escalation evaluation points in Part 1 of the study after evaluating the clinical benefit and the available safety, PK, and PD data (including laboratory test results) for a patient. Patients should have blood drawn (locally or at the clinic) 72 to 84 hours after starting the new dose for measurement of LDH and liver function tests (ALT, AST, GGT, and ALP).

7.2.4 Patient Reported Outcomes Interview – Day 28 (± 1 week) and Day 84 (± 1 week)

Follow-up interviews for all patients will be conducted as described in Section 6.16 at the end of Part 1 (Day 28 ± 1week); patients continuing in Part 2 will also be interviewed at the end of Part 2 (Day 84, ± 1 week). For patients who terminate early, a follow-up interview will be obtained at the time of termination.

7.2.5 Dosing Taper

It is recommended that patients who discontinue ACH-0144471 for any reason have study drug tapered over 6 days, as described in Section 5.2.1. On Days 3 and 6 of the taper period, patients will have blood drawn for local determination of chemistry and hematology parameters as indicated in Appendix 1 (Schedule of Assessments).

If a long-term extension study is available at the end of the patient's participation in this study, and the patient chooses to enroll in it, the dosing taper will not be required.

7.2.6 Follow-Up Visit

Patients will have a follow-up visit approximately 2 weeks after the last dose of study drug. The procedures indicated in Appendix 1 should be followed.

If a long-term extension study is available at the end of the patient's participation in this study, and the patient chooses to enroll in it, this visit will not be required.

7.2.7 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
- Conduct a physical exam and obtain resting supine vital signs (BP, HR, RR)
- Measure body temperature
- Collect blood samples for laboratory safety analysis as described in the Hematology and Chemistry columns of Table 2 and for determination of LDH
- 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, PK and PD, and safety parameters. Summary statistics will be computed for selected efficacy and safety parameters so that meaningful clinical interpretations can be made. Graphic presentations will also be produced for selected efficacy and safety parameters.

Data from Part 1 and Part 2 will be analyzed together. 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 untreated PNH patients and exploratory nature of this study to evaluate effectiveness of ACH-0144471.

9.3 Analysis Populations

All patients who receive at least one dose of ACH-0144471 will be included in the efficacy and safety analysis.

9.4 Demographics and Baseline Characteristics

Demographic parameters (age, gender, race, weight, BMI) and baseline PNH disease characteristics will be summarized to provide an overall description of study population.

9.5 Efficacy Analysis

The primary efficacy endpoint will be change in LDH level from baseline on Day 28.

Summary statistics will be provided for the primary efficacy endpoint. Ninety-five percent (95%) confidence interval for mean change from baseline will be computed.

Summary statistics will also be provided for secondary efficacy endpoints: change from baseline in hemoglobin level on Day 28 and, if data from patients continuing into Part 2 of the study are deemed clinically meaningful, Day 84. Data on transfusions due to low hemoglobin levels will also be summarized.

LDH levels and changes from baseline LDH levels over time will be plotted for each patient. Mean (or median) LDH level and mean (or median) change from baseline over time will also be plotted.

Graphic presentations for hemoglobin endpoints may also be provided.

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 vital signs and ECGs 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 population. The PK characteristics of ACH-0144471 from untreated PNH patients, including, but not limited to, the standard PK parameters outlined in the table below, will be derived from the individual plasma concentration time data on study Days with intensive PK sampling. Descriptive statistics (number of patients, mean / geometric mean, SD, median, minimum, and maximum) will be used to summarize the calculated PK parameters by appropriate study Days.

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-144471 in the body at steady state prior to daily dose. Graphic presentations will also be provided to depict PK profiles of ACH-0144471 from untreated PNH 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 pathway activity. Analysis on data from LDH measurements is described in Section 9.5 above. Analyses for the remaining markers are either secondary or exploratory.

Except for results from AP-Wieslab assay, change from baseline values at various time points will be computed for the PD markers. Summary statistics may be provided for 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. The relationship between LDH levels and other endpoints with alternative pathway markers may also be explored.

9.9 PK/PD Assessments

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

9.10 Patient-Reported Outcomes Assessments

9.10.1 Quality of Life Scales

Total score and change from baseline total score on the FACIT Fatigue scale instrument will be computed for each patient at each time point. Both mean change total scores and individual patients' change total scores may be plotted over time to provide visual examination on the improvement of fatigue condition.

Similar analysis and presentations may be provided for each domain score of the EORTC QLQ-C30 instrument.

9.10.2 Patient Interviews

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 [19]. A validated software package [20] will be used to facilitate the storage, coding, analysis, and retrieval of qualitative data.

Other analysis procedures relevant to interview data may also be explored. A separate analysis plan and/or report will be provided for the 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 amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

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 date of birth, subject number, 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.

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

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

10.6 Study Monitoring

10.6.1 Access to Information for Monitoring

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

The Study Monitor is responsible for routine review of the CRFs at regular intervals throughout the study, to verify adherence to the protocol, and the completeness, consistency, and accuracy of the data being entered. The Study monitor should have access to any 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 Violations/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.

The interviews will be audio recorded in a de-identified way. The audio files will serve as source documents and will be archived in Trial Master File. Any additional copy of audio recordings

temporarily retained by interviewers and / or transcription unit will be destroyed after transcription process completion. The audio recordings will be transcribed word by word for the analysis.

10.13 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 5. Schedule of Assessments

	Screening			Part 1										Part 2[1]								Taper and Follow-up			Unscheduled	
	Day																									
	-60 to -1	-42	-14	1 (B/L)	3	6	7	13	14	17	20	24	28	35	42	49	56	63	70	77	84 or E/T[4]	T3[5]	T6[5]	F/U[6]	Dose Esc[2]	Other[3]
Clinic Visit Days	X	X[7]	X[7]	X	X	X		X			X		X		X		X		X		X			X		X
Dose Escalation Day[8]							X		X																	
Screening Assessments																										
Informed Consent	X																									
Inclusion/ Exclusion Criteria	X																									
Protocol restrictions	X																									
Medical History (including transfusion history)	X																									
Vaccination History	X																									
Demographics	X																									
Pregnancy Test[10]	X	X[11]	X[11]	X[9]									X				X				X			X		
FSH[12]	X																									
Urine Drug Screen[13]	X																									
HCV Ab, HbsAg, HIV Ab	X																									
Erythropoietin	X																									
Vaccinations[14]		X	X																							
Patient-Reported Outcomes Assessment Interviews	X[15]												X[16]								X[16]					
Dosing and Drug Distribution																										
ACH-0144471 Dosing[17]				X	X	X[17]	X[18]	X[17]	X[18]		X[17]		X		X[19]		X[19]		X[19]		X[19]	X	X			
Study Drug Dispensing[20]				X	X	X		X			X		X[19]		X[19]		X[19]		X[19]		X					
Clinical Assessments																										
Physical Exam	X			X[9]		X		X			X		X		X		X		X		X					X
Vital Signs				X[9]	X	X		X			X		X		X		X		X		X					X
Body Temperature	X			X[9]	X	X		X			X		X		X		X		X		X					X
Height, BMI	X																									
Weight	X			X[9]									X								X					

	Screening			Part 1										Part 2[1]								Taper and Follow-up			Unscheduled	
	Day																									
	-60 to -1	-42	-14	1 (B/L)	3	6	7	13	14	17	20	24	28	35	42	49	56	63	70	77	84 or E/T[4]	T3[5]	T6[5]	F/U[6]	Dose Esc[2]	Other[3]
Patient-Reported Outcome Measures Assessments (QoL Questionnaires)	X				X	X		X			X		X				X				X			X		
12-Lead ECGs (single)	X			X[9]		X		X			X		X				X				X					
AEs/SAEs	X	X[7]	X[7]	X	X	X	X	X	X		X		X		X		X		X		X			X		X
Concomitant Medications including Transfusions	X	X[7]	X[7]	X	X	X	X	X	X		X		X		X		X		X		X			X		X
Laboratory Assessments																										
Hematology, Chemistry, and Urinalysis[21]	X			X[9,22]	X	X		X[22]			X		X[22]		X		X		X		X			X		X
PT, PTT, INR	X			X[9,22]									X[22]						X							
Haptoglobin	X			X[9,22]		X		X[22]			X		X[22]								X					
Free Hemoglobin	X			X[9,22]		X		X[22]			X		X[22]		X		X		X		X			X		
LDH (local)						X[23]		X[23]																	X	
Safety Labs (local)										X[24]		X[24]		X[24]		X[24]		X[24]		X[24]		X[24]	X[24]		X[25]	
D-dimer	X					X		X					X								X					
PK samples[26]						X[27]		X[27]			X[27]		X		X		X		X		X			X		
Direct Coombs	X												X								X			X		
PNH Clone Size	X												X		X		X				X			X		
C3 fragment deposition				X[9]									X		X						X			X		
AP Wieslab[26]				X[9]		X[27]		X[27]			X[27]		X		X		X		X		X			X		
Bb[26]				X[9]		X[27]		X[27]			X[27]		X		X		X		X		X			X		
fD, C3, CH50				X[9]							X[27]		X				X				X			X		
Plasma/Serum Samples for Additional Non-genetic Biomarker Testing				X[9]		X[27]		X[27]			X[27]		X				X				X			X		
Sample for genetic Biomarker testing (white blood cells)	X																									
Sample for assessment of patient response to vaccines[28]	X			X[9]							X[27]										X					

	Screening			Part 1										Part 2[1]								Taper and Follow-up			Unscheduled	
	Day																									
	-60 to -1	-42	-14	1 (B/L)	3	6	7	13	14	17	20	24	28	35	42	49	56	63	70	77	84 or E/T[4]	T3[5]	T6[5]	F/U[6]	Dose Esc[2]	Other[3]

AE = Adverse Event; AP = alternative pathway; B/L = Baseline; BMI = Body Mass Index; ECG = Electrocardiogram; E/T = Early Termination; fD = Factor D; F/U = Follow-up Visit; INR = International Normalized Ratio; LDH = Lactate Dehydrogenase; PK = Pharmacokinetic; PT = Prothrombin time; PTT = Partial thromboplastin time; SAE = Serious Adverse Event

Note that ALT and other liver function tests are included in the clinical laboratory safety tests conducted on Days 1, 3, 6, 13, 17, 20, 24, and 28 in Part 1, weekly on Days 35, 42, 49, 56, 63, 70, 77, and 84 in Part 2, and on Days 3 and 6 of the taper.

1 During Part 2, visits may take place within a window of ±1 day relative to the specified day.

2 Measurement of LDH and liver function tests (ALT, AST, GGT, ALP), to be drawn locally or at the clinic 72-84 hours after escalation, as described in Section 7.2.3.

3 See Section 7.2.5 for activities.

4 For patients who terminate early in either Part 1 or Part 2, these assessments should be conducted.

5 T3 = Day 3 of the taper; T6 = Day 6 of the taper.

6 The follow-up visit should be 14 days after the last dose of study drug (including taper). For patients who complete Part 1 but do not participate in Part 2 this will be Day 48; for patients who participate in both Part 1 and Part 2 this will be Day 104. If a long-term extension study is available at the end of the patient's participation in this study, and the patient chooses to enroll in it, this visit will not be required.

7 Only for patients who need to receive vaccinations. See Section 6.3.

8 Unless the PI feels a clinic visit is required, dose escalation decisions and modified dosing instructions may be provided by phone. Information on concomitant medications, AEs, and SAEs should be collected.

9 Prior to dosing.

10 Serum pregnancy test at Screening and urine pregnancy tests at other timepoints 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.

11 Female patients of childbearing potential requiring vaccinations (see Section 6.3) must have a negative urine pregnancy test on the days of vaccination, before any vaccine or booster is administered.

12 FSH for postmenopausal women at screening only.

13 For all patients, urine drug screen should include, at a minimum, amphetamines, barbiturates, cotinine, cocaine metabolites, opiates, benzodiazepines, and cannabinoids.

14 Vaccinations should be given if needed, per the guidance in Section 6.3.

15 The patient reported outcomes assessment interview during screening should be conducted no more than 1 week prior to the first dose of ACH-0144471, and will only be conducted for those patients who did not participate in the prescreening study ACH471-102.

16 Interview may be scheduled ± 1 week. Patients who terminate before Day 28 will receive an interview at the time of their termination. Patients who enter Part 2 but terminate before Day 84 will receive an interview at the time of their termination.

17 Patients will take ACH-0144471 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). On Clinic Visit Days, patients will be instructed to abstain from taking their study medication on the mornings of their study visits so that they can be dosed in the clinic See Section 5.3 for details of the timing of dosing both in the clinic and at home.

18 Doses taken at home. Patients will take ACH-0144471 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). Patients should record the times they take their doses. Doses should be taken at approximately the same time each day.

19 Only for patients continuing on to Part 2.

20 As discussed in Section 6.12, patients should be provided with sufficient study drug for 1 week of dosing during Part 1 or 2 weeks of dosing during Part 2. Treatment compliance assessments should be performed at each visit.

21 Hematology, chemistry, and urinalysis, as described in Table 2.

	Screening			Part 1									Part 2[1]								Taper and Follow-up			Unscheduled	
	Day																								
	-60 to -1	-42	-14	1 (B/L)	3	6	7	13	14	17	20	24	28	35	42	49	56	63	70	77	84 or E/T[4]	T3[5]	T6[5]	F/U[6]	Dose Esc[2]	Other[3]

22 Day 1, 13 and 28 samples should be drawn under fasting conditions.

23 On Days 6 and 13 only, a sample should be drawn for local determination of LDH for dose escalation decisions. Other analytes should not be reported. Values will be reviewed according to the procedures outlined in Section 3.2.2. Depending on when the data is received and reviewed, if the patient is going to dose escalate, the site should call the patient as soon as possible (Days 6-9 or Days 13-15) to provide new dosing instructions.

24 On Days 17, 24, 35, 49, 63, and 77, and Days 3 and 6 of the taper, samples should be drawn for local determination of chemistry and hematology parameters as described in Table 2. Day 49 and 77 samples should be drawn under fasting conditions.

25 Liver function tests (ALT, AST, GGT, ALP) only.

26 Except on Days 6, 13, and 20 these are trough samples only; collect prior to first daily dose.

27 For PK or PD schedule on these days, refer to Table 6.

28 Samples for vaccine response will be required only if vaccination(s) were administered during the Screening period. If required, samples will be collected during screening, pre-dose and 2 hours after dosing ACH-0144471 on Day 1, Day 20, and Day 84.

Table 6. PK and PD Sampling on Days 6, 13, and 20

	Time After Dosing (hr)									
	0[a]	**1**	**1.5**	**2**	**2.5**	**3**	**4**	**6**	**8**	**12**
PK plasma samples	X	X	X	X	X	X	X	X	X	X
AP Wieslab, Bb	X			X			X	X	X	X
fD, C3, CH50[b]	X[b]									
Plasma/Serum Samples for Biomarker Testing	X			X			X	X	X	X
Sample for assessment of patient response to vaccines[b]	X[b]		X[b]							

a Prior to dosing.

b Day 20 only.

Appendix 2. Quality of Life Assessments

FACIT Fatigue Scale (Version 4)

EORTC QLQ-C30 (Version 3)

These QoL assessments will be done at the clinic visits specified in Appendix 1.

FACIT Fatigue Scale (Version 4)

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

		Not at all	A little bit	Some -what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
An4	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4

An16	I have to limit my social activity because I am tired	0	1	2	3	4

English (Universal)

16 November 2007

EORTC QLQ-C30 (Version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year):

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 3. 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)

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

Appendix 4. 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 subject; 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.