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

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Clinical Trial Protocol

ACH471-101

Study Title:	A Phase 2 Open-label Study of ACH-0144471 in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) Who Have an Inadequate Response to Eculizumab Monotherapy
Study Number:	ACH471-101
Study Phase:	2
Product Name:	ACH-0144471 Tablets
EudraCT Number:	2016-003526-16
Universal Trial Number (UTN):	U1111-1209-4655
IND Number:	127,367
Indication:	Paroxysmal Nocturnal Hemoglobinuria (PNH)
Investigators:	Multi-center
Sponsor:	Achillion Pharmaceuticals, Inc.
Sponsor Contact:	PPD
Medical Monitor:	PPD

	Date
Original Protocol:	14 September 2017 (Version 1.0)
Amendment 1	13 December 2017 (Version 2.0)
Amendment 1.1	17 January 2018 (Version 2.1)
Amendment 2	13 March 2018 (Version 3.0)
Amendment 3	15 February 2019 (Version 4.0)
Amendment 3.1	19 February 2019 (Version 4.1)

Sponsor Signature(s)

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Study Number: ACH471-101

Protocol Date: 19 February 2019

This clinical study protocol has been approved by the sponsor.

PPD

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

Date

PPD

2/19/2019 | 1:19 PM EST

Investigator's Signature(s)

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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 Ingredients:	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 Study of ACH-0144471 in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) Who Have an Inadequate Response to Eculizumab Monotherapy
Study Number:	ACH471-101
Study Phase:	Phase 2
Primary Objective:	To evaluate the efficacy of ACH-0144471 plus eculizumab based on the increase in hemoglobin (Hgb) relative to baseline during 24 weeks of treatment
Secondary Objectives:	• To evaluate the efficacy of ACH-0144471 plus eculizumab based on the reduction in the number of RBC units transfused during the 24 weeks of treatment with ACH-0144471 compared to the 24 weeks prior to initiation of treatment with ACH 0144471 • To evaluate the efficacy of ACH-0144471 plus eculizumab based on the percentage of patients who are RBC transfusion-independent during 24 weeks of treatment • To evaluate the efficacy of ACH-0144471 plus eculizumab based on the change from baseline in lactate dehydrogenase (LDH) during 24 weeks of treatment • To evaluate the safety and tolerability of 24 weeks of treatment with ACH-0144471 plus eculizumab based on serious adverse events (SAEs), Grade 3 and Grade 4 adverse events (AEs), and events leading to discontinuation of study drug

Exploratory Objectives:	• To explore the effect of ACH-0144471 plus eculizumab on complement biomarkers including alternative pathway (AP) activity, Bb, fD, and C3 fragment deposition during 24 weeks of treatment
	• To evaluate health-related quality of life (QOL) measures during 24 weeks of treatment
	• To explore the benefits of ACH-0144471 plus eculizumab treatment as perceived by patients with PNH by:
	  ○ Exploring patients' experiences of PNH, its impact on everyday lives and the disease trajectory, from first symptoms to definitive diagnosis and beyond, including prior treatment with eculizumab alone
	  ○ Documenting the evolution of PNH over the course of treatment with ACH-0144471 plus eculizumab from a patient's perspective

	○ Comparing patients' experience with eculizumab alone and ACH-0144471 plus eculizumab treatment • To explore patients' expectations towards treatment with ACH-0144471 plus eculizumab
Study Design:	This is a multiple-center, open-label, multiple-dose Phase 2 study in patients with PNH who have inadequate response to eculizumab treatment. This study will include up to 14 patients who will receive 24 weeks of daily oral treatment with ACH-0144471 plus intravenous (IV) eculizumab administered at the patient's usual dose and schedule. This will be followed by a long-term extension phase. There will be 4 groups studied based on initial dose of ACH-0144471, which will be enrolled sequentially. Group 1 will start at 100 mg three times daily (TID). Group 2 will start at 150 mg TID. Group 3 will start at 200 mg TID. Group 4 will start at the optimal dose determined from Groups 1-3. The initial dose level of Groups 2 and 3 could be lower based on emerging safety data from the prior group(s). The decision to enroll subsequent groups at initial lower dose levels than planned will be made by the Sponsor in collaboration with the investigators. There will be a minimum of 4 weeks of treatment required at each dose level before dosing of the subsequent group of patients at the next highest dose level. The first three groups will include 2 patients per group to determine an optimal ACH-0144471 dose for the remaining 8 patients in the fourth group. ACH-0144471 dose may be increased within each patient, to a maximum of 200 mg TID based on safety and Hgb values at protocol-specified time points, after a minimum of 4 weeks of treatment at the lower dose level during the 24-week treatment phase. All dose escalations will be made on a patient-by-patient basis at the discretion of the PI, in consultation with the Sponsor. Upon completion of 24 weeks of treatment, patients will then enter a long-term extension phase of this study with the same ACH-0144471 dose plus eculizumab as they were receiving at the end of 24-week treatment phase. Patients will be evaluated for history of vaccination against *Neisseria meningitidis* (*N. meningitidis), Haemophilus influenzae* (*H. influenzae*), and *Streptococcus pneumoniae* (*S. pneumoniae*). Those who have not been vaccinated may receive vaccinations during this study, as described in Section 6.3. Those who have been previously vaccinated may receive recommended boosters as described in Section 6.3. Patients who are not already on antibiotic prophylaxis when they enter the trial as part of Standard of Care (SOC) will be prescribed prophylactic penicillin V (or an appropriate alternative) from the start of dosing with ACH-0144471 (Day 1), plus eculizumab, through the end of dosing. Patients will return to the clinic for safety, PK, and other assessments at Week 1, Week 2, Week 4, Week 8 and Week 12, and then every 4 weeks until Week 24. Patients will have local safety labs drawn at Week 3, Week 6, and Week 10. Patients will also be asked to return to the clinic or a local lab 72-96 hours after any dose escalation. At the Week 12 visit, subjects will remain at the clinic for 8 hours for intensive PK/PD sampling and collection of a time-matched ECG at the maximum plasma concentration of ACH-0144471 (3 hours after dosing). After Week 24, if patients are receiving clinical benefit they will continue with treatment in an extension phase, during which they will return to the clinic every 8 weeks, with a local lab visit 4 weeks after every clinic visit starting at Week 28. Clinical benefit will be assessed by the PI based on improvement in Hgb. Additionally, patients must not have developed any comorbidity that might make it unsafe to continue on therapy, or any

	safety concern related to treatment with ACH-0144471. Patients will continue to receive the same dose of eculizumab on the same schedule that they were receiving prior to the start of the study. Patients will be allowed to continue therapy in this study until: 1) ACH-0144471 is commercially available in their country; 2) the development of ACH-0144471 as a potential therapy for PNH is terminated; or 3) the therapy is no longer tolerated or effective. In addition, 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. If a patient discontinues from the study, dosing of ACH-0144471 will be tapered over 6 days, as described in Section 5.3.1.3, and two follow-up visits will be conducted approximately 14 days and 28 days after the last dose of ACH-0144471. Patients will continue to receive the same dose of eculizumab on the same schedule that they were receiving during the taper and follow-up periods and then resume therapy for their PNH as directed by their physician.
Treatment Groups:	All patients will receive ACH-0144471 administered orally TID over a period of 24 weeks while patients continue to receive eculizumab at their usual dose and schedule. Four treatment groups are planned based on the starting dose of ACH-0144471: Group 1 starting at 100 mg TID, Group 2 starting at 150 mg TID, Group 3 starting at 200 mg TID and Group 4, an expansion group starting at the optimal dose determined from Groups 1-3. For Groups 1 and 2, the starting dose of ACH-0144471 may be escalated within patient to a maximum dose of 200 mg TID based on accumulating safety data and Hgb response within that patient. Additional groups of patients may be enrolled at each initial dose level based on emerging safety data from the prior group(s). At the end of 24 weeks, patients who are receiving clinical benefit in the opinion of the PI will continue extended dosing of ACH-0144471 plus eculizumab. For patients not continuing on with long-term treatment, a taper of ACH-0144471over six days will be implemented, followed by 28 days of follow-up.
Study Population:	Adult PNH patients with RBC-transfusion-dependent anemia (defined as having received at least one RBC transfusion within 12 weeks prior to screening) and who are receiving a stable dose of eculizumab (have been receiving eculizumab at approved or higher doses for at least 24 weeks prior to entry without change in dose or schedule for at least 8 weeks).
Number of Patients:	Up to 14 patients are planned
Inclusion Criteria:	1. Diagnosed with PNH 2. Have received at least one RBC transfusion within 12 weeks prior to screening 3. Anemia (Hgb <10 g/dL) with adequate reticulocytosis (absolute reticulocyte count $\geq 100 \times 10^9$/L) 4. Must be on a stable regimen of eculizumab (have been on eculizumab for at least 24 weeks without change in dose or schedule for at least the past 8 weeks) 5. Platelet count ≥40,000/μL without the need for platelet transfusions 6. Documentation of vaccination for *N. meningitidis*, *H. influenzae*, and *S. pneumoniae*, or willingness to receive vaccinations as described in Section 6.3 7. Willingness to receive antibiotic prophylaxis if not already prescribed within standard of care, as described in Section 5.2.3 8. Age 18 years to 65 years, inclusively (or ≥ minimum adult age in accordance with local legal requirements)

	9. 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. 10. 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. 11. Must agree to provide written informed consent 12. Must be willing and able, at all times, to have transportation and telephone access, and to be within 1 hour of an emergency medical center
Exclusion Criteria	1. Current evidence of bone marrow failure or aplastic anemia requiring treatment 2. History of a major organ transplant (e.g., heart, lung, kidney, liver) or hematopoietic stem cell/marrow transplant (unless HSCT engraftment has failed) 3. Received another investigational agent within 30 days or 5 half-lives of the investigational agent prior to study entry, whichever is greater 4. Documented C5 mutations 5. Known or suspected complement deficiency 6. Contraindication to one or more of the required vaccinations 7. Active bacterial infection or clinically significant active viral infection, a body temperature >38°C, or other evidence of infection on Day 1, or have a history of febrile illness within 14 days prior to first study drug administration 8. History of meningococcal infection, or a first-degree relative or household contact with a history of meningococcal infection 9. 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 PI would make it difficult to properly provide prophylactic antibiotic therapy or treat an active infection. 10. 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) 11. Laboratory abnormalities at screening, including: • Alkaline phosphatase (ALP) >1.5 × upper limit of normal (ULN) • Absolute neutrophil counts (ANC) <1,000/µL • Alanine aminotransferase (ALT) >1.5 × ULN

	• Direct bilirubin >1.5 × ULN (unless due to extravascular hemolysis, in the opinion of the investigator) • Any other clinically significant laboratory abnormality that, in the opinion of the Principal Investigator (PI), would make the patient inappropriate for the study or put the patient at undue risk 12. Females who are pregnant, nursing, or planning to become pregnant during the study or within 90 days of study drug administration 13. Prior history or current evidence of biliary cholestasis 14. Gilbert's syndrome Patients with history or family history suggestive of Gilbert's syndrome will be tested and excluded from study if positive for UGT1A1 genotyping polymorphism or missense change 15. 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 16. Taking medications known to prolong the QT/QTc interval (see Section 5.5.2), or have a family history of prolonged QT syndrome or with a screening QTcF >450 msec for males or >470 msec for females 17. Have eGFR<30 mL/min/1.73 m^2 and/or are on dialysis
Criteria to Escalate to a Higher Dose of ACH-0144471:	Decisions to change the dose of ACH-0144471 will be made by the site PI in consultation with the Sponsor after review of ongoing safety data and documented accordingly. • 1st Dose Escalation Point (Week 4) On a patient-by-patient basis, if the starting dose for a group is well tolerated and the available safety data are satisfactory, a patient may be escalated to the next highest dose (to a maximum dose of 200 mg TID) if his/her Hgb level from Week 4 has not increased by ≥1.5 g/dL from their baseline value (Day 1), or the patient received a transfusion during the previous 4 weeks. • 2nd Dose Escalation Point (Week 8) On a patient-by-patient basis, a patient may be escalated to the next highest dose, to a maximum of 200 mg TID, if his/her Hgb level from Week 8 has not increased by ≥3 g/dL from their baseline value (Day 1), or the patient received a transfusion during the previous 4 weeks. • 3rd Dose Escalation Point (Week 12) On a patient-by-patient basis, a patient may be escalated to the next highest dose, to a maximum dose of 200 mg TID, if his/her Hgb level from Week 12 has not normalized, or the patient received a transfusion during the previous 4 weeks. At each time point: ○ Patients currently taking 100 mg TID may escalate to 150 mg TID ○ Patients currently taking 150 mg TID may escalate to 200 mg TID ○ Patients taking 200 mg TID will stay on the same dose

	Any patient who has not already been dose escalated up to 200 mg ACH-0144471 by his/her Week 12 visit, may be escalated in the same manner up to a maximum of 200 mg ACH-0144471 TID, if they have been on their previous dose for at least 4 weeks. Depending on when data are received and reviewed, if the patient is going to dose escalate, the site should contact the patient as soon as possible to provide new dosing instructions. If necessary, the patient may be asked to return to the clinic for new drug supplies prior to their next clinic visit. Patients should have blood drawn (locally or at the clinic) 72 to 96 hours after starting the new dose for measurement of LDH, Hgb, and liver function tests (ALT, aspartate aminotransferase [AST], gamma glutamyl transferase [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 dose of 200 mg TID has already been reached • Hgb level has increased from baseline and is in the normal range 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 Achillion medical monitor.
Individual Stopping Criteria:	Any individual patient who meets any of the following criteria will be discontinued from further dosing of ACH-0144471: • 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 6.19 Discontinuation of ACH-0144471 treatment will also be considered for: • ALT or AST >8 × ULN • ALT or AST >5 × ULN for more than 2 weeks • ALT or AST >3 × ULN and clinically significant elevation in Total Bilirubin relative to baseline • ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) • If there is a marked prolongation of the QT/QTc interval during treatment with the study drug, especially if the measurement is obtained from more than one ECG • Development of a meningococcal infection or severe sepsis 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 will 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. Patients who discontinue from ACH-0144471 treatment will follow the procedures for early termination indicated in Appendix 1, but continue to receive their usual regimen of eculizumab.
Study Stopping Criteria	Dosing in the study will be terminated if one or more of the following occurs: • Two or more patients experience the same or similar study drug-related serious adverse event • Two or more patients experience the same or similar study drug-related Grade 4 or higher adverse events • Two or more patients discontinue study therapy due to liver function test abnormalities as detailed below ○ ALT or AST >8 × ULN ○ ALT or AST >5 × ULN for more than 2 weeks ○ ALT or AST >3 × ULN and total bilirubin >2 × ULN or INR >1.5, in the absence of warfarin anticoagulation ○ ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) • Two or more patients develop a meningococcal infection or severe sepsis
Test Product, Dosage Form, and Strength:	ACH-0144471, administered as 50, 75, or 100 mg tablets
Mode of Administration:	Oral
Duration of Treatment, Confinement, and Total Study Participation	The maximum screening period is 60 days. Each patient will receive daily oral doses of ACH-0144471 TID plus eculizumab according to the patient's usual dose and schedule for a total of 24 weeks (168 days). If a patient is receiving clinical benefit, in the opinion of the PI, the patient will enter the long-term treatment extension phase of the study. If a patient discontinues from the study there will be a 6-day taper at the end of treatment and follow-up for an additional 28 days after the end of the study period. Therefore the maximum duration for patient participation for those patients not continuing on to long-term treatment could be up to 262 days (60 days screening, 168 days of treatment, 6 days of taper, and 28 days follow-up). For those patients entering the long-term treatment extension, patients will continue therapy in this study until: 1) ACH-0144471 is commercially available in their country; 2) the development of ACH-0144471 as a potential therapy for PNH is terminated; or 3) the therapy is no longer tolerated or effective. If patients discontinue during the extension phase, they will have ACH-0144471 tapered and have follow-up visits. No overnight stays in the clinic are required.
Safety Assessments:	Safety will be evaluated by assessment of AEs, clinical laboratory tests, ECGs, and vital signs measurements at 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 prophylactic antibiotics, and will be carefully monitored for the development of fever (see Appendix 4).

	Additionally, the site must report any Grade 3 or Grade 4 AEs which are possibly, probably, or definitely related to study drug (see Section 6.16.7) to the Sponsor within 24 hours.
Pharmacokinetic Assessments:	Blood samples will be collected as described in Section 6.13, at the times indicated in the schedule of assessments in Appendix 1 to determine plasma concentrations of ACH-0144471. At the Week 12 visit, patients will remain in the clinic for 8 hours post-dose to collect additional PK samples. PK parameters of ACH-0144471, including t_{max}, C_{max} and $AUC_{0\text{-}tau}$ will be determined using validated bioanalytical methods. Single trough PK samples will be taken at other time points. Blood samples will be collected prior to dosing of ACH-0144471 at each visit throughout the study to determine trough concentrations of ACH-0144471.
Pharmacodynamic and Efficacy Assessments:	Pharmacodynamics will be evaluated as described in Section 6.14 using serum, plasma, or whole blood collected during the study. Samples will also be collected and retained for additional genetic and non-genetic complement-associated biomarker testing, as discussed in Section 6.11.2.
Patient-reported Outcomes Assessments:	Quality of Life (QoL) questionnaires will be administered at various time points as specified in the Schedule of Assessments in Appendix 1 using the tools in Appendix 2. The FACIT Fatigue scale (version 4) questionnaire and the EORTC-QLQ-C30 (version 3.0) scale will be administered to patients to collect patients' health-related QoL during screening (baseline) and after treatment with ACH-0144471, respectively. In addition, interviews by independent outcomes researchers chosen by the Sponsor will be conducted with patients enrolled in the trial prior to initiation of study treatment (during screening period), and follow-up interviews will be conducted during the trial at the time points specified in Appendix 1. These interviews will be conducted to collect patients' experience of PNH, its impact on everyday lives and the disease trajectory and patients' experience of ACH-0144471 plus eculizumab 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. For patients that 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:
	
	• Primary efficacy parameter:
	  ○ For the Optimal Dose Group: median Hgb during the 24-week treatment phase compared to the baseline (Day 1) Hgb
	  ○ For the groups treated at doses lower than the optimal dose level: median Hgb over the time period that the patient received the highest dose level during the 24-week treatment phase compared to baseline (Day 1) Hgb
	• Secondary efficacy parameters:
	  ○ Number of units of RBCs transfused during 24 weeks of treatment
	  ○ RBC transfusion status: number and percent of patients without RBC transfusions during 24 weeks of treatment
	  ○ Change from baseline in LDH during 24 weeks of treatment
	• Safety parameters:

	○ SAEs ○ AEs leading to discontinuation of the study medication ○ AEs (related and regardless of relationship with study drugs) ○ Grade 3 and Grade 4 laboratory abnormalities • PK, PD, and biomarker parameters: ○ Selected blood chemistry, hematology, and urinalysis laboratory measurements ○ PK parameters (AUC, C_{max}, and T_{max}) at Week 12 visit, and trough concentrations at various time points ○ Complement biomarkers to evaluate alternative pathway activities: Bb, fD, and C3 fragments deposition. • Patient-reported outcomes: ○ FACIT-Fatigue (version 4) ○ EORTC QLQ-C30 (version 3) A statistical analysis plan (SAP) will be developed for analyses of data collected during the initial 24-week treatment phase to provide details of the data analysis procedures and presentations as patient data are emerging with progression of the dose optimization process.

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
1A1	Cytochrome P450 family 1 subfamily A member 1
AA	Aplastic anemia
ACE	Angiotensin converting enzyme
ACIP	Advisory Committee on Immunization Practices
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANC	Absolute neutrophil count
AP	Alternative Pathway (of complement)
ARB	Angiotensin receptor blocker
AST	Aspartate transaminase
AUC	Area under the curve
BA	Bioavailability
Bb	Bb fragment of complement factor B
BID	Twice daily
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
°C	Degrees Celsius
C3	C3 complement protein
C3G	C3 glomerulopathy
C5	C5 complement protein
CBC	Complete blood count
CH50	An assay to measure overall activity of complement classical pathway
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine kinase
Cmax	Maximum plasma concentration
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A	Cytochrome P-450 3A
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
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practices
GPI	glycosylphosphatidylinositol
HBsAg	Hepatitis B surface antigen
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
IC50	50% Inhibitory concentration
ICF	Informed Consent Form

Abbreviation	Definition
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IC-MPGN	Immune-complex membranoproliferative glomerulonephritis
IEC	Independent Ethics Committee
IM	Intramuscular
INR	International normalized ratio
IRB	Institutional review board
IV	Intravenous
kDa	Kilodalton
LDH	Lactate dehydrogenase
LFC	Liquid filled capsule
LFT	Liver function test
LLN	Lower limit of normal
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
MMF	Mycophenolate mofetil
NOAEL	No observed adverse effect level
P450	Cytochrome P450
PD	Pharmacodynamic(s)
P-gp	P-glycoprotein
PI	Principal investigator
PIGA	Phosphatidylinositol N-acetylglucosaminyltransferase subunit A
PK	Pharmacokinetic(s)
PNH	Paroxysmal Nocturnal Hemoglobinuria
PO	Per oral
PR interval	Period that extends from the beginning of the P wave until the beginning of the QRS complex
PRO	Patient Reported Outcomes
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's 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
SMS	Short message service
TEAE	Treatment-emergent adverse event
TID	Three times daily
tmax	Time after administration of a drug when the maximum plasma concentration is reached
UGT	Uridine diphosphate glucuronosyltransferase
UGT1A1	Uridine diphosphate glucuronosyltransferase family 1 member A1
ULN	Upper limit of normal
µL	Microliter
µM	Micromolar

Abbreviation	**Definition**
WBC	White blood cells

1 Introduction

This is a multiple-center, open-label study in patients with PNH who have inadequate response to eculizumab treatment. This study will enroll up to 14 patients who will receive 24 weeks of daily oral treatment with ACH-0144471 plus intravenous (IV) eculizumab administered at the patient's usual dose and schedule. Patients enter the study in sequential groups with escalating initial dose levels, with a minimum of 4 weeks before dosing for the subsequent group of patients. The first three groups will include 2 patients per group to determine an optimal ACH-0144471 dose for use in combination with eculizumab for the remaining 8 patients in the fourth group. The initial dose level of Groups 2 and 3 could be lower based on emerging safety data from the prior group(s). ACH-0144471 dose may be increased within each group of patients based on Hgb values at protocol-specified time points during the 24-week treatment phase. All dose escalations will be made on a patient-by-patient basis at the discretion of the PI, in consultation with the Sponsor. The decision to enroll subsequent groups at initial lower dose levels than planned will be made by the Sponsor in collaboration with the investigators.

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 for treatment of 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 in healthy volunteers are complete and results reported in the IB [3]: ACH471-001 Single Ascending Dose Study (SAD), ACH471-002 Multiple Ascending Dose Study (MAD), and ACH471-006 Relative Bioavailability Study (Rel BA).

A drug-drug interaction study (ACH471-010) was recently completed in healthy volunteers. This study was conducted to assess the effect of ACH-0144471on CYP3A, P-glycoprotein (P-gp), and UDP-gluronosyltransferase (UGT). The single-dose PK of each substrate was compared to administration alone versus when given in the presence of steady-state levels of ACH-0144471 (150 mg TID administered for 4 days). Preliminary results indicate that ACH-0144471 is a weak inhibitor of CYP3A, a moderate inhibitor of P-gp, and had no effect on UGT.

A monotherapy study of ACH-0144471 in PNH patients without prior treatment for PNH (Study ACH471-100) and a long-term extension to this study (ACH471-103) are ongoing (see Section 3.2.2).

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 alternative pathway (AP) activation [2, 4]. 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, 4]. 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 AP activity and inflammation [5, 6]. 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 is currently under way under the auspices of the PNH Registry [7].

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 [8].

PNH is caused by a somatic mutation in the phosphatidylinositol N-acetylglucosaminyltransferase subunit A (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 AP via tickover mechanism [9]. In addition to anemia that requires frequent red blood cell (RBC) transfusions, there are other serious sequelae related to the liberation of intracellular hemoglobin (Hgb) 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. 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.

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. However, approximately 30% of patients on eculizumab continue to have ongoing extravascular hemolysis.

1.3.3 Potential Advantages of Addition of ACH-0144471 to Standard of Care with Eculizumab 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 only 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.

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 available data from eculizumab therapy and individual case reports of congenital complement system deficiencies, including complement fD, inhibition of the complement system may result in an increased risk of infection, notably *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 ACH471-101. Patients will be required to be previously vaccinated, or to receive vaccinations for *N. meningitidis*, *Streptococcus pneumoniae* (*S. pneumoniae*), and *Haemophilus influenzae* (*H. influenzae*) (see Section 6.3).

Patients on an eculizumab regimen may already be taking a prophylactic antibiotic, according to standard of care in their region. Those patients will continue receiving the antibiotic during the duration of this trial. If a patient is not already on a prophylactic antibiotic when entering the study, penicillin V (or an appropriate alternative) will be prescribed from the beginning of dosing of ACH-0144471 to the end of dosing. If a patient has an allergy to or cannot tolerate penicillin V, the use of an alternative antibiotic will be considered on a case-by-case basis in consultation with the PI and the Sponsor to determine an appropriate alternative.

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 will also be asked to monitor themselves between clinic visits (Appendix 4).

Additionally, the site must report any Grade 3 or Grade 4 AEs which are possibly, probably, or definitely related to study drug (see Section 6.16.7) to the Sponsor within 24 hours.

1.3.4.2 Risk of Hepatic Injury

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 (ALP), gamma-glutamyl transferase (GGT), total/direct/indirect bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) will be closely monitored in all clinical studies with ACH-0144471.

In humans, elevations in ALT levels have been observed in healthy volunteers in the MAD study (ACH471-002) with the high doses of 500 mg twice daily and 800 mg twice daily for 14 days (see IB [3]). These ALT elevations were not associated with signs or symptoms of hepatic failure, occurred after completion of dosing, and were self-limited. One participant in the ongoing monotherapy PNH trials ACH471-100/ACH471-103 had elevated transaminases associated with breakthrough hemolysis and discontinued ACH-0144471. All abnormal transaminase findings were transient, were not associated with evidence of hepatic decompensation, and resolved within a short time period.

2 Study Objectives

2.1 Primary Objective

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

2.2 Secondary Objectives

The secondary objectives of this study are:

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

2.3 Exploratory Objectives

The exploratory objectives of this study are:

- To explore the effect of ACH-0144471 plus eculizumab on complement biomarkers including alternative pathway (AP) activity, Bb, fD, and C3 fragment deposition during 24 weeks of treatment
- To evaluate health-related quality of life (QOL) measures during 24 weeks of treatment
- To explore the benefits of ACH-0144471 plus eculizumab treatment as perceived by patients with PNH by:
    - Exploring patients' experiences of PNH, its impact on everyday lives and the disease trajectory, from first symptoms to definitive diagnosis and beyond, including prior treatment with eculizumab alone
    - Documenting the evolution of PNH over the course of treatment with ACH-0144471 plus eculizumab from a patient's perspective
    - Comparing patients' experience with eculizumab alone and ACH-0144471 plus eculizumab treatment
- To explore patients' expectations towards treatment with ACH-0144471 plus eculizumab

3 Investigational Plan

3.1 Overall Study Design and Plan

This is a multiple-center, open-label, multiple-dose Phase 2 study in patients with PNH who have inadequate response to eculizumab treatment. This study will include up to 14 patients who will receive 24 weeks of daily oral treatment with ACH-0144471 plus intravenous (IV) eculizumab administered at the patient's usual dose and schedule. This will be followed by a long-term extension phase.

There will be 4 groups studied based on initial dose of ACH-0144471, which will be enrolled sequentially. Group 1 will start at 100 mg TID. Group 2 will start at 150 mg TID. Group 3 will

start at 200 mg TID. Group 4 will start at the optimal dose determined from Groups 1-3. The initial dose level of Groups 2 and 3 could be lower based on emerging safety data from the prior group(s). The decision to enroll subsequent groups at initial lower dose levels than planned will be made by the Sponsor in collaboration with the investigators.

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

In order to be eligible, PNH patients must have RBC-transfusion-dependent anemia (defined as having received at least one RBC transfusion within 12 weeks prior to screening) and who are receiving a stable dose of eculizumab (have been receiving eculizumab at approved or higher doses for at least 24 weeks prior to entry without change in dose or schedule for at least 8 weeks). Table 1 provides a visual view of the study design.

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 may receive vaccinations during this study, as described in Section 6.3. Those who have been previously vaccinated, depending on evolving recommendations in this patient population and/or the results of any testing that may be performed to examine the patient response to vaccines, may receive recommended boosters as described in Section 6.3.

Patients will return to the clinic for safety, PK, and other assessments at Week 1, Week 2, Week 4, Week 8 and Week 12, and then every 4 weeks until Week 24. Patients will have local safety labs drawn at Week 3, Week 6, and Week 10. Patients will also be asked to return to the clinic or a local lab 72-96 hours after any dose escalation. At the Week 12 visit, subjects will remain at the clinic for 8 hours for intensive PK/PD sampling and collection of a time-matched ECG at the maximum plasma concentration of ACH 0144471 (3 hours after dosing).

Quality of Life (QoL) Questionnaires (FACIT Fatigue Scale [version 4] and 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 during screening and after treatment with ACH-0144471 plus eculizumab, respectively.

In addition, Patient Reported Outcomes (PRO) interviews by independent outcomes researchers chosen by the Sponsor will be conducted with patients enrolled in the trial at times indicated in Appendix 1 to collect patients' experience of PNH, its impact on everyday lives and the disease trajectory.

Table 1. Study Design

Group	N	Treatment							
		Weeks 1 – 4	**Weeks 5 – 8**		**Weeks 9 – 12**		**Weeks 13 – 24[1]**		**Beyond Week 24**
Group 1	2	100 mg ACH-0144471 TID + eculizumab[2]	If Week 4 Hgb is ≥1.5 g/dL increase from Baseline, Stay at current dose of ACH-0144471	If Week 4 Hgb is <1.5 g/dL increase from Baseline, or patient received a transfusion in previous 4 weeks, Escalate to next highest dose[4] of ACH-0144471	If Week 8 Hgb is ≥3 g/dL increase from Baseline, Stay at current dose of ACH-0144471	If Week 8 Hgb <3 g/dL increase from Baseline, or patient received a transfusion in the previous 4 weeks, Escalate to next highest dose[4]of ACH-0144471	If Week 12 Hgb is in the normal range Stay at current dose of ACH-0144471	If Week 12 Hgb is < normal, or if the patient received a transfusion in the previous 4 weeks, Escalate to next highest dose[4] of ACH-0144471	Patients will enter the long-term extension phase and remain on the same dose of ACH-0144471 they were receiving at Week 24 + eculizumab[2]
Group 2[3]	2	150 mg ACH-0144471 TID + eculizumab[2]							
Group 3[3]	2	200 mg ACH-0144471 TID + eculizumab[2]							
Group 4	8	Optimal dose of ACH-0144471 identified from Groups 1 – 3 + eculizumab[2]							

Hgb = hemoglobin; TID = three times daily

[1] Any patient who has not already been dose escalated up to 200 mg ACH-0144471 by his/her Week 12 visit, may be escalated in the same manner up to a maximum of 200 mg ACH-0144471 TID, if they have been on their previous dose for at least 4 weeks

[2] Patients will continue to receive eculizumab at their usual dose and schedule throughout the trial

[3] Patients in Groups 2 and 3 could start at 100 mg TID or 150 mg TID, respectively, based on emerging safety data from the prior group(s)

[4] From 100 mg TID to 150 mg TID, or from 150 mg TID to 200 mg TID if patient has not already escalated to 200 mg TID

After Week 24, if patients are receiving clinical benefit, they will continue treatment in an extension phase and return to the clinic every 8 weeks, with a local lab visit 4 weeks after every clinic visit. Clinical benefit will be assessed by the Principal Investigator (PI) based on an improvement in Hgb. Additionally, patients must not have developed any comorbidity that might make it unsafe to continue on therapy, or any safety concern related to treatment with ACH-0144471. Patients will continue to receive the same dose of eculizumab on the same schedule that they were receiving prior to the start of the study. Patients will continue therapy in this study until: 1) ACH-0144471 is commercially available in their country; 2) the development of ACH-0144471 as a potential therapy for PNH is terminated; or 3) until the therapy is no longer tolerated or effective.

Patients who do not enter the long-term extension phase, or discontinue from the study, will have the dose of ACH-0144471 tapered over 6 days, as described in Section 5.3.1.3, and two follow-up visits will be conducted approximately 14 days and 28 days after the last dose of ACH-0144471. Patients will continue to receive the same dose of eculizumab on the same schedule that they were receiving during the taper and follow-up periods as directed by their physician.

3.2 Rationale for Study Design

3.2.1 Justification of Design

The purpose is to evaluate whether patients with PNH who exhibit only a partial response to eculizumab (when administered a therapeutic dose) as evidenced by ongoing hemolysis and anemia, may benefit from the addition of ACH-0144471.

C3 fragment deposition on PNH RBCs during eculizumab treatment is a likely cause for suboptimal response in the subset of PNH patients who experience extravascular clearance of PNH RBCs coated by C3 fragments [16]. ACH-0144471 inhibits the complement cascade upstream of C3 and also blocks the complement amplification loop. ACH-0144471 has been shown to prevent deposition of C3 fragments on PNH erythrocytes ex vivo [17] and therefore is expected to reduce extravascular hemolysis.

A recent report also showed that eculizumab failed to completely block terminal pathway activity in several clinically relevant situations ex vivo. Terminal pathway inhibition by eculizumab became less effective the more that complement was activated. The degree of residual terminal pathway activity in the presence of eculizumab correlated with the number of surface-deposited C3b molecules [18]. Addition of ACH-0144471 to reduce the density of C3b is expected to convert the incomplete terminal pathway inhibition by eculizumab into complete inhibition, leading to a synergistic effect. To test this, Achillion has conducted an in vitro study to assess the synergy of ACH-0144471 combined with eculizumab. The study of ACH-0144471 with eculizumab was performed in an AP-dependent hemolytic assay using RBCs from a PNH patient and 20% normal human serum in the presence of 10 mM Mg^{++}+EGTA. A strong synergy in protection of PNH RBCs from hemolysis was observed, suggesting the potential for a similar synergistic effect in the clinical setting. This experiment indicates that ACH-0144471 doses of < 200 mg TID could contribute meaningfully in a combination regimen with eculizumab.

3.2.2 Justification of Dose

In the SAD study, single doses of ACH-0144471 up to 1200 mg and 2400 mg (given as two 1200 mg doses separated by 12 hours) were well tolerated in healthy subjects. In the MAD study, multiple doses of 200 mg twice daily (BID) for 14 days or 75 mg TID for 7 days were also well tolerated in healthy subjects. However, Grade 3 or Grade 4 ALT elevations occurred in two subjects in the higher dose cohorts (500 mg BID and 800 mg BID for 14 days) following completion of dosing in the MAD study [3].

Achillion partnered with the DILIsym group to employ DILIsym® to assess the clinical relevance of the liver enzyme elevations as well as the risk of liver injury at doses planned in the patient studies. The simulations indicate that the maximal loss of hepatocytes that occurred with doses up to 2400 mg daily would not have a significant effect on liver function and doses up to 200 mg TID were not predicted to increase ALT [19, 20].

The 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.

Data to date on doses from 100 to 200 mg TID have demonstrated clinically significant improvements in Hgb, LDH, increase in PNH RBC Type III clone size, and patient reported well-being. Treatment has been generally well tolerated. Continued monitoring over time to demonstrate maintenance and/or improvement of these responses is needed.

These data from the ongoing monotherapy studies provide clinical evidence that addition of ACH-0144471, at a dose of 100 mg TID or greater, in combination with eculizumab, could provide additive or synergistic benefit to patients with sub-optimal response to eculizumab monotherapy.

Therefore, in study ACH471-101, the starting dose for Group 1 of ACH-0144471 will be 100 mg TID daily (see Section 3.2.3). Dose adjustments will be made based on safety monitoring and Hgb levels and will not exceed 200 mg TID. Patients will continue to receive eculizumab according to their usual dose and schedule.

3.2.3 Criteria to Escalate to a Higher Dose

Decisions to change the dose of ACH-0144471 will be made by the site PI in consultation with the Sponsor after review of ongoing safety data.

- **1st Dose Escalation Point (Week 4)**

On a patient-by-patient basis, if the starting dose for a group is well tolerated and the available safety data are satisfactory, a patient may be escalated to the next highest dose (to a maximum dose of 200 mg TID) if his/her Hgb level from Week 4 has not increased by ≥1.5 g/dL from their baseline value (Day 1), or the patient received a transfusion during the previous 4 weeks.

- **2nd Dose Escalation Point (Week 8)**

On a patient-by-patient basis, a patient may be escalated to the next highest dose, to a maximum of 200 mg TID, if his/her Hgb level from Week 8 has not increased by ≥3 g/dL from their baseline value (Day 1), or the patient received a transfusion during the previous 4 weeks.

- **3rd Dose Escalation Point (Week 12)**

On a patient-by-patient basis, a patient may be escalated to the next highest dose, to a maximum dose of 200 mg TID, if his/her Hgb level from Week 12 has not normalized, or the patient received a transfusion during the previous 4 weeks.

At each time point:

- Patients currently taking 100 mg TID may escalate to 150 mg TID
- Patients currently taking 150 mg TID may escalate to 200 mg TID
- Patients taking 200 mg TID will stay on the same dose

Any patient who has not already been dose escalated up to 200 mg ACH-0144471 by his/her Week 12 visit, may be escalated in the same manner up to a maximum of 200 mg ACH-0144471 TID, if they have been on their previous dose for at least 4 weeks.

Depending on when data are received and reviewed, if the patient is going to dose escalate, the site should contact the patient as soon as possible to provide new dosing instructions. If necessary, the patient may be asked to return to the clinic for new drug supplies prior to their next clinic visit. Patients should have blood drawn (locally or at the clinic) 72 to 96 hours after starting the new dose for measurement of LDH, Hgb, and liver function tests (ALT, aspartate aminotransferase [AST], gamma glutamyl transferase [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 dose of 200 mg TID has already been reached
- Hgb level has increased from baseline and is in the normal range

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 Achillion medical monitor.

3.2.4 Individual Stopping Criteria

The PI may stop dosing ACH-0144471 in any patient who meets an individual stopping rule. However, the Achillion medical monitor should be notified immediately, if possible, before dosing is terminated. If dosing of ACH-0144471 is to be terminated, the taper schedule described in Section

5.3.1.3 will be implemented and treatment with eculizumab will continue at the patient's usual dose and schedule. If dosing of ACH-0144471 is terminated for safety-related reasons, the PI may discontinue dosing ACH-0144471 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.

Any individual patient who meets any of the following criteria will be discontinued from further dosing of ACH-0144471:

- The patient experiences any serious adverse event (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 6.19

Discontinuation of ACH-0144471 treatment will also be considered for:

- ALT or AST >8 × ULN
- ALT or AST >5 × ULN for more than 2 weeks
- ALT or AST>3 × ULN and clinically significant elevation in Total Bilirubin relative to baseline
- ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- If there is a marked prolongation of the QT/QTc interval during treatment with the study drug, especially if the measurement is obtained from more than one ECG
- Development of a meningococcal infection or severe sepsis

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 will 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.

Patients who discontinue from ACH-0144471 treatment will follow the procedures for early termination, taper, and follow-up indicated in Appendix 1, but continue to receive their usual regimen of eculizumab.

3.2.5 Study Stopping Criteria

Dosing in the study will be terminated if one or more of the following occurs:

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

- Two or more patients discontinue study therapy due to liver function test abnormalities as detailed below
  - ALT or AST >8 × ULN
  - ALT or AST >5 × ULN for more than 2 weeks
  - ALT or AST >3 × ULN and TBL >2 × ULN or INR >1.5 in the absence of warfarin coagulation
  - ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- Two or more patients develop a meningococcal infection or severe sepsis

3.2.6 Study Duration and Dates

The maximum screening period is 60 days. Each patient will receive daily oral doses of ACH-0144471 TID plus eculizumab according to the patient's usual dose and schedule for a total of 24 weeks (168 days). If a patient is receiving clinical benefit, in the opinion of the PI, the patient will enter the long-term treatment extension phase of the study. If a patient discontinues from the study there will be a 6-day taper at the end of treatment and follow-up for an additional 28 days after the end of the study period. Therefore the maximum duration for patient participation for those patients not continuing on to long-term treatment could be up to 262 days (60 days screening, 168 days of treatment, 6 days of taper, and 28 days follow-up). For those patients entering the long-term treatment extension, patients will continue therapy in this study until: 1) ACH-0144471is commercially available in their country; 2) the development of ACH-0144471as a potential therapy for PNH is terminated; or 3) the therapy is no longer tolerated or effective. In addition, 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.

No overnight stays in the clinic are required.

4 Study Population Selection

4.1 Study Population

The study population is adult PNH patients with RBC transfusion- dependent anemia (defined as having received at least at least one RBC transfusion within 12 weeks prior to screening) and are receiving a stable dose of eculizumab (have been receiving eculizumab at approved or higher doses for at least 24 weeks prior to entry and without change in dose or schedule for at least 8 weeks). Up to fourteen patients are planned to be enrolled in the trial.

4.2 Inclusion Criteria

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

1. Diagnosed with PNH
2. Received at least one RBC transfusion within 12 weeks prior to screening

3. Anemia (Hgb <10 g/dL) with adequate reticulocytosis (absolute reticulocyte count ≥100 × 10^9/L)
4. Must be on a stable regimen of eculizumab (have been on eculizumab for at least 24 weeks without change in dose or schedule for at least the past 8 weeks)
5. Platelet count ≥40,000/µL without the need for platelet transfusions
6. Documentation of vaccination for *N. meningitidis, H. influenzae, and S. pneumoniae,* or willingness to receive vaccinations as described in Section 6.3
7. Willingness to receive antibiotic prophylaxis if not already prescribed within standard of care, as described in Section 5.2.3
8. Age 18 years to 65 years, inclusively (or ≥ minimum adult age in accordance with local legal requirements)
9. Female participants of childbearing potential must agree to use an acceptable method of contraception (as defined in Section 5.5.5) from 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.
10. 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.
11. Must agree to provide written informed consent
12. Must be willing and able, at all times, to have transportation and telephone access, and to be within 1 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. Current evidence of bone marrow failure or aplastic anemia requiring treatment
2. History of a major organ transplant (e.g., heart, lung, kidney, liver) or hematopoietic stem cell/marrow transplant (unless HSCT engraftment has failed)
3. Received another investigational agent within 30 days or 5 half-lives of the investigational agent prior to study entry, whichever is greater
4. Documented C5 mutations
5. Known or suspected complement deficiency
6. Contraindication to one or more of the required vaccinations

7. Active bacterial infection or clinically significant active viral infection, a body temperature >38°C, or other evidence of infection on Day 1, or have a history of febrile illness within 14 days prior to first study drug administration
8. History of meningococcal infection, or a first-degree relative or household contact with a history of meningococcal infection
9. 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 PI would make it difficult to properly provide prophylactic antibiotic therapy or treat an active infection.
10. 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)
11. Laboratory abnormalities at screening, including:
    - Alkaline phosphatase (ALP) >1.5 × upper limit of normal (ULN)
    - Absolute neutrophil counts (ANC) <1,000/µL
    - Alanine aminotransferase (ALT) >1.5 × ULN
    - Direct bilirubin >1.5 × ULN (unless due to extravascular hemolysis, in the opinion of the investigator and in consultation with the sponsor)
    - 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
12. Females who are pregnant, nursing, or planning to become pregnant during the study or within 90 days of study drug administration
13. Prior history or current evidence of biliary cholestasis
14. Gilbert's syndrome

    Patients with history or family history suggestive of Gilbert's syndrome will be tested and excluded from study if positive for UGT1A1 genotyping polymorphism or missense change
15. 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
16. Taking medications known to prolong the QT/QTc interval (see Section 5.5), or have a family history of prolonged QT syndrome or with a screening QTcF >450 msec for males and >470 msec for females
17. Have eGFR< 30 mL/min/1.73 m^2 and/or are on dialysis

5 Study Treatment(s)

5.1 Study Drug - Investigational Drug ACH-0144471

ACH-0144471 will be dosed as a tablet 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. ACH-0144471 will be administered as 50, 75, or 100 mg tablets.

5.2 Treatments Administered

5.2.1 ACH-0144471 and Background Therapy (Eculizumab)

ACH-0144471 will be administered orally three times daily (TID) over a period of 24 weeks while patients continue to receive eculizumab at their usual dose and schedule. If a patient discontinues from the study, a taper of ACH-0144471 will be implemented, according to the schedule in Section 5.3.1.3, and patients will continue to be dosed with eculizumab according to their usual dose and schedule. If dosing of ACH-0144471 is terminated for safety-related reasons, the PI may discontinue dosing ACH-0144471 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 patient who discontinues treatment with ACH-0144471 will have the assessments indicated for Follow-up in Appendix 1 and then terminate from the study.

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.

5.2.3 Prophylactic Antibiotics

The prophylactic antibiotic specified in this study is penicillin V (or an appropriate alternative). Patients on an eculizumab regimen may already be taking a prophylactic antibiotic, according to standard of care in their region. Continued use of antibiotics other than penicillin V will be considered on a case-by-case basis with decisions made jointly between the PI and Sponsor during screening to determine whether the patient's existing regimen is appropriate.

If a patient is not already on a prophylactic antibiotic when entering the study, penicillin V (500 mg/day PO) or an appropriate alternative will be prescribed from the beginning of dosing of ACH-0144471 (Day 1) to the end of dosing. If a patient has an allergy to penicillin V, the use of an alternative antibiotic will be considered on a case-by-case basis in consultation with the PI and the Sponsor to determine an appropriate alternative.

5.3 Selection of Timing and Dose for Each Patient

5.3.1 ACH-0144471

The starting dose of ACH-0144471 will be based upon Group assignment. Two patients assigned Group 1 and will start treatment with 100 mg TID. Four weeks later, if there are no safety signals, two patients assigned to Group 2 will start treatment with 150 mg TID. Four weeks later, if there are no safety signals, two patients assigned to Group 3 will start treatment with 200 mg TID. Four weeks later, 8 patients assigned to Group 4 will start treatment with the optimal dose determined from Groups 1-3. In Groups 1 and 2, on an individual patient basis, the dose may be increased multiple times at 4-week intervals, each time to the next higher dose level allowed based on safety data and Hgb level as described in Section 3.2.3. The initial dose level of Groups 2 and 3 could be lower based on emerging safety data from the prior group(s). The decision to enroll subsequent groups at initial lower dose levels than planned will be made by the Sponsor in collaboration with the investigators.

Patients will be dosed with ACH-0144471TID (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.

5.3.1.1 Clinic Visit Dose Administration Instructions

The morning doses of ACH-0144471on the days of each visit to the clinic will be administered in the clinic by study site personnel. For Clinic Visit days, patients will be instructed to fast for at least 8 hours overnight and to abstain from taking their ACH-0144471study medication on the mornings of their study visits so that they can be dosed in the clinic following safety and pharmacokinetic assessments. At the next day's Clinic Visit, patients will first have blood drawn for clinical laboratory and other evaluations as described in Appendix 1, then have breakfast, and then 15-30 minutes later take the dose of study medication assigned for that day. Patients will be required to bring back all remaining study drug at each visit, so that study site personnel may perform a drug accountability assessment.

5.3.1.2 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 will be instructed to keep their study medication at room temperature.

5.3.1.3 ACH-0144471 Taper Schedule

If a patient discontinues from the study, a taper of ACH-0144471 will be implemented, according to the schedule Table 2, and patients will continue to be dosed with eculizumab according to their usual dose and schedule.

Table 2. ACH-0144471 Dosing Taper Schedule

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

If a dosing regimen not specified in Table 2 is assigned to a patient, then the Sponsor's medical monitor will define a taper schedule prior to dosing termination.

5.3.2 Eculizumab

On Day 1 (± 1) of the study, patients will receive their eculizumab treatment according to their usual procedure and dose. The reason for the ± 1 day window is because the location where patients would receive ACH-0144471 may not be the same as the location where they regularly receive their eculizumab treatments. Every attempt should be made to try to dose both drugs on the same day if possible. Patients will continue to receive eculizumab according to their usual dose and schedule for the remainder of the study. The dose and schedule of eculizumab should not be altered during the course of the study, except that patients may switch from eculizumab to an approved eculizumab biosimilar or ravulizumab after completion of the primary endpoint at Week 24.

5.4 Method of Assigning Patients to Treatment Groups

Patients will be enrolled to one of four treatment groups sequentially once the prior treatment group has completed enrollment and each patient has completed 4 weeks of treatment. Each patient will be assigned a sequential patient identification number within the study site.

5.5 Restrictions

5.5.1 Prior Therapy

Patients may not commence treatment with ACH-0144471 if they have had a transfusion of RBCs ≤2 weeks prior to the start of dosing. Therefore, the patient must remain in screening until at least 2 weeks have passed from the time of their last transfusion to the start of study drug.

5.5.2 Concomitant Therapy

Based on in vitro data, ACH-0144471 has the potential to inhibit several CYP enzymes as well as some transporters. In vitro results for ACH-0144471 interactions with various CYP enzymes and transporters are described in the IB [3].

As described in Section 1.2, a drug-drug interaction study in healthy volunteers with ACH-0144471 has been conducted to determine the potential for ACH-0144471 to affect CYP3A, P-gp and UGT. Preliminary results indicate that ACH-0144471 is a weak inhibitor of CYP3A, a moderate inhibitor of P-gp, and had no effect on UGT. Therefore, use of specific concomitant medications other than eculizumab will be considered on a case-by-case basis with decisions made jointly between the PI and Sponsor, based on available knowledge of ACH-0144471 as well as the characteristics of the potential concomitant medication. Per protocol, all subjects are to be treated with study medication in combination with eculizumab background therapy (Section 5.2.1); for the purpose of data collection and analysis, eculizumab used in this manner will be considered a concomitant medication. If patients switch from eculizimab to an approved eculizumab biosimilar or ravulizumab after completion of the primary endpoint at Week 24 (Section 5.3.2), this medication used in this manner will be also considered a concomitant medication.

Although QT prolongation has not been observed in the studies with ACH-0144471 conducted to date, a Thorough QT/Qtc study has not been conducted. Therefore, a conservative approach is being taken for drugs that are known to prolong the QT interval and their use is excluded in this study.

Details of all concomitant medication use, including all medications administered for the treatment of AEs, must be recorded in the patient's case report form (CRF). The following are some general guidelines for concomitant medication use based on currently available data:

- Concomitant administration of folic acid, and/or erythropoiesis-stimulating agents is permitted if on stable doses for at least 4 weeks prior to Day 1.
- Concomitant administration of steroids or other immunosuppressants is permitted if the dosage regimen is stable for at least 12 weeks 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.
- Concomitant administration of drugs with the potential to cause QTc prolongation is prohibited. These include antiarrhythmics such as disopyramide, flecainide, mexiletine, systemic lidocaine, propafenone, quinidine and amiodarone

The use of concomitant medications during the trial will be assessed at the timepoints indicated in the Schedule of Assessments (Appendix 1).

5.5.3 Fluid and Food Intake

Patients will 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.

5.5.4 Patient Activity and Other Restrictions

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

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

5.5.5 Contraception

5.5.5.1 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 from the date of screening until 90 days after their last dose of study drug

5.5.5.2 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 child-bearing 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 for ACH-0144471 will be performed at each visit. Patients will be required to bring back 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 may also receive automated reminders (e.g., via text or phone call) and they must respond to and record the time they take each daily dose of ACH-0144471 in an effort to ensure compliance. The site will be notified 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 to 25°C), with allowed excursion of 15 to 30°C. Patients will be instructed to keep their study medications in the original container at room temperature.

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

The PI or designee (e.g., pharmacist) is responsible for ensuring storage as per the label on the drug product at the site and adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study drug (quantity and condition) and patient dispensing records and returned or destroyed drug. Dispensing records will document quantities received from Achillion Pharmaceuticals, Inc. (or designee) and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, patient initials, and the initials of the person dispensing the medication. All drug supplies and associated documentation will be periodically reviewed and verified by the Study Monitor over the course of the study.

5.9 Investigational Product Retention at Study Site

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

Inc. requirements for disposal, arrangements will be made between the site and Achillion Pharmaceuticals, Inc. or its representative, for destruction or return of unused study drug supplies.

6 Study Procedures

The required study procedures are detailed in this section. The schedule for these procedures is 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 to determine whether the patient meets the eligibility criteria. The history will include all surgeries and past medical procedures, all past significant illnesses or current chronic conditions, all medication use currently and within the past 90 days (including over the counter medications, and use of herbal and nutrient supplements), all eculizumab use during the prior 24 weeks, and any prior use of alcohol, illicit drugs and/or controlled substances. The history will 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 must also include at least 24 weeks and up to 3 years (if available) of RBC transfusion history. The medical history will be reviewed at screening and at each 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 case report form (CRF).

6.3 Vaccination

Inhibition by ACH-0144471 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 or boosters 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 or boosters 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 or boosters 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 7) for possible evaluation of response to vaccines or boosters.

If local practice dictates, vaccinations or boosters for *N. meningitidis*, *S. pneumoniae* and *H. influenzae* may all be administered on Day 1 of the treatment period. The criteria for determining whether vaccinations or boosters are required will be the same as those described above, as will the guidance on the selection of specific vaccines.

In addition, boosters may also be given during trial participation based on evolving vaccination guideline recommendation changes.

6.4 Prophylactic Antibiotics

As described in Section 5.2.3, participants who are not already on antibiotic prophylaxis will be prescribed penicillin V (or an appropriate alternative) from the start of dosing with ACH-0144471 (Day 1) through the end of dosing.

6.5 Physical Examination

A complete physical examination will be conducted by the PI (or designee) at the times indicated in the Schedule of Assessments (Appendix 1). This will include an examination of all major body/organ systems (including skin, head, eyes, ears, nose, throat, neck, thyroid, lungs, heart, abdomen, lymph nodes, and extremities), height, weight and calculation for BMI (height and BMI at Screening visit only). Measurements of height and weight will 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 will 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 (Table 7, Table 8 and Table 9). All ECG recordings will be 12-lead, and will 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 will also be noted by the PI or designee. Please note, at the Week 12 visit, patients will remain at the clinic for an additional 8 hours to collect intensive PK and PD samples. An additional ECG will be collected at 3 hours post-dose; this ECG should be in triplicate, with approximately 1 minute between tracings. If patients have a dose escalation after Week 12, the time-matched ECG/PK assessments will be repeated (see Section 7.2.1.1).

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 6.16 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 3, 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 3. Clinical Laboratory Tests

Hematology	Chemistry	Urinalysis	Additional Tests only at Screening	Other Assessments[10]
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 (ALP) Aspartate aminotransferase (AST) Bicarbonate (HCO_3) Bile acids Bilirubin(fractionated)[1] Blood urea nitrogen (BUN) Calcium Calculated eGFR[2] Chloride Creatine kinase (CK)[3] Creatinine Gamma-glutamyl transferase (GGT) Glucose[4] 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 Microscopic examination of sediment[5] Nitrite Leukocytes Occult blood pH Protein Specific gravity Urobilinogen	Cr-1 Polymorphisms Erythropoietin FSH[6] HCV Ab HbsAg HIV Ab Sample for genetic biomarker testing (white blood cells)[7] Serum Pregnancy test[8] Urine drug screen[9]	AP Wieslab Bb C3 C3fragment deposition CH50 D-dimer Direct Coombs Factor D Free hemoglobin Haptoglobin Plasma/Serum samples for additional non-genetic biomarker testing[7] PNH Clone Size PT/PTT/INR Urine pregnancy test[9] Samples for potential 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 Provide estimated Glomerular Filtration Rate (eGFR) based on Modification of Diet in Renal Disease (MDRD) equation

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

4 If glucose is > ULN, reflexively test HbA1c

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

6 For postmenopausal women

7 See Section 6.11.2

[8] 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.

[9] Urine drug screen will be measured at screening. Test will include, at a minimum, amphetamines, barbiturates, cocaine metabolites, opiates, benzodiazepines, and cannabinoids.

[10] Refer to the Schedule of Assessments (Appendix 1) for times when these tests will be done

6.10 Pregnancy Testing

Females of child-bearing 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 receive vaccinations or boosters (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 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 AP hemolysis assay, and the plasma concentrations of fB, Ba, 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: 1) if a patient does not respond to the investigative drug; 2) if a patient experiences drug-related toxicity; or 3) to further characterize the underlying disease. Serum samples will be collected to potentially assess patient response to vaccinations at various time points in the study. Achillion may store samples for future use.

6.11.3 Pharmacokinetic Plasma Samples

For samples collected for PK analysis, whole blood (2 mL) will be collected into vacutainers containing K_2EDTA. The vacutainers will be gently inverted 5 to 8 times to thoroughly mix the preservative with the blood and kept chilled in an ice bath. The tubes will be centrifuged at 4°C for

15 minutes at 1300 g within 30 minutes of blood collection. Approximately 400 µL of plasma will 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 backup samples will remain at the clinic. Information on when and where to ship samples will be provided separately.

6.11.4 Blood Volumes

Approximate blood volumes are detailed in Table 4. The total approximate planned blood volume to be collected per individual is 745.5 ml over 24 weeks plus the taper and follow-up periods. During the extension phase, the planned maximum volume for blood collection for local laboratory visits is 14.5 mL and 49.0 mL for clinic visits. These volumes do 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.

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.

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). Additionally, the site must report any Grade 3 or Grade 4 AEs which are possibly, probably, or definitely related to study drug (see Section 6.16.7) to the Sponsor within 24 hours.

Table 4. Approximate Total Blood Volumes for First 24 Weeks of Treatment

		24-Weeks Treatment and Follow-up					Extension Phase	
Test	**Volume Drawn/ Test (mL)**	**Screening**	**24-weeks Treatment**	**Taper & Follow-up**	**Total**		**Local Lab Visits**	**Clinic Visits**
		# Tests	**# Tests**	**# Tests**	**# Tests**	**Blood Drawn (mL)**		
Screening Visit Labs (chemistry, LDH, erythropoietin, hematology, serum pregnancy, FSH, Serology [HIV, HBsAg, HCV Ab]	14.0	1	0	0.0	1	14.0	0.0	0.0
Clinical Labs (chemistry [including LDH & haptoglobin] & hematology)	10.5	0	15	4	19	199.5	10.5	10.5
PT, PTT/INR	4.5	1	7	1	9	40.5	0.0	0.0
Free hemoglobin	4.0	1	12	2	15	60.0	4.0	4.0
D-dimer	4.5	1	7	1	9	40.5	0.0	4.5
Direct Coombs	2.0	1	5	2	8	16.0	0.0	2.0
Flow Cytometry: Clone Size	2.0	1	7	2	10	20.0	0.0	2.0
Flow Cytometry: C3 Fragment Deposition	4.0	0	7	2	10	36.0	0.0	4.0
AP Wieslab, AP Hemolysis, fD	5.0	1	13	4	18	90.0	0.0	5.0
Bb	2.0	1	9	4	14	28.0	0.0	2.0
CH50, C3	4.0	1	9	4	14	56.0	0.0	4.0
Sample for assessment of patient response to vaccines	3.5	2	4	0	6	21.0	0.0	3.5
Samples for non-genetic biomarkers	5.5	0	11	2	13	71.5	0.0	5.5
Sample for CR1 polymorphisms test; potential genetic assessment of complement genes	8.5	1	0	0	1	8.5	0.0	0.0
PK samples	2.0	0	17	3	20	40.0	0.0	2.0
Total Volume						**741.5**	**14.5**	**49.0**

6.13 Pharmacokinetic Assessments

Serial blood samples will be collected at the Week 12 visit, at the times indicated in Table 9 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 as indicated in Table 7 and Table 8.

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.

6.14 Pharmacodynamic and Efficacy Assessments

Pharmacodynamics will be evaluated using serum, plasma, and whole blood collected during the study with the assays outlined in Table 5 and the Schedule of Assessments (Appendix 1). Please note, at the Week 12 visit, patients will remain at the clinic for an additional 8 hours to collect intensive PK and PD samples. Additional information on sample collection and shipping instructions will be provided in a separate laboratory manual.

Samples will also be collected and retained for potential additional 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 Hgb levels and other measures of hemolysis, as well as RBC transfusion requirements.

Table 5. Pharmacodynamic Markers

Assay Identifier*	Assay Descriptions
CR1 polymorphisms	Genetic test
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 or immunoturbidity assay
CH50	MAC-mediated lysis of the antibody sensitized target; serial diluted serum
AP Wieslab assay	ELISA; LPS as activator; measurement of MAC
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.

6.15 Patient-Reported Outcomes Assessments

6.15.1 Quality of Life (QoL) Questionaires

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 assessments during screening (baseline) and after initiating treatment with ACH-0144471.

6.15.2 Patient Reported Outcomes (PRO) Interviews

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 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 will be interviewed during the screening period and at the times indicated in Appendix 1. For patients who enter the long-term treatment extension, an interview will be conducted at Week 48 (± 1 week). A single follow-up interview will be obtained for any patient that terminates early.[1]

[1] 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

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

6.16 Adverse Events Assessments

6.16.1 Definitions

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

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during treatment, having been absent prior to treatment, or worsens relative to the pretreatment state. In this study, any AE first assessed after receipt of the first dose of ACH-0144471 until the final follow-up visit will be considered treatment-emergent. All TEAEs will be recorded and reported.

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

- Any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality.
- Any new disease or exacerbation of an existing disease.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.
- Any case of abuse of alcohol, illicit drugs, or prescription drugs; abuse of study drug(s) or protocol -specified drug(s); addiction.
- A pregnancy that occurs or becomes confirmed during a clinical study (see Section 6.16.8).
- 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.

6.16.2 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

6.16.3 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 6.16.7.

Additionally, the site must report any Grade 3 or Grade 4 AEs which are possibly, probably, or definitely related to study drug (see Section 6.16.7) to the Sponsor within 24 hours.

6.16.4 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.

6.16.5 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.

6.16.6 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) [21]. The PI (or designee) should determine the severity of the AE based on the overall clinical importance or significance of the finding for that individual patient.

If an AE that was reported during the study increases or decreases in severity, then that AE is given a resolution date and time and a new record initiated with the new severity. If the severity of an AE remains the same, the AE will be kept open through to resolution.

6.16.7 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'.

6.16.8 Pregnancy

Any pregnancy, including female partner pregnancies of male patients that occurs or becomes confirmed during a clinical study (time frames outlined in Section 6.16.5) 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.

6.16.9 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 6.16.5).

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.

6.16.10 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.

6.17 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.

6.18 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. Additionally, the site must report any Grade 3 or Grade 4 AEs which are possibly, probably, or definitely related to study drug (see Section 6.16.7) to the Sponsor within 24 hours.

6.19 Removal of Patients from the Trial or Study Drug

A patient is free to withdraw from the study at any time without jeopardizing future medical care. In addition, the PI (or designee) may decide, for reasons of medical prudence or patient noncompliance, to discontinue dosing ACH-0144471 in a patient. The PI will also stop dosing ACH-0144471 in any patient who meets an individual stopping rule (Section 3.2.4). In either case, whenever possible, the Achillion medical monitor will be notified immediately, and if possible, before dosing is terminated. When dosing of ACH-0144471 is terminated, study participation is not necessarily also terminated. Instead, whenever possible, the patient will complete all the activities for the Week 24 or Early Termination Visit as described in Appendix 1, complete a dosing taper as described in Section 5.3.1.3, and return for a Follow-up visit two weeks after the last dose of study drug. Patients will continue to receive their eculizumab regimen, as per the PI's judgment.

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
- 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.

- Physical examinations, assessment of vital signs, ECG measurements, all required safety laboratory testing, and collection of blood and urine samples for PK and PD evaluation will be performed at various time points throughout the study. For patients not continuing on to an extension study, there will be a follow up visit approximately 2 weeks and 4 weeks after the last dose of study drug.
- Dosing should be at approximately the same times each day
- Transfusion information will be collected at every visit

During the treatment periods when multiple assessments occur at the same time, they will be conducted in the following order (unless otherwise specified):

1. ECG and vital signs prior to blood sampling
2. PK samples will be taken prior to dosing
3. Blood for laboratory safety tests will be taken prior to dosing

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 (Day -60 to Day -1)

Prospective patients will 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. 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 will 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 will be reviewed as described in Section 6.2, and a complete physical examination will be conducted as described in Section 6.5. A urine drug screen will be performed during Screening. The urine drug screen will include, at a minimum, amphetamines, barbiturates, cocaine metabolites, opiates, benzodiazepines, and cannabinoids. The PI, in consultation with the Sponsor, will use professional judgment in allowing the patient to continue participation in the study when evaluating the results of the drug screen if any positive results are obtained. 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 and ALT), or if the patient has a history of unexplained jaundice, unexplained high bilirubin levels, or a history otherwise suggestive of Gilbert's syndrome, the patient will be tested for this condition.

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 will 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) (Day -42 to Day 1)

As part of the screening process, participants will be evaluated to determine whether vaccination against *N. meningitidis*, *S. pneumoniae*, or *H. influenzae* is required, as described in Section 6.3. Any participant without sufficient history of these vaccines may be vaccinated or provided boosters, as appropriate. For participants who receive vaccinations and/or boosters, they may be either administered during the screening period, after all other screening assessments have been completed, or may be administered on Day 1 of the treatment period. For participants who will receive vaccinations, all other screening procedures must be completed, and patients must qualify for the study prior to vaccinations being administered. Female participants 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.

In addition, boosters may also be given during trial participation based on evolving vaccination guideline recommendation changes.

7.1.3 Patient Reported Outcomes (PRO) Phone Interview – Screening

Patient Reported Outcomes interviews will be conducted during the screening period, prior to initiation of study treatment. Patients must pass all other screening tests and be considered eligible for the study prior to being scheduled for their interview. The procedures indicated in Section 6.15.2 will be followed.

7.2 Clinic Visits

During the Treatment Period, physical examinations, assessment of vital signs, ECG measurements, all required safety laboratory testing, pregnancy testing for women of child-bearing potential, QoL assessments, PRO interviews, and collection of blood and urine samples for PK and PD evaluation

will be performed at various time points as specified in Appendix 1. The assessments listed in the Schedule of Assessments, including collection of blood for determination of trough levels of study drug and measurement of the listed complement markers will be performed prior to the administration of the first daily dose.

Patients will be instructed to fast prior to coming to a clinic visit and to bring their supply of ACH-0144471 with them for administration at the site.

Visits may take place within a window of ±1 day relative to the specified day.

The site will need to administer a meal or snack (see Section 5.5.3) within 15 - 30 minutes prior to dosing with ACH-0144471.

At the clinic, patients will be provided enough ACH-0144471 to last until their next visit. Clinic staff will also instruct the patient how to take their medication at home (Section 5.3.1.2) and record the time they took each dose and whether or not the dose was taken with food. The first dose of the day should be taken at the same time each morning; all doses should be taken approximately 15-30 minutes after completion of a meal or snack. (see Section 5.5.3). Patients will be instructed to store their study drug at room temperature.

Patients will continue to receive eculizumab at their usual location according to their usual dose and schedule for the entirety of the study.

Patients will take penicillin V from Day 1 through the end of dosing in this trial (see Section 5.2.3).

7.2.1 Weeks 1 Through 24

On Day 1 (± 1) of the study, patients will receive their usual eculizumab treatment at their regular location. Patients will continue to receive eculizumab at their usual location according to their usual dose and schedule for the remainder of the study.

If a patient is not already on a prophylactic antibiotic when entering the study, penicillin V (500 mg/day PO) or an appropriate alternative will be prescribed starting on Day 1. Patients will begin daily oral dosing on Day 1 with the dose of ACH-0144471 TID (depending on the group) as described in Section 3.1. Patients will return to the clinic at Week 1, Week 2, Week 4, Week 8, and Week 12 for the assessments indicated in Appendix 1, Table 7, and then every 4 weeks until Week 24.

QoL questionnaires (see Section 6.15.1) will be administered and a PRO Phone Interview (see Section 6.15.2) will be conducted at the times outlined in the Schedule of Assessments (Appendix 1).

7.2.1.1 Dose Escalation Evaluations (Week 4, Week 8, and Week 12)

After review of results of the patient's Week 4, Week 8, and Week 12 Hgb level and safety data, depending on patient's assigned group and current dose level, a patient may be dose escalated during the study (see Section 3.2.3 and Table 1). If the PI plans to dose escalate the patient, the site should contact the patient as soon as possible to provide new dosing instructions. If necessary, the patient

may be asked to return to the clinic for new drug supplies. Any patient who has not already been dose escalated up to 200 mg ACH-0144471 by his/her Week 12 visit, may continue to be escalated up to 200 mg ACH-0144471 TID, at the discretion of the PI if they have been on their previous dose for at least 4 weeks.

In addition to the assessments indicated in Table 7, at the Week 12 visit, patients will remain in the clinic for 8 hours post-dose to have additional PK, PD and ECG assessments done as described in Table 9. Patients will be instructed to fast prior to coming to the clinic visit and to bring their supply of ACH-0144471 with them for administration at the site.

In the event a patient is further dose escalated after Week 12, the additional PK, PD, and ECG assessments in Table 9 should be repeated accordingly, and the patient should have blood drawn (locally or at the clinic) 72 to 96 hours after starting the new dose for measurement of LDH, Hgb, and liver function tests (ALT, AST, GGT, and ALP) (see Section 7.3).

7.2.1.2 Week 24 Visit or Early Termination

At the Week 24 visit, patients will have all assessments as indicated in Table 8. Patients will also be evaluated for continuation of treatment with ACH-0144471. Clinical benefit will be assessed by the PI based on an improvement in Hgb. Additionally, patients must not have developed any comorbidity that might make it unsafe to continue on therapy, or any safety concern related to treatment with ACH-0144471. Patients continuing treatment with ACH-0144471 plus eculizumab will continue on the same dose of ACH-0144471 they were receiving at the Week 24 visit. The procedures outlined in Section 7.4 will be followed if a patient is continuing on to long-term treatment. Patients will be provided with enough ACH-0144471 to last until their next visit. Any patients continuing with treatment will not have the ACH-0144471 taper visits (Section 7.2.2) or follow-up visits (Section 7.2.3).

Patients who do not continue to extended treatment will come back to the clinic for visits during the taper period (Section 7.2.2) and follow-up period (Section 7.2.3). At Week 24, these patients will be provided with study drug and dosing instructions for their taper doses, and continue their standard of care eculizumab therapy as directed by their physician. Patients will continue taking their medication at home in the same way as previously described (see Section 5.3.1.2).

7.2.2 ACH-0144471 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 5.3.1.3. On Days 3 (T1) and 6 (T2) of the taper period, patients will have assessments performed as indicated in Appendix 1.

Patients will be instructed to fast prior to coming to the T1 and T2 clinic visits and to bring their study drug with them for administration at the site. Patients will continue taking their medication at home in the same way as previously described (see Section 5.3.1.2). Patients will continue to receive eculizumab at their usual dose and schedule.

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

7.2.3 Follow-Up Visits

Patients who discontinue ACH-0144471 for any reason will have two follow-up visits approximately 2 weeks and 4 weeks after the last dose of ACH-0144471. The procedures indicated in Appendix 1 will be followed. Patients will continue their normal standard of care and receive eculizumab at their usual dose and schedule.

7.2.4 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 will include at a minimum:

- Assess for compliance with protocol restrictions
- Assess for AEs and SAEs
- Collect transfusion information
- Record concomitant medications
- Conduct a brief 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 3
- 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.

7.3 Local Laboratory Visits – Weeks 1 through 24

Patients will have local laboratory visits at Week 3, Week 6, and Week 10 for the assessments indicated in Appendix 1, Table 7.

For dose escalations, patients should have blood drawn (locally or at the clinic) 72 to 96 hours after starting the new dose for measurement of LDH, Hgb, and liver function tests (ALT, AST, GGT, and ALP).

7.4 Long-Term Treatment Extension

Patients who enter the long-term extension will continue taking ACH-0144471 at the dose they were taking at Week 24 and will continue to receive eculizumab at their usual dose and schedule. Patients will also continue taking penicillin V, 500 mg/day PO. In the event a patient is further dose escalated after Week 24, the additional PK, PD, and ECG assessments in Table 9 should be repeated accordingly, and the patient should have blood drawn (locally or at the clinic) 72 to 96 hours after starting the new dose for measurement of LDH, Hgb, and liver function tests (ALT, AST, GGT, and ALP).

Patients will continue therapy in this study with ACH-0144471 plus eculizumab and be followed in the clinic until: 1) ACH-0144471 is commercially available in their country; 2) the development of ACH-0144471 as a potential therapy for PNH is terminated; or 3) the therapy is no longer tolerated or effective. In addition, 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.

If a patient discontinues during the extension phase, the procedures indicated in Sections 7.2.2 and 7.2.3 will be followed.

7.4.1 Clinic Visits

After Week 24, patients who are continuing on to long-term treatment will return to the clinic every 8 weeks starting at Week 32 and have the assessments described in Appendix 1. Women of childbearing potential will receive urine pregnancy tests at each of these visits. Patients will be instructed to fast prior to coming to a clinic visit and to bring their supply of ACH-0144471 with them for administration at the site. Clinic visits during the long-term extension may take place within a window of ±3 days relative to the specified day for the first 24 weeks, and then within a window of ±7 days relative to the specified day for the duration of the study.

At the clinic, patients will be provided enough ACH-0144471 to last until their next visit. Clinic staff will also instruct the patient how to take their medication at home (Section 5.3.1.2) and record the time they took each dose and whether or not the dose was taken with food. The first dose of the day will be taken at the same time each morning; all doses should be taken approximately 15-30 minutes after completion of a meal or snack. (see Section 5.5.3). Patients will be instructed to store their study drug at room temperature.

7.4.2 Local Laboratory Visits

In between clinic visits, patients will have blood drawn at a local clinical laboratory every 8 weeks (starting at Week 28) for assessment of Hgb, free Hgb, and LDH levels (Appendix 1, Table 8). These visits should occur within a window of ±7 days relative to the specified day. Women of childbearing potential will also receive a urine pregnancy test at these visits.

7.4.3 Quality of Life Questionnaires and Patient-Reported Outcomes (PRO) Phone Interviews

QoL questionnaires (see Section 6.15.1) will be administered and a PRO Phone Interview (see Section 6.15.2) will be conducted at Week 48 (± 1 week). After Week 48, QoL questionnaires will be administered approximately every 6 months for the duration of the study.

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 will provide adequate time and space for monitoring visits.

The monitor will query any missing or spurious data with the PI (or designee), which will 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

Data from the initial 24-week treatment phase and the study extension phase will be presented and analyzed separately. The planned analysis described in the following sections will focus on data from the 24-week treatment phase. Planned analysis on data from the study extension phase will depend on the results of 24-week treatment phase.

Subject (Patient) listings will be provided for all efficacy/PD, PK, and safety parameters for all patients receiving at least one dose of ACH-0144471.

Data from the group of 8 (or more) patients who receive the optimal dose of ACH-0144471 for 24 weeks, in combination with eculizumab, will be presented and summarized separately from the

other groups of patients whose dose levels of ACH-0144471 will be less than the optimal dose level for the full 24-week treatment phase. This group of patients receiving the optimal dose will be referred to as the **Optimal Dose Group**. The other 6 (or fewer) patients will form groups based on the initial ACH-0144471 dose: 100 mg TID, 150 mg TID, or 200 mg TID.

As indicated above, the Optimal Dose Group may include more than 8 patients at the end of the dose optimization process if the optimal dose level of ACH-0144471 is achieved prior to the enrollment of patients in the Optimal Dose Group (e.g., 2 or more groups, all started with same optimum dose of ACH-0144471 plus eculizumab, may be combined for analyses of this dose).

Summary tables on efficacy/PD and safety parameters will be presented for the Optimal Dose Group. Inferential statistical procedures (e.g., confidence intervals, comparisons with baseline values, etc.) may be employed on selected efficacy parameters for group(s) of patients receiving less than the optimal dose level.

A statistical analysis plan (SAP) will be developed for analyses of data collected during both the initial 24-week treatment phase and the long-term extension to this study, in order to provide details of the data analysis procedures and presentations as patient data are emerging with progression of the dose optimization process.

9.2 Determination of Sample Size

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

9.3 (Data) Analysis Sets

9.3.1 Full Analysis Set

The full analysis set will include all patients who receive at least one dose of ACH-0144471, and will be used for the efficacy / PD, PK, and safety analysis.

9.3.2 Optimal Dose Analysis Set

The optimal dose analysis set includes data from patients receiving the identified optimal dose of ACH-0144471 in combination with eculizumab, starting on Day 1 of treatment (the Optimal Dose Group). Other analysis sets may be developed if clinically deemed meaningful with emerging patient data.

9.4 Demographics and Baseline Characteristics

Demographic parameters (age, gender, race, weight, BMI) and baseline PNH disease characteristics, including RBC transfusion history, will be summarized for the full analysis set and the optimal dose analysis set to provide an overall description of the study population.

9.5 Efficacy Analysis

The primary efficacy endpoint is:

- For the Optimal Dose Group: median Hgb during the 24-week treatment phase compared to the baseline (Day 1) Hgb
- For the groups treated at doses lower than the optimal dose level: median Hgb over the time period that the patient received the highest dose level during the 24-week treatment phase compared to baseline (Day 1) Hgb

Summary statistics will be provided for the Optimal Dose Group for the primary efficacy endpoint of change in median Hgb over the 24-week treatment phase. The ninety-five percent (95%) confidence interval for mean of median changes from baseline will be computed. Other statistical analysis procedures may be applied if clinically deemed meaningful.

The secondary efficacy endpoints are:

- Number of units of RBCs transfused during 24 weeks of treatment
- RBC transfusion status: number and percent of patients without RBC transfusions during 24 weeks of treatment
- Change from baseline in LDH during 24 weeks of treatment

Similar to the primary efficacy endpoint, summary presentations will be provided for the Optimal Dose Group only.

Summary statistics for continuous variables will be provided for the secondary efficacy endpoints, RBC transfusion units received during 24 weeks of dosing, and LDH change from baseline at protocol-specified time points. Red blood cell transfusion status during the 24-week treatment phase will be summarized using frequency count and percentage.

In addition, comparison in RBC transfusion units '24 weeks after' and '24 weeks before' the initiation of ACH-0144471 will be provided and summarized. The time period '24 weeks after' is defined as the period of time inclusive of Day 1 through Week 24 of the treatment phase.

Hemoglobin levels and changes from baseline Hgb level over the 24-week treatment phase will be plotted for each patient. Mean (or median) Hgb level and mean (or median) change from baseline over time will also be plotted.

Details on analysis and presentations of efficacy endpoints will be described in the SAP.

9.6 Safety Analysis

The safety of ACH-0144471 in combination with eculizumab during the 24-week treatment phase will be assessed by measuring the frequency of SAEs, all AEs (and grades) regardless of relationship with study drugs, discontinuations due to AEs, and Grade 3 and 4 laboratory abnormalities. Summary tables will be provided for both the Optimal Dose Group and other groups of patients

started at other ACH-0144471 levels. Note that 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 for the Optimal Dose Group. Data on vital signs and ECGs will be examined either through patient listings or by summary statistics of selected parameters for the Optimal Dose Group.

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

Details on analysis and presentations of safety parameters will be described in the SAP.

9.7 Pharmacokinetic (PK) Analysis

Pharmacokinetic analysis will be done using a validated computer program for the full analysis set. The PK characteristics of ACH-0144471 from patients, including, but not limited to, the standard PK parameters outlined in Table 6 below, will be derived from the individual plasma concentration time data at Week 12 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.

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

Table 6. PK Analysis Parameters

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

9.8 Patient-Reported Outcome Measures Assessments

9.8.1 Quality of Life Questionnaires

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 patient fatigue conditions.

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

9.8.2 Patient Reported Outcomes (PRO) Interviews

De-identified transcripts of the patients' interviews will be analyzed using a thematic analysis based on the grounded theory. 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. A validated software package 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 will be recorded.

10.2 Institutional Review Board or Independent Ethics Committee and Regulatory Approval

10.2.1 Ethics 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 will 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 will 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 will comply with the applicable regulatory requirements and will 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 into the ICF and approved by the EC, all patients still actively participating in the study must be re-consented.

Written informed consent will 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 will supply all enrolled patients with a copy of their signed informed consent form. 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 will 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 will be completed by the investigator (or designee), who will 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 will 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, will be recorded in the patient's medical/study records by the investigator (or designee). The investigator (or designee) will 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 will 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 will 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 will 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 will 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.

11 References

1. Merle NS, Noe R, Halbwachs-Mecarelli L, et al. Complement System Part II: Role in Immunity. Front Immunol. 2015;6:257.

2. Volanakis JE, Narayana SV. Complement factor D, a novel serine protease. Protein Science. 1996;5(4):553-64.

3. Apelian D. ACH-0144471 Investigator's Brochure Version 4.0. New Haven (CT): Achillion Pharmaceuticals, Inc.; 2016. 57 p.

4. Figueroa JE, Densen P. Infectious diseases associated with complement deficiencies. Clinical microbiology reviews. 1991;4(3):359-95.

5. Miyata T, Inagi R, Oda O, et al. Deterioration of immune complex solubilization activity of serum by increased concentration of factor D. Nephron. 1991;59(3):409-15.

6. Kobayakawa H, Miyata T, Inagi R, et al. Effects of excess factor D on early- and late-phase activation of the complement cascade. Nihon Jinzo Gakkai Shi. 1992;34(1):103-6.

7. Späth-Schwalbe E, Schrezenmeier H, Heimpel SH. [Paroxysmal nocturnal hemoglobinuria. Clinical experiences with 40 patients at one center over 25 years]. Dtsch Med Wochenschr 120:1027-1033, 1995. PMID: 7628314.

8. Pramoonjago P, Pakdeesuwan K, Siripanyaphinyo U, Chinprasertsuk S, Kinoshita T, Wanachiwanawin W. Genotypic, immunophenotypic and clinical features of Thai patients with paroxysmal nocturnal haemoglobinuria. Br J Haematol. 1999 May;105(2):497-504.

9. Schubert J, Roth A. Update on paroxysmal nocturnal haemoglobinuria: on the long way to understand the principles of the disease. Eur J Haematol. 2015;94(6):464-73.

10. Hill A, Rother RP, Arnold L, et al. Eculizumab prevents intravascular hemolysis in patients with paroxysmal nocturnal hemoglobinuria and unmasks low-level extravascular hemolysis occurring through C3 opsonization. Haematologica. 2010;95(4):567-73.

11. Rondelli T, Risitano AM, Peffault de Latour R, et al. Polymorphism of the complement receptor 1 gene correlates with the hematologic response to eculizumab in patients with paroxysmal nocturnal hemoglobinuria. Haematologica. 2014;99(2):262-6.

12. Nishimura J, Yamamoto M, Hayashi S, et al. Genetic variants in C5 and poor response to eculizumab. The New England Journal of Medicine. 2014;370(7):632-9.

13. Hiemstra PS, Langeler E, Compier B, Keepers Y, Leijh PC, van den Barselaar MT, Overbosch D, Daha MR. Complete and partial deficiencies of complement factor D in a Dutch family. J Clin Invest. 1989 Dec;84(6):1957-61.

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14. Biesma DH, Hannema AJ, van Velzen-Blad H, Mulder L, van Zwieten R, Kluijt I, Roos D. A family with complement factor D deficiency. J Clin Invest. 2001 Jul;108(2):233-40.

15. Sprong T, Roos D, Weemaes C, Neeleman C, Geesing CL, Mollnes TE, van Deuren M. Deficient alternative complement pathway activation due to factor D deficiency by 2 novel mutations in the complement factor D gene in a family with meningococcal infections. Blood. 2006 Jun 15;107(12):4865-70.

16. Risitano AM, Notaro R, Marando L, Serio B, Ranaldi D, Seneca E, Ricci P, Alfinito F, Camera A, Gianfaldoni G, Amendola A, Boschetti C, Di Bona E, Fratellanza G, Barbano F, Rodeghiero F, Zanella A, Iori AP, Selleri C, Luzzatto L, Rotoli B. Complement fraction 3 binding on erythrocytes as additional mechanism of disease in paroxysmal nocturnal hemoglobinuria patients treated by eculizumab. Blood. 2009 Apr 23;113(17):4094-100. doi: 10.1182/blood-2008-11-189944. Epub 2009 Jan 29.

17. Yuan X, Gavriilaki E, Thanassi JA, Yang G, Baines AC, Podos SD, Huang Y, Huang M, Brodsky RA. Small-molecule factor D inhibitors selectively block the alternative pathway of complement in paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. Haematologica. 2017 Mar;102(3):466-75. doi: 10.3324/haematol.2016.153312. Epub 2016 Nov 3.

18. Harder MJ, Kuhn N, Schrezenmeier H, Höchsmann B, von Zabern I, Weinstock C, Simmet T, Ricklin D, Lambris JD, Skerra A, Anliker M, Schmidt CQ. Incomplete inhibition by eculizumab: mechanistic evidence for residual C5 activity during strong complement activation. Blood. 2017 Feb 23;129(8):970-80. doi: 10.1182/blood-2016-08-732800. Epub 2016 Dec 27.

19. Siler S, Howell B. DILIsym Services Final Report "Assessment of Clinical Biomarkers and Prediction of Hepatocyte Loss for ACH4471 Clinical Trials." Research Triangle Park, NC, USA. January 12, 2017.

20. Yang, K, Siler S, Howell B, DILIsym Services Final Report "Prediction of Hepatotoxicity Risk for ACH4471 Based on Mechanistic Modeling with DILIsym®" Research Triangle Park, NC, USA April 14, 2017.

21. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. [CTCAE 4.03 June 2010]. Downloaded from https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf 01 April 2017.

12 Appendices

Appendix 1. Schedule of Assessments

Table 7. Screening Through Week 13 Visits

Test	Screening			ACH-0144471 + Eculizumab Visit									
	Day -60 to -1	Day -42	Day -14	Day 1 (B/L)	Wk 1 (Day 7)	Wk 2	Wk 3	Wk 4[1]	Wk 6	Wk 8[1]	Wk 10	Wk 12[1]	Post-Escalation
Clinic Visit Days	X	X[2]	X[2]	X	X	X		X		X		X	
Local Laboratory Visit							X[3]		X[3]		X[3]		X[4]
Screening Procedures													
Informed Consent	X												
Inclusion/Exclusion Criteria	X												
Medical History	X			X									
Demographics	X												
Vaccination History	X												
FSH[5]	X												
Urine Drug Screen[6]	X												
HCV Ab, HbsAg, HIV Ab	X												
CR1 Polymorphism Test	X												
Erythropoietin	X												
Height, BMI	X												
Sample for other genetic testing (white blood cells)	X												
Vaccinations		X[2]	X[2]	X[7,8]									
Vaccination Boosters[8]	See Section 6.3												
Patient Reported Outcomes Interviews[9]	X							X		X		X	
Dosing and Drug Distribution													
Eculizumab Dosing[10]				X	Administered according to the patient's usual dose and schedule								
ACH-0144471 Dosing[10]				X	X	X	X	X	X	X	X	X	
ACH-0144471 Dispensing[11]				X	X	X		X		X		X	
Clinical Assessments													
Physical Exam[12]	X			X	X	X		X		X		X	
Vital Signs	X			X	X	X		X		X		X	

Test	Screening			ACH-0144471 + Eculizumab									
				Visit									
	Day -60 to -1	**Day -42**	**Day -14**	**Day 1 (B/L)**	**Wk 1 (Day 7)**	**Wk 2**	**Wk 3**	**Wk 4[1]**	**Wk 6**	**Wk 8[1]**	**Wk 10**	**Wk 12[1]**	**Post-Escalation**
Body Temperature[13]	X			X	X	X		X		X		X	
Weight	X			X				X		X		X	
12-lead ECG (single)	X					X		X		X		X[14]	
QoL Questionnaires	X							X				X	
RBC Transfusion Review	X	X[2]	X[2]	X	X	X		X		X		X	
AE/SAE		X[2]	X[2]	X	X	X	X	X	X	X	X	X	
Concomitant Medications/Protocol Restrictions	X	X[2]	X[2]	X	X	X	X	X	X	X	X	X	
Laboratory Assessments[15]													
Hematology, Chemistry, and Urinalysis[16]	X			X	X	X	X	X	X	X	X	X	X[4]
Pregnancy Test[17]	X	X[8]	X[8]	X[8]				X		X		X	
PT/PTT/INR, D-Dimer[18]	X			X		X		X		X		X	
Free Hemoglobin, haptoglobin	X			X	X	X	X	X	X	X	X	X	
Direct Coombs	X			X				X				X	
PK Samples[19]				X	X	X		X		X		X[14]	
AP Wieslab, Bb, fD, C3, CH50, AP hemolysis	X			X	X	X		X		X		X[14]	
Flow cytometry: Clone Size	X			X		X		X		X		X	
Flow cytometry: C3 fragment deposition				X		X		X		X		X	
Plasma/Serum samples for additional non-genetic biomarker testing (fB, Ba, C5a, and soluble C5b-9)				X		X		X		X		X[14]	
Sample for potential assessment of patient response to vaccines[20]	X			X								X	

[1] Weeks 4, 8, and 12 are dose escalation timepoints. See Section 3.2.3 for dose escalation information

[2] Only for patients who need to receive vaccinations during the screening period (see Section 6.3 for guidance)

Test	Screening			ACH-0144471 + Eculizumab									
				Visit									
	Day -60 to -1	Day -42	Day -14	Day 1 (B/L)	Wk 1 (Day 7)	Wk 2	Wk 3	Wk 4[1]	Wk 6	Wk 8[1]	Wk 10	Wk 12[1]	Post-Escalation

[3] At Weeks 3, 6, and 10, hematology, chemistry, and urinalysis, as described in Section 6.9 will be collected at the local laboratory. Site will call patient within 1 day to confirm that local laboratory visit occurred. Site will also assess AEs, SAEs, and concomitant medications.

[4] If a dose escalation occurs, measurement of LDH, Hgb, and liver function tests (ALT, AST, GGT, ALP), should be drawn locally or at the clinic 72-96 hours after escalation

[5] FSH for postmenopausal women at screening only.

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

[7] If local practice dictates, vaccinations for N. meningitidis, S. pneumoniae and H. influenzae may all be administered on Day 1 of the treatment period. (see Section 6.3 for guidance)

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

[9] Interview could be scheduled ± 1 week

[10] Refer to section 5.3 for dosing of ACH-0144471 and eculizumab

[11] Patients will be provided with sufficient study drug to last until their next appointment. Treatment compliance assessments will be performed at each visit. Depending on when subjects are dose escalated (see Section 3.1), patients may need to return to the clinic in between visits to be dispensed ACH-0144471 and new dosing instructions.

[12] Full physical exam at Screening and Day 1. Brief physical exam at all other timepoints.

[13] Patients will be monitored for fever at every clinic visit and will monitor themselves in between visits. See Appendix 4 for instructions on fever management.

[14] For PK, PD, and ECG schedule at this visit, refer to Table 9

[15] Blood and urine samples will be collected prior to dosing

[16] Hematology, chemistry, and urinalysis, as described in Section 6.9

[17] Serum pregnancy test at screening. Urine pregnancy test at baseline and every 4 weeks for the duration of the study including follow-up 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 follow-up serum pregnancy test.

[18] D-Dimer only assessed at Screening, Week 4, and Week 12.

[19] Except at Week 12, PK trough samples only; collected prior to first daily dose

[20] Samples for vaccine response will be required only if vaccination(s) were administered during the Screening period. If required, a sample will be collected during screening, pre-dose and 2 hours after dosing ACH-0144471 on Day 1 and Week 12. A pre-dose sample should also be collected at the next scheduled clinic visit after any dose escalation beyond Week 12.

Table 8. Week 14 through Follow-up Visits and Long-Term Extension

Test	ACH-0144471 + Eculizumab									Follow-up[7]	
	Wk 16	Wk 20	Wk 24 or ET[1]	Post-Escalation[2]	Long-term Extension[3]		Un-scheduled[6]	Taper[7]			
					Local Laboratory Visit[4]	Clinic Visit[5]		T1[8]	T2[8]	F/U1[9]	F/U2[9]
Clinic Visits	X	X	X			X	X	X	X	X	X
Patient Reported Outcomes Interviews			X[10]			X[11]					
Dosing and Drug Distribution											
Eculizumab Dosing[12]	Administered according to the patient's usual dose and schedule										
ACH-0144471 Dosing[13]	X	X	X			X		X	X		
ACH-0144471 Dispensing[13]	X	X	X			X		X			
Clinical Assessments											
Vaccination Boosters[15]	See Section 6.3										
Physical Exam[16]	X	X	X			X	X			X	X
Vital Signs	X	X	X			X	X	X	X	X	X
Body Temperature[17]	X	X	X			X	X	X	X	X	X
Weight			X			X					X
12-lead ECG (single)		X	X			X[18]	X				X
QoL Questionnaires			X			X[11]					
RBC Transfusion Review	X	X	X			X	X	X	X	X	X
AE/SAE	X										
Concomitant Medications/ Protocol Restrictions	X										
Laboratory Assessments[19]											
Hematology, Chemistry, and Urinalysis[20]	X	X	X	X		X	X	X	X	X	X
Pregnancy Test[21]	X	X	X		X	X					X
PT/PTT/INR, D-Dimer[22]	X	X	X								X
Free Hemoglobin, haptoglobin	X	X	X			X	X			X	X
Local Lab tests: Hgb, free Hgb, and LDH					X						
Direct Coombs		X	X			X				X	X
PK Samples (Trough)	X	X	X			X	X	X	X		X

Test	ACH-0144471 + Eculizumab									Follow-up[7]	
	Wk 16	Wk 20	Wk 24 or ET[1]	Post-Escalation[2]	Long-term Extension[3]		Un-scheduled[6]	Taper[7]			
					Local Laboratory Visit[4]	Clinic Visit[5]		T1[8]	T2[8]	F/U1[9]	F/U2[9]
AP Wieslab, Bb, CH50, AP hemolysis assay	X	X	X			X	X	X	X	X	X
fD, C3		X	X			X	X			X	X
Flow cytometry: Clone Size, C3 fragment deposition		X	X			X	X			X	X
Plasma/Serum samples for additional non-genetic biomarker testing (fB, Ba, C5a, and soluble C5b-9)		X	X			X	X			X	X
Sample for potential assessment of patient response to vaccines						X[23]					

1 At the Week 24 visit, patients will be evaluated for continuation of treatment with ACH-0144471 plus eculizumab as described in Section 3.1

2 For any patients who have a dose escalation beyond Week 12 (See section 3.2.3), measurement of LDH, Hgb, and liver function tests (ALT, AST, GGT, ALP), should be drawn locally or at the clinic 72-96 hours after escalation

3 If a patient discontinues from ACH-0144471 during the long-term treatment phase, the taper and follow-up procedures will be performed.

4 Patients who enter the long-term extension will have local laboratory visits every 8 weeks, starting at Week 28. These visits should occur within a window of ±7 days relative to the specified day.

5 Patients who enter the long-term extension will return to the clinic every 8 weeks, starting at Week 32. Clinic visits during the long-term extension may take place within a window of ±3 days relative to the specified day for the first 24 weeks, and then within a window of ±7 days relative to the specified day for the duration of the study (see Section 7.4).

6 See Section 7.2.4

7 For patients who discontinue from the study.

8 T1 = Day 3 of the taper; T2 = Day 6 of the taper

9 F/U 1 = follow-up visit 1 will be 14 days after the last dose of study drug (including taper) F/U 2 = follow-up visit will be 28 days after the last dose of study drug (including taper).

10 Interview could be scheduled ± 1 week

11 QoL questionnaires and Patient Reported Outcomes Interview will be administered at Week 48 ± 1 week. After Week 48, QoL questionnaires will be administered approximately every 6 months for the duration of the study.

12 Eculizumab will be administered following the usually prescribed procedures for the patient.

13 Patients will take ACH-0144471 as described in Section 3.2.3.

Test	ACH-0144471 + Eculizumab									Follow-up[7]	
	Wk 16	Wk 20	Wk 24 or ET[1]	Post-Escalation[2]	Long-term Extension[3]		Un-scheduled[6]	Taper[7]			
					Local Laboratory Visit[4]	Clinic Visit[5]		T1[8]	T2[8]	F/U1[9]	F/U2[9]

[14] Patients will be provided with sufficient study drug to last until their next visit. Patients will be instructed on how to take their medication at home (see Section 5.3.1.2). Treatment compliance assessments will be performed at each visit.

[15] Female patients of childbearing potential receiving vaccination boosters (see Section 6.3) must have a negative urine pregnancy test on the days of vaccination, before any vaccine or booster is administered.

[16] Full physical exam at Week 24. Brief physical exam at all other timepoints.

[17] Patients will be monitored for fever at every clinic visit and will monitor themselves in between visits. See Appendix 4 for instructions on fever management.

[18] Every other visit (Weeks 32, 48, 64 etc.)

[19] Blood and urine samples will be collected prior to dosing

[20] Hematology, chemistry, and urinalysis, as described in Section 6.9

[21] For women of childbearing potential, urine pregnancy tests will be performed every 4 weeks. Any positive urine pregnancy test will be confirmed by a follow-up serum pregnancy test.

[22] PTT/PT/INR assessed at Weeks 16, 20, 24 and Follow-Up visit 2. D-Dimer to be assessed at Weeks 16, 20, 24, and every 8 weeks during the long-term extension.

[23] A sample will be collected prior to administration of a booster and at the next clinic visit. A sample should also be collected at the next scheduled clinic visit after any dose escalation beyond Week 12.

Table 9. PK and PD Sampling and ECG Collection at Week 12 Visit*

Test	Time After Dosing (hr)								
	0[a]	**1**	**1.5**	**2**	**2.5**	**3**	**4**	**6**	**8**
PK plasma samples	X	X	X	X	X	X	X	X	X
AP Wieslab, AP hemolysis, Bb	X			X			X	X	X
fD, C3, CH50	X								
Plasma/Serum samples for additional non-genetic biomarker testing (fB, Ba, C5a, and soluble C5b-9)	X			X			X	X	X
Samples for potential assessment of patient response to vaccines	X			X					
Triplicate 12-lead ECGs	X[b]					X[b]			

*In the event a patient is further dose escalated after Week 12, the additional PK, PD, and ECG assessments described above should be repeated accordingly

[a] Prior to dosing

[b] Tracings should be separated by approximately 1 minute

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 past 7 days.**

		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 starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing 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

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 patients for signs and symptoms of infection.

Minimum Requirements

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

A. General Management for Outpatients

All patients in this study will:

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

2. Be educated and counseled by site staff regarding high risk behaviors, which include drinking from the same beverage containers, sharing eating utensils with others, avoiding large crowds, and smoking (including second-hand exposure)

3. Be provided a thermometer and taught how to use it. All patients need to take these thermometers with them at all times. They need to be able to take their temperature if feeling warm or unwell

4. Be instructed to contact the investigator immediately and/or seek emergency medical attention for any temperature >38.0°C /100.4°F

5. They will be advised not to wait for site staff to return their phone call before seeking emergency medical attention. They should go to the nearest emergency medical facility for evaluation.

6. Be taught to be alert to the signs of possible serious infections, which are often flu-like symptoms

7. At all times, have immediate access to transportation and telephone, and be within one hour of an emergency medical center

8. Be provided with a study contact card and instructed to carry this with them at all times. The study contact card should be provided to the emergency medical personnel who should be asked to contact the study site

B. General Management for Any Fever Detected in the Clinic

For Any Fever, the site needs to:

1. Assess for symptoms - Consider meningococcal disease as a diagnosis. When meningococcal disease is suspected, early treatment is critical
2. Repeat and confirm all temperature measurements >38.0°C
3. Notify the PI and Sponsor for all confirmed temperature measurements >38.0°C
4. Consider if referring to an emergency medical facility is appropriate. If so, refer. Otherwise:
    a. PI or designee to perform a complete physical examination (including assessing if fever is accompanied by a severe headache, stiff neck, or other signs of meningeal irritation, shortness of breath, skin rashes, or other unusual signs or symptoms), document a plan based on her/his clinical judgment, and possibly an ID consult depending on assessment
    b. CBC (if not done in the last 12 hours) and blood culture
    c. Treat any suspicion of meningococcal infection aggressively; consider initiation of empirical antimicrobial therapy (assuming there are no other obvious sources of fever) at least until culture results become available and/or an alternative etiology is found
    d. Infectious disease consult is required once the PI or designee initiates empiric antibiotic treatment
    e. Measure temperature hourly until <38.0°C
    f. All cases of fever will be assessed by the Investigator, regardless of apparent causality from use of the study treatment(s)
    g. All activities performed as part of the Fever Management Plan will 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.