Clinical Trial Protocol

ACH471-103

Study Title	An Open-label Study to Evaluate Efficacy and Safety of Long-term Treatment with ACH-0144471 in Patients with PNH who Completed Clinical Study ACH471-100
Study Number	ACH471-103
Study Phase	2
Product Name	ACH-0144471 Tablets (also known as danicopan and ALXN2040)
EudraCT Number	2017-000665-79
Universal Trial Number (UTN)	U1111-1196-0653
Indication	Paroxysmal Nocturnal Hemoglobinuria (PNH)
Investigators	Multi-center
Sponsor	Achillion Pharmaceuticals, Inc., a wholly owned subsidiary of Alexion Pharmaceuticals Inc.
Sponsor Contact	PPD PPD PPD Alexion Pharmaceuticals, Inc. 121 Seaport Blvd Boston, MA 02210 USA Phone: PPD Email: PPD

	Date
Original Protocol	05 April 2017 (Version 1.0)
Amendment 1	31 May 2017 (Version 2.0)
Amendment 2	09 October 2017 (Version 3.0; Italy only)
Amendment 3	22 December 2017 (Version 4.0)
Amendment 4	13 March 2018 (Version 5.0)
Amendment 5	04 June 2021 (Version 6.0)

Confidentiality Statement

Sponsor Signature

Study Title	An Open-label Study to Evaluate Efficacy and Safety of Long-term Treatment with ACH-0144471 in Patients with PNH who Completed Clinical Study ACH471-100
Study Number	ACH471-103
Protocol Version and Date	Protocol ACH471-103, Amendment 5 04 June 2021, Version 6

This clinical study protocol has been approved by the Sponsor.

PPD , PPD
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121 Seaport Blvd
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15 - June - 2021
Date

Investigator's Signature

Study Title	An Open-label Study to Evaluate Efficacy and Safety of Long-term Treatment with ACH-0144471 in Patients with PNH who Completed Clinical Study ACH471-100
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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

Rationale for Amendment

Amendment 5 (04 June 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union (EU) because it significantly impacts the safety or physical/mental integrity of participants and the scientific value of the study.

Overall Rationale for the Amendment: Global Amendment 4 (dated 13 March 2018) was amended to update the following:

- Change in Sponsor name and study contacts.
- Dosing taper schedule updated to remove the 75 mg dose as the 75 mg tablets used in this study will expire and are no longer being manufactured.
- Instructions for dose tapering during the Taper Period has been updated.
- Patient Reported Outcomes (PRO) interviews were discontinued effective 30 April 2019.
- PK/PD samples are no longer required at the long-term extension clinic visits, the taper visits, or follow-up visits.
- Clarification regarding study requirements for patients enrolled in Study ACH471-103 who will enroll into Study ACH228-110 added.
- Option for patients to enter into another appropriate Alexion clinical study, if available, has been added.
- To ensure patient safety and treatment continuity during the coronavirus disease 2019 (COVID-19) outbreak:
    - Physical visits may become telephone or videoconference visits
    - Safety laboratory tests may be done using home healthcare laboratory sampling, local laboratories, or other appropriate clinical facilities
- The instructions for reporting serious adverse events and any pregnancies were updated due to a transition in the safety reporting process.
- Language regarding COVID-19 risk assessment has been added as per the Medicines and Healthcare products Regulatory Agency (MHRA) requirements.

Synopsis

Sponsor	Achillion Pharmaceuticals, Inc., a wholly owned subsidiary of Alexion Pharmaceuticals Inc. 1777 Sentry Parkway West, Building 14, Suite 200 Blue Bell, PA 19422 USA
Name of Finished Product	ACH-0144471 Tablet, 50, 75, and 100 mg
Name of Active Ingredient	ACH-0144471
Name of Inactive Ingredient	ACH-0144471 Tablet: Lactose, Microcrystalline Cellulose, Croscarmellose Sodium, Sodium Lauryl Sulphate, Magnesium Stearate, Colloidal Silicon Dioxide, and Hypromellose Acetate Succinate. The coating components are polyvinyl alcohol, titanium dioxide, macrogol/polyethylene glycol, and talc
Study Title	An Open-Label Study to Evaluate Efficacy and Safety of Long-term Treatment with ACH-0144471 in Patients with PNH who Completed Clinical Study ACH471-100
Study Number	ACH471-103
Study Phase	Phase 2
Primary Objective	To evaluate the safety and efficacy of long-term therapy with ACH-0144471 in patients with PNH
Secondary Objective	To evaluate health-related quality of life measures in patients with PNH based on patient reported outcome instruments and its evolution over the course of long-term therapy with ACH-0144471
Exploratory Objectives	N/A
Study Design	This is an open-label extension study designed to evaluate long-term safety and efficacy of ACH-0144471 in patients with PNH who have demonstrated clinical benefit from ACH-0144471 in study ACH471-100. Clinical benefit will be assessed by the investigator, based on an improvement in hemoglobin and/or LDH. The PI may escalate or reduce dosing to manage clinical benefit or for safety or tolerability reasons, as described in Section 3.2.2. Patients will be allowed to continue therapy until 1) ACH-0144471 is commercially available in their country; 2) the development of ACH-0144471 as a potential therapy for PNH is terminated; 3) the therapy is no longer tolerated or effective; or 4) another appropriate Alexion clinical study is available or in the opinion of the PI, another treatment option is available. 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. Considering PNH is a serious life-threatening disease, a long-term extension study, beyond the dosing included in this study, may be offered to patients, if supported by clinical and nonclinical data. Pending regulatory and ethics committee approval of such a study, patients who, in the opinion of the Principal Investigator (PI), are receiving benefit from ACH-0144471 may be enrolled directly into that study without interruption from this study, and will continue to receive daily treatment with ACH-0144471 and safety and efficacy monitoring. Any patients so enrolled will not require a dosing taper or the follow-up visits described in this protocol.
Treatment Groups	A single treatment group is planned

Study Population	The study population will include patients with PNH who are not currently receiving eculizumab and have completed Achillion Study ACH471-100 must have demonstrated a clinical benefit, as assessed by the PI.
Number of Patients	It is anticipated that no more than 12 patients will be entered into this study.
Inclusion Criteria	1. Patients must have completed treatment in study ACH471-100 and must have demonstrated a clinical benefit from ACH-0144471, in the opinion of the PI, with no significant safety or tolerability concerns. 2. Female participants of childbearing potential must agree to use an acceptable method of contraception (as defined in Section 5.5.4) from the date of signing the informed consent to the first day of dosing (Day 1), and must agree to use a highly effective method of contraception (as defined in Section 5.5.4) from the first day of dosing to 30 days after their last dose of study drug. Female participants of childbearing potential must also have a negative serum pregnancy test during Screening and negative urine pregnancy test on Day 1. Female participants of non-childbearing potential need not employ a method of contraception. 3. Non-sterile male participants must agree to use a highly effective method of contraception (as defined in Section 5.5.4) with their partner(s) of childbearing potential from the first day of dosing to 90 days after their last dose of study drug. 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. 4. Must agree to provide written informed consent. 5. Must be willing, at all times, to have transportation and telephone access, and to be within one hour of an emergency medical center
Exclusion Criteria	1. Have developed any clinically relevant co-morbidities while participating in ACH471-100 that would make the patient inappropriate for continuation of treatment with ACH-0144471, in the opinion of the investigator. 2. Have developed a clinically significant laboratory abnormality while participating in ACH471-100 that, in the opinion of the investigator, would make the patient inappropriate for the study or put the patient at undue risk. 3. Females who are pregnant, nursing, or planning to become pregnant during the study or within 90 days of study drug administration or patients with a female partner who is pregnant, nursing, or planning to become pregnant during the study or within 90 days of study drug administration

Individual Stopping Criteria	Any individual patient who meets any of the following criteria will be discontinued from further dosing: • The patient experiences any SAE assessed as related to treatment with ACH-0144471 (exceptions may be considered at the request of the investigator if the event can be managed by dose reduction or interruption) • The PI believes that patient continuation in the study is not advisable, or the patient withdraws from the study or meets one of the conditions described in Section 6.18 Discontinuation of treatment should also be considered if: • ALT or AST* >8× ULN • ALT or AST* >5× ULN for more than 2 weeks • ALT or AST* >3× ULN and clinically significant elevation in Total Bilirubin* relative to baseline * Because patients may have ongoing hemolysis which may result in increased bilirubin and AST, increases in bilirubin and/or AST during the study must be evaluated in the context of any continuing hemolysis. The PI should evaluate LDH and Hgb levels as well as baseline bilirubin and AST levels to determine if the increases observed are due to an effect on liver function or are secondary to hemolysis.
Test Product; Dosage Form; and Strength	ACH-0144471 will be supplied as 50, 75, and 100 mg tablets
Mode of Administration	Oral
Duration of Treatment, Confinement, and Total Study Participation	Patients may remain in the 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; 3) the therapy is no longer tolerated or effective; or 4) another appropriate Alexion clinical study is available or in the opinion of the PI, another treatment option is available.
Safety Assessments	Safety will be evaluated by monitoring and assessment of AEs, clinical laboratory tests, physical examination findings, 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 entering study ACH471-100 will have been vaccinated for *Neisseria meningitidis (N. meningitidis)*, *Streptococcus pneumoniae* (*S. pneumonia*e), and *Haemophilus influenzae* (*H. influenzae*). Patients continuing on in this study will receive boosters as described in Section 6.2.
Pharmacokinetic Assessments	Samples will be collected at each clinic visit for measurement of ACH-0144471 trough concentrations. Samples for PK assessments are no longer required upon implementation of Protocol Amendment 5.0.
Pharmacodynamic and Efficacy Assessments	Efficacy will be evaluated by measuring LDH levels, Hgb levels, and reticulocyte counts at various time points during the study. The number and frequency of red blood cell transfusions will also be examined. Samples for AP Weislab, fD, flow cytometry: clone size, and complement-associated biomarkers are no longer required in the extension phase upon implementation of Protocol Amendment 5.0.

Patient-reported Outcomes Assessments	Quality of Life (QoL) assessments will be conducted at various time points as specified in schedule of assessment in Appendix 1 using the tools in Appendix 2. The FACIT Fatigue scale (Version 4) questionnaire and the EORTC-QLQ-C30 scale will be administered to patients to collect patients' health-related QoL at various time points during long-term treatment with ACH-0144471. In addition, interviews by independent outcomes researchers chosen by the Sponsor were conducted. Patients were interviewed after approximately 3 and 9 months of treatment in this study (i.e., after approximately 6 and 12 months of treatment with ACH-0144471, including approximately 3 months of treatment during ACH471-100) to collect patients' experience of ACH-0144471 treatment and their perception of the evolution of their condition. The interviews were conducted over the phone by a trained, experienced interviewer and lasted approximately 30 minutes. These interviews were discontinued effective 30 April 2019.
Statistical Methods	Descriptive statistical methods will be used to evaluate the efficacy and safety of long-term therapy of ACH-0144471.

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse event
ACIP	Advisory Committee on Immunization Practices
ALT	Alanine aminotransferase
AP	Alternative Pathway (of complement)
AST	Aspartate aminotransferase
BA	Bioavailability
BP	Blood pressure
BMI	Body mass index
°C	Degrees Celsius
C3	C3 complement protein
C5	C5 complement protein
COVID-19	Coronavirus Disease 2019
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
fB	(Complement) Factor B
fD	(Complement) Factor D
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GPI	Glycosylphosphatidylinositol
Hct	Hematocrit
Hgb	Hemoglobin
HIPAA	Insurance Portability and Accountability Act of 1996
HR	Heart rate
HSCT	Hematopoietic stem cell transplantation
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional review board
kDa	Kilodalton
LDH	Lactate dehydrogenase
LFC	Liquid-filled capsule
LLN	Lower limit of normal
MAC	Membrane attack complex
MAD	Multiple ascending dose
MDRD	Modification of Diet in Renal Disease equation
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
PD	Pharmacodynamic(s)
PI	Principal investigator
PIGA	Phosphatidylinositol N-acetylglucosaminyltransferase subunit A
PK	Pharmacokinetic(s)
PNH	Paroxysmal Nocturnal Hemoglobinuria
PR interval	Period that extends from the beginning of the P wave until the beginning of the QRS complex
PRO	Patient Reported Outcomes
QoL	Quality of Life
QRS	Group of electrocardiogram waves comprising the Q, R, and S waves

Abbreviation	Definition
QT	QT interval
QTcF	QT interval Fridericia Correction Formula
RBC	Red blood cells
Rel BA	Relative bioavailability study
RR	Respiration rate
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WBC	White blood cells

1 Introduction

This protocol is an extension study to evaluate long-term safety and efficacy of ACH-0144471 in patients with PNH who have completed clinical study ACH471-100, did not experience any ACH-0144471-related SAEs, and demonstrated clinical benefit.

1.1 Results of Nonclinical Studies

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

1.2 Previous Human Experience with ACH-0144471

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

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

The MAD study was conducted to evaluate the safety and tolerability of multiple ascending doses of ACH-0144471 and to determine a recommended dose and schedule for treatment of patients with PNH in phase 2 studies. Healthy volunteers were dosed with ACH-0144471 in four separate groups. Groups 1 through 3 received multiple daily doses of 200, 500, and 800 mg, respectively, twice daily for 14 days. Group 4 received doses of 75 mg every 8 hours for 7 days. All doses were given in the fasted state. ACH-0144471 administered as 200 mg every 12 hours for 14 days was well-tolerated. The higher doses studied (500 and 800 mg administered every 12 hours for 14 days) were associated with elevations in alanine aminotransferase (ALT) levels in some patients. In Group 4, a dosing regimen of 75 mg administered every 8 hours for 7 days was well-tolerated and resulted in ACH-0144471 trough concentrations that have the potential for efficacy in PNH and other complement-mediated diseases.

The pharmacodynamics and potential for clinical efficacy for ACH-0144471 is primarily associated with maintenance of exposure above a target trough level. Exploratory ex vivo AP hemolysis experiments using patient PNH cells showed that ACH-0144471 at concentrations of >20 ng/mL provided protection from hemolysis similar to eculizumab at a concentration of 35 μg/mL (an efficacious eculizumab trough concentration in PNH patients) [2]. Pharmacokinetic (PK) modeling based on data from the SAD and MAD studies predicts that plasma trough ACH-0144471 concentrations can be increased substantially with minimal increase C_{max} or AUC, and that ACH-0144471 trough concentrations of >30 and

>60 ng/mL can be achieved with doses of 100 and 150 mg 3 times daily (TID), respectively. Based on these analyses, 100 mg TID was expected to be pharmacologically active, and was selected as the starting dose for ACH471-100. The starting dose was increased to 150 mg TID as emerging data from the first 2 patients enrolled suggested that a higher dose was needed to provide clinical efficacy. All patients enrolled in ACH471-100 to date have dose escalated to 200 mg TID with no clinically significant alterations in liver enzymes.

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

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 [3, 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 [3, 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 alternative pathway 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 found among adults, with a median age at diagnosis of approximately 40 years. Men and women are affected equally, and no familial tendencies exist. It has been suggested

that PNH, like aplastic anemia, with which it is associated, may be more frequent in Southeast Asia and in the Far East.

PNH is caused by a somatic mutation in the PIGA gene in hematopoietic stem cells, resulting in the loss of glycosylphosphatidylinositol (GPI) anchored proteins, including the complement regulatory proteins CD55 and CD59, from the surface of mutant red blood cells (RBCs). This leaves these mutant RBCs vulnerable to intravascular hemolysis mediated by the membrane attack complex (MAC) and to extravascular hemolysis presumably mediated by C3 fragment opsonization primarily due to constitutive activation of the complement alternative pathway via tickover mechanism [8]. In addition to anemia that requires frequent RBC transfusions, this condition has other serious sequelae related to the liberation of intracellular hemoglobin and its consequent derangement of nitric oxide levels in the vasculature. These effects include an increased risk of thrombotic events as well as painful vascular crises.

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

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

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

- Patients who have a suboptimal response to eculizumab (approximately 25%-30%), presumably largely due to extravascular hemolysis that is mediated by C3 opsonization. Eculizumab treatment spares the hemolytic destruction of PNH erythrocytes by the MAC (terminal stage of the complement pathway); however, it does not prevent deposition of C3 fragments on PNH erythrocyte membranes which can direct their extravascular hemolysis [9]. ACH-0144471 has a potential mechanistic advantage since it acts upstream of C3 cleavage and has been shown to block C3 fragment deposition.
- Patients who respond partially to eculizumab due to a genetic polymorphism in CR1 (e.g., HindIII H/L and L/L genotypes [10]), 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) [11] could also benefit from ACH-0144471 because ACH-0144471 acts at a different target in the complement cascade and should be unaffected by a mutation in C5.

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

1.3.4 Safety Considerations

1.3.4.1 Risk of Infection

One of the primary functions of the complement system is to fight infections as part of the innate immune system. As suggested by individual case reports with complement system deficiencies including fD, inhibition of the complement system may result in a lifetime increased risk of infection, notably with *Neisseria meningitidis (N. meningitidis)* [12, 13, 14], and other encapsulated organisms.

Because of this potential risk, patients who were enrolled in clinical study ACH471-100 were required to be previously vaccinated, or to receive vaccinations for *N. meningitidis*, *Streptococcus pneumoniae* (*S. pneumonia*e), and *Haemophilus influenzae* (*H. influenzae*) prior to receiving ACH-0144471. Patients in this extension study will receive booster vaccinations as described in Section 6.2.

During clinic visits, subjects will be monitored for the development of fever. A specific Fever Management Plan (Appendix 4) has been developed for this study.

Patients will also be counseled about behaviors to avoid and also be asked to monitor themselves between clinic visits (Appendix 4).

1.3.4.2 Hepatic Injury

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

Additionally, DILIsym simulations indicate maximal loss of hepatocytes that occurred at the high doses in the MAD study would not have a significant effect on liver function [15]. Simulated dosing at 250, 300, and 325 mg TID for up to 1 year predicted minor, clinically insignificant (<1× ULN) ALT increases [16].

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

2 Study Objectives

2.1 Primary Objective

The primary objective of this study is to evaluate the safety and efficacy of long-term therapy with ACH-0144471 in patients with PNH.

2.2 Secondary Objective

The secondary objective of this study is to evaluate health-related quality of life measures in patients with PNH based on patient reported outcome (PRO) instruments and its evolution over the course of long-term therapy with ACH-0144471.

2.3 Exploratory Objectives

No exploratory objectives have been identified for this study.

3 Investigational Plan

3.1 Overall Study Design and Plan

This is an open-label extension study designed to evaluate long-term safety and efficacy of ACH-0144471 in patients with PNH who have demonstrated clinical benefit from ACH-0144471 in study ACH471-100. Patients may remain in the 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; 3) the therapy is no longer tolerated or effective; or 4) another appropriate Alexion clinical study is available or in the opinion of the PI, another treatment option is available. 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.

In order to be eligible for long-term treatment with ACH-0144471 in this extension study, patients must have demonstrated a clinical benefit from ACH-0144471 in ACH471-100. Clinical benefit will be assessed by the investigator, based on an improvement in hemoglobin and/or LDH. 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. The principal investigator will ensure that all eligibility criteria are met and determine whether a patient is an appropriate candidate for long-term continuation of ACH-0144471. Patients will continue therapy with ACH-0144471 from their primary study into this extension study without interruption. Day 84 of the primary study will be Day 1 (Week 1) of this study, and data collected as part of the final visit for ACH471-100 may be entered as the Day 1 data for this study as appropriate. The PI may escalate or reduce dosing to manage clinical benefit or for safety or tolerability reasons, as described in Section 3.2.2.

Figure 1. Study Schematic

Months 1-6

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	18	20	21	22	23	24
Clinic Visits	X				X				X				X				X				X			
Local Lab Visits																								

Months >6

Week	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	**49**	**50**	**51**	**52**	53	54	55	56
Clinic Visits	X								X								X								X							
Local Lab Visits					X								X								X							X			

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

3.2 Rationale for Study Design

3.2.1 Justification of Design

This study is designed as an extension study to provide long-term treatment and evaluate long-term safety and efficacy of ACH-0144471 in patients with PNH who have demonstrated clinical benefit from ACH-0144471 in a prior study, ACH471-100, with no significant safety or tolerability findings.

3.2.2 Justification of Dose

All patients enrolled in ACH471-100 to date have dose escalated to 200 mg TID with no clinically significant alterations in liver enzymes, but the available data suggests that some patients may receive additional clinical benefit from further dose escalation. In this study, patients will continue to receive ACH-0144471 at the same dose that they were receiving at their completion of participation in Study ACH471-100. If necessary in order to improve control of hemolysis, the PI, in consultation with the Sponsor, may escalate dosing in increments of 25 mg to a maximum of 250 mg TID after evaluating the clinical benefit and the available safety, PD, and PK data (including laboratory test results). Patients should have blood drawn (locally or at the clinic) 72 to 84 hours after starting the new dose for measurement of LDH and liver function tests (ALT, AST, GGT, and alkaline phosphatase [ALP]). At the next clinic visit, after approximately 2 weeks at their new dose, a predose PK samples will be obtained in addition to all other safety and efficacy evaluations. The timing of dose escalation may be managed to coincide with a scheduled clinic visit, in which case all normal activities should be performed. Patients may be dose reduced for safety or tolerability reasons if the investigator feels it would be in the best interests of the patient. Whenever possible, this decision should be discussed with the Medical Monitor prior to dose reduction.

3.2.3 Stopping Criteria

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

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

- The patient experiences any SAE assessed as related to treatment with ACH-0144471 (exceptions may be considered at the request of the investigator if the event can be managed by dose reduction or interruption)
- The PI believes that patient continuation in the study is not advisable, or the patient withdraws from the study or meets one of the conditions described in Section 6.18

Discontinuation of treatment should also be considered if:

- ALT or AST* >8× ULN
- ALT or AST* >5× ULN for more than 2 weeks
- ALT or AST* >3× ULN and clinically significant elevation in Total Bilirubin* relative to baseline

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

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

3.3 Study Duration and Dates

All patients may remain in the study until 1) ACH-0144471is commercially available in their country; 2) the development of ACH-0144471 as a potential therapy for PNH is terminated; 3) the therapy is no longer tolerated or effective; or 4) another appropriate Alexion clinical study is available or in the opinion of the PI, another treatment option is available. If patients discontinue during the extension phase, they will have ACH-0144471 tapered and have follow-up visits.

4 Study Population Selection

4.1 Study Population

This study will be conducted in patients who have successfully completed Achillion Study ACH471-100, which was conducted in patients with PNH who are not currently receiving eculizumab, have demonstrated clinical benefit from ACH-0144471, and who wish to continue therapy with ACH-0144471. Clinical benefit will be assessed by the investigator, based on an improvement in hemoglobin and/or LDH.

4.2 Inclusion Criteria

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

1. Patients must have completed treatment in study ACH471-100 and must have demonstrated a clinical benefit from ACH-0144471, with no significant safety or tolerability concerns.
2. Female participants of childbearing potential must agree to use an acceptable method of contraception (as defined in Section 5.5.4) from the date of signing the informed consent to the first day of dosing (Day 1), and must agree to use a highly effective method of contraception (as defined in Section 5.5.4 from the first day of dosing to 30 days after their last dose of study drug. Female participants of childbearing potential must also have a negative serum pregnancy test during Screening and negative urine pregnancy test on Day 1.

   Female participants of non-childbearing potential need not employ a method of contraception.
3. Non-sterile male participants must agree to use a condom from the date of first dose of study drug to 90 days after their last dose of study drug, and in addition must agree to use a highly effective method of contraception (as defined in Section 5.5.4) with their partner(s) of childbearing potential from the first day of dosing to 90 days after their last dose of study drug.

   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.
4. Must agree to provide written informed consent.
5. Must be willing, at all times, to have transportation and telephone access, and to be within one hour of an emergency medical center

4.3 Exclusion Criteria

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

1. Have developed any clinically relevant co-morbidities while participating in ACH471-100 that would make the patient inappropriate for continuation of treatment with ACH-0144471, in the opinion of the investigator.
2. Have developed a clinically significant laboratory abnormality while participating in ACH471-100 that, in the opinion of the investigator, would make the patient inappropriate for the study or put the patient at undue risk.

3. Females who are pregnant, nursing, or planning to become pregnant during the study or within 90 days of study drug administration or patients with a female partner who is pregnant, nursing, or planning to become pregnant during the study or within 90 days of study drug administration

5 Study Treatment

5.1 Description of Treatment

5.1.1 Study Drug

ACH-0144471 will be dosed as a tablet formulation containing the drug substance, lactose, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulphate, magnesium stearate, colloidal silicon dioxide, and hypromellose acetate succinate. The coating components are polyvinyl alcohol, titanium dioxide, macrogol/polyethylene glycol, and talc. ACH-0144471 will be administered as 50, 75, or 100 mg tablets. The 75 mg tablets are no longer manufactured; therefore, the 75 mg tablet will not be provided once the current supply expires.

5.2 Treatments Administered

5.2.1 ACH-0144471

A single treatment group is planned for patients who completed study ACH471-100.

At the end of dosing, or if a patient is discontinued, it is recommended that a taper be implemented, according to the schedule in Table 1. If dosing is terminated for safety-related reasons, the PI may discontinue dosing immediately if they feel it in the best interest of the patient. Whenever possible, this decision should be discussed with the Medical Monitor prior to dosing termination.

Table 1. Dosing Taper Schedule

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

Abbreviations: T = taper; TID = three times a day
During the end of treatment visit, the site staff will provide instructions for when the patient should start Taper Period 1. Taper day visits may be done at the clinic or by phone call on Day 3 and Day 6 respectively.
On Taper Day 3, site staff should assess safety and give instructions to further taper dosing. On Taper Day 6, site staff should give instructions to terminate dosing.

Patients entering this study should not have their ACH-0144471 dose tapered as described for the end of treatment in study ACH471-100. Patients who enter into Study ACH228-110 or those who are eligible to participate in other ACH-0144471 (danicopan) clinical studies will not need to have their ACH-0144471 dose tapered as long as there is no gap in dosing before starting the next clinical study.

5.2.2 Vaccines

Patients entering this study will have been previously vaccinated against *N. meningitidis*, *S. pneumoniae*, and *H. influenza*. Patients in this study will receive booster vaccinations as described in Section 6.2.

5.3 Selection of Timing and Dose for Each Patient

Each patient will enter this study at the dose they were receiving at the completion of ACH471-100. If necessary to improve control of hemolysis, the PI, in consultation with the Sponsor, may escalate dosing in increments of 25 mg to a maximum of 250 mg TID after evaluating the clinical benefit and the available safety, PD, and PK data (including laboratory test results), as described in Section 3.2.2. Patients may be dose reduced for safety or tolerability reasons if the investigator feels it would be in the best interests of the patient. Whenever possible, this decision should be discussed with the Medical Monitor prior to dose reduction.

Patients will be dosed three times daily (TID) (a dose in the morning, a second dose approximately 8 hours later, and a third dose approximately 8 hours after the second dose). Doses should be taken at approximately the same time each day and as close as possible to 8 hours apart. All doses should be taken approximately 15-30 minutes after completion of a meal or snack. If a dose is missed, it should be taken within 4 hours of the originally scheduled time. After 4 hours, the missed dose should be skipped. In either case, the next dose should be taken according to the original dosing schedule.

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

5.4 Method of Assigning Patients to Treatment Groups

All patients will receive ACH-0144471 and will be assigned to the same treatment group. Each patient will retain the same subject identification as in study ACH471-100.

5.5 Restrictions

5.5.1 Concomitant Therapy

Based on in vitro data, ACH-0144471 has the potential to inhibit several cytochrome (CYP) enzymes as well as some transporters. In contrast, the PK profile of ACH-0144471 is not likely to be affected by other drugs. Specific in vitro results for various CYP enzymes and transporters are described in the IB [1]. At the doses administered in this study, it is unlikely that any clinically relevant drug-drug interactions will occur.

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

- Concomitant administration of folic acid and/or erythropoiesis-stimulating agents is permitted.
- Concomitant administration of steroids or other immunosuppressants is permitted; the dose should remain stable with that administered in the primary study.
- Oral, injectable, implantable, transdermal, or intravaginal hormonal therapies are allowed for either contraception or hormonal replacement therapy.

- If it is necessary to treat a fever (see Appendix 4), or any minor ailment occurring while on study, ibuprofen (maximum 400 mg/day and up to 1200 mg/week) and/or acetaminophen (maximum 1000 mg/day) are permitted without prior approval.
- Administration of eculizumab or any other complement inhibitor is not permitted during this study.

5.5.2 Fluid and Food Intake

Patients should be instructed to take each dose of ACH-0144471 with food. As described in Section 5.3, ACH-0144471 should be taken TID, approximately 8 hours apart. An appropriate schedule would be to take the three daily doses after finishing breakfast, dinner and a bedtime snack. All doses should be taken approximately 15-30 minutes after completion of the respective meal or snack.

5.5.3 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 should be counseled to avoid the consumption of alcohol while participating in this study.

5.5.4 Contraception

5.5.4.1 Contraception for Male Participants

All non-sterile male participants must use a 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 childbearing potential:
  - Oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
  - Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation
  - Intrauterine device (IUD) or Intrauterine hormone-releasing system (IUS)
  - Bilateral tubal occlusion
- Sexual abstinence, defined as refraining from heterosexual intercourse during the entire period from the first day of dosing (Day 1) through 90 days after their last dose of study drug. Periodic abstinence (e.g., calendar, symptothermal, post-ovulation methods) is not an acceptable method of contraception. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. If a

participant is usually not sexually active but becomes active, they, with their partner(s), must comply with the contraceptive requirements described in this section.

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

5.5.4.2 Contraception for Female Participants

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

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

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

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

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

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

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

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

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

5.6 Treatment Compliance

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

Additional efforts may be implemented to ensure compliance. Patients may be asked to record each daily dose of ACH-0144471 and may also receive automated reminders for dosing (e.g., via SMS text or phone call). In such instances, the site will receive notification of any non-response or noncompliance 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
- Caution Statement such as “For Clinical Trial Use Only” or “Caution: New Drug—Limited by Federal (or United States) law to investigation use” or similar statements.

5.8 Storage and Accountability

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

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

The PI or designee (e.g., pharmacist) is responsible for ensuring storage as per the label on the drug product at the site and adequate accountability of all used and unused study drug. This includes

acknowledgment of receipt of each shipment of study drug (quantity and condition) and patient dispensing records and returned or destroyed drug. Dispensing records will document quantities received from Achillion Pharmaceuticals, Inc. (or designee) and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, patient initials, and the initials of the person dispensing the medication. All drug supplies and associated documentation will be periodically reviewed and verified by the Study Monitor over the course of the study.

5.9 Investigational Product Retention at Study Site

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

6 Study Procedures

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

6.1 Informed Consent

The PI or designee is responsible for administering and obtaining freely given consent, in writing, before entering the patient into the study and performing any study-related procedures. Each patient will sign an Ethics Committee (EC) or Institutional Review Board (IRB) -approved written informed consent form (ICF).

6.2 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.

Patients in Protocol ACH471-103 will have been previously vaccinated against *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* as described in Protocol ACH471-100. The need for booster vaccinations during Protocol ACH471-103 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 booster vaccinations against each organism and/or serotype.

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.

6.3 Physical Examination

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.

6.4 Vital Signs

The PI or designee will obtain blood pressure (BP), heart rate (HR), and respiration rate (RR) at the visits indicated in the Schedule of Assessments (Appendix 1). Vital signs will be measured in the supine position following a 5-minute rest. All vital sign measurements for an individual should be taken on the dominant arm (if possible) throughout the study. Vital signs may be measured using an automated vital

signs machine. Vital sign values will be recorded in the patient's source documents and in the patient's CRF.

6.5 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).

6.6 Electrocardiography

The PI or designee will obtain ECG measurements at the times indicated in Appendix 1. All ECG recordings should be 12-lead, and should be performed after the patient has rested quietly for at least 5 minutes in a supine position and before blood is drawn (whenever possible). The following parameters and intervals will be assessed: HR, RR, PR, QRS, QT, and QTcF. The occurrence of depolarization or repolarization disorders, arrhythmic disorders or other abnormalities will be noted. A designation of clinical significance shall also be noted by the PI or designee.

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

All ECGs must be read by the PI or designee. The PI/designee needs to evaluate the finding of ECG abnormalities promptly (refer to Section 6.15.1 for a discussion of the circumstances under which ECG findings are to be reported as AEs).

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

6.7 Clinical Laboratory Measurements

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

Table 2. Clinical Laboratory Tests

Hematology	Chemistry	Urinalysis	Other Assessments[1]
Complete Blood Count (CBC), including: - Red blood cell (RBC) count - White blood cell (WBC) count - WBC differential (absolute and percent): - neutrophils - lymphocytes - monocytes - eosinophils - basophils - Hematocrit (Hct) - Hemoglobin (Hgb) - Mean corpuscular volume (MCV) - Mean corpuscular hemoglobin (MCH) - Mean corpuscular hemoglobin concentration (MCHC) - Mean platelet volume (MPV) - Platelet count - Red cell distribution width (RDW) - Reticulocyte count	Alanine aminotransferase (ALT) Albumin Alkaline phosphatase Aspartate aminotransferase (AST) Bicarbonate (HCO_3) Bile acids Bilirubin (fractionated)[2] Blood urea nitrogen (BUN) Calcium Calculated eGFR[3] Chloride Creatine kinase[4] Creatinine Gamma-glutamyl transferase (GGT) Glucose[5] Lactate dehydrogenase (LDH) Lipid Profile including: - Cholesterol/HDL ratio - High-density lipoprotein cholesterol (HDL-C) - Low-density lipoprotein cholesterol (LDL-C) - Non-HDL-C - Total cholesterol - Triglycerides - Very low-density lipoprotein cholesterol (VLDL-C) Potassium Sodium Total protein Uric acid	Bilirubin Color Glucose Ketones Hemosiderin Leukocytes Microscopic examination of sediment[6] Nitrite Occult blood pH Protein Specific gravity Urobilinogen	D-dimer Direct Coombs Free hemoglobin Haptoglobin PNH Clone Size Factor D AP Wieslab Urine pregnancy test[7]

All tests to be performed as per the schedule outlined in Appendix 1. Patients should fast prior to testing.

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

2 Fractionate and obtain measurements of direct and indirect bilirubin for all patients. If indirect bilirubin levels are > ULN but ALT and AST are normal, test for Gilbert's syndrome unless testing has already been done.

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

4 The central lab will report as a reflex only if AST > ULN.

5 If glucose is > ULN, central lab will reflexively test HbA1c.

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

7 Pregnancy tests as per the schedule in Appendix 1 for women of childbearing potential only. See Section 6.8.

6.8 Pregnancy Testing

All female patients of childbearing potential (as determined at screening in the primary study) will have a urine pregnancy test every 4 weeks for the duration of the previous study, ACH471-100. A urine pregnancy test must be performed at every visit for the duration of this study, including follow-up, until the patient is no longer of childbearing potential, as defined in Section 5.5.4. The urine pregnancy tests must be done before dosing and must be negative to continue dosing. If there is no interruption in

therapy, Day 84 of ACH471-100 will be Day 1 of this study, and the final urine pregnancy test on Day 84 of ACH471-100 may serve as the Day 1 urine pregnancy test for this study.

Female patients of childbearing potential who require vaccination or boosters (see Section 6.2) 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.

6.9 Sample Collection, Storage, and Shipping

6.9.1 Blood Collection for Complement Assays

Samples will be collected for measurement of factor D levels and AP Wieslab activity; additional samples will be collected and retained for potential assessment of other non-genetic complement-associated biomarkers. Depending on the test, either serum or plasma may be required; aliquots of both serum and plasma will therefore be collected at each visit. Whole blood will be collected and processed to obtain cell-free serum or plasma, which will be aliquoted into cryovials, frozen on dry ice, stored in a -80°C freezer and shipped frozen to the designated laboratories. It is important that samples be collected, prepared, and shipped in a way that ensures minimum freeze-thaw cycles and avoids potential in vitro complement activation before testing. Specific instructions for sample collection, processing, and shipping will be provided in a separate laboratory manual.

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

6.9.2 PK Plasma Samples

Samples will be collected for pharmacokinetic analysis. Whole blood (2 mL) will be collected and processed to obtain cell-free plasma, which will be aliquoted into cryovials, frozen on dry ice, stored in a -80°C freezer and shipped frozen to the bioanalytical laboratory. It is important that samples be collected, prepared, and shipped in a way that ensures minimum freeze-thaw cycles. Specific instructions for sample collection, processing, and shipping will be provided in a separate laboratory manual.

6.9.3 Blood Volumes

Approximate blood volumes for each visit are detailed in Table 3 below. Because the duration of the study is not defined, calculation of the total planned blood volume to be collected per individual is not possible. Unanticipated additional blood may be collected throughout the study for such things as safety monitoring and PK or PD assessments, should it be necessary. Please refer to the laboratory manual for specific instructions regarding blood and urine volume, collection, processing, and handling.

Table 3. Approximate Total Blood Volumes

Test	Blood Volume/Time Point (mL)	Blood Drawn (mL)
Clinical Labs (chemistry [including LDH] & hematology)	9.0	8.5
Additional Hematology Tests (free Hgb, haptoglobin)[1]	4.5	4.5
D-dimer[1]	4.5	2.7
Direct Coombs[1]	4.0	2.0
Flow Cytometry: PNH Clone Size[1]	4.0	2.0
AP Wieslab, fD serum sample[1]	3.0	7.0
Samples for complement assays[2]	5.0	5.5
PK samples[2]	2.0	2.0
Total Volume		**34.2**

[1] Not drawn at every visit. See the schedule in Appendix 1.

[2] Samples will be collected and may be analyzed or stored, as described in Section 6.9. Samples for PK, AP Wieslab, fD, and flow cytometry: PNH clone size, and samples for complement assays are no longer required during the extension phase upon implementation of Protocol Amendment 5.0.

Abbreviations: AP = alternative pathway (of complement); fD = factor D; LDH = lactate dehydrogenase; PK = pharmacokinetics; PNH = paroxysmal nocturnal hemoglobinuria

6.10 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 clinic visit.

6.11 Safety Assessments

Safety will be evaluated by monitoring and assessment of AEs, clinical laboratory tests, physical examination findings, ECG, and vital signs measurements at each visit as described in Section 7 and the Schedule of Assessments (Appendix 1).

6.12 Pharmacokinetic Assessments

Blood samples will be collected prior to dosing at each clinic visit for determination of trough plasma concentrations of ACH-0144471.

Concentrations of ACH-0144471 will be determined using a validated bioanalytical method.

Samples for PK assessments are no longer required the extension phase upon implementation of Protocol Amendment 5.0. Sampling may be performed in response to a drug-related safety event or clinical deterioration as determined by the Investigator and in discussion with the Medical Monitor. In this scenario, the date and time of the most recent dose should be recorded when available.

6.13 Pharmacodynamic and Efficacy Assessments

Pharmacodynamics will be evaluated using serum, plasma, and whole blood collected during the study with the assays outlined in Table 4 and the Schedule of Assessments (Appendix 1). Additional PD markers and PNH- and/or complement-related items may be evaluated using the stored samples described in Section 6.9.1; this will be determined on a case-by-case basis. Efficacy will be assessed

using LDH and hemoglobin levels and other measures of hemolysis, as well as RBC transfusion requirements.

Samples for AP Weislab, fD, flow cytometry: PNH clone size, and complement-associated biomarkers are no longer required in the extension phase upon implementation of Protocol Amendment 5.0. Sampling may be performed in response to a drug-related safety event or clinical deterioration as determined by the Investigator and in discussion with the Medical Monitor. In this scenario, the date and time of the most recent dose should be recorded when available.

Table 4. Pharmacodynamic Markers

Assay Identifier	Assay Descriptions
LDH	Blood test
CBC components	Blood test
Free hemoglobin	Blood test
Haptoglobin	Blood test
D-dimer	Blood test
Direct Coombs test	Blood test
PNH clone size	Flow cytometry
AP Wieslab assay	ELISA; LPS as activator; measurement of TCC
fD	ELISA
Additional complement-associated biomarkers	ELISA or other

Refer to Appendix 1 for the schedule for each of these tests.

6.14 Patient Reported Outcomes Assessments

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

In addition, patients were 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 were conducted over the phone by a trained, experienced interviewer and lasted approximately 30 minutes. Patients were interviewed after approximately 3 and 9 months of treatment in this study (i.e., after approximately 6 and 12 months of treatment with ACH-0144471, including approximately 3 months of treatment during ACH471-100). Patients who terminated early may have been interviewed at the time of termination. As of 30 April 2019, PRO interviews were discontinued by the Sponsor.

6.15 Adverse Events Assessments

6.15.1 Definitions

Adverse Events (AEs) must be assessed for the investigational product 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 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 6.15.8).
- 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;
- Pre-existing diseases or conditions or laboratory abnormalities present or detected prior to the screening evaluation that do not worsen;
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions, etc.);

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

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

- Are considered clinically significant by the investigator.

Whenever possible, the etiology of the abnormal findings (rather than the abnormal finding(s) itself) should be documented as the adverse event. Repeated additional tests and/or other evaluations required to establish the significance and etiology of an abnormal result should be obtained when clinically indicated.

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

Surgical procedures themselves are not AEs, but are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an adverse event, if it occurs or is detected during the study period. Planned surgical measures permitted by the clinical study protocol (if any) and the condition(s) leading to these measures are not AEs, 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.

6.15.2 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

6.15.3 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 6.15.7.

6.15.4 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 Medical Monitor (or designee).

6.15.5 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 pre-existing 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 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.

6.15.6 Severity and Grading of Adverse Events

The intensity of an adverse event will be graded according to the CTCAE Adverse Event Severity Grading Table (Appendix 3) [17]. 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.

6.15.7 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'.

6.15.8 Pregnancy

Any pregnancy, including female partner pregnancies of male patients that occurs or becomes confirmed during a clinical study (time frames outlined in Section 6.15.5) 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.

6.15.9 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 6.15.5).

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

SAE

- Record the SAE within 24 hours of becoming aware of the event in **BOTH** the CRF **AND** by completing a SAE report within the Fusion eClinical Suite.
- This will trigger an email notification to the Axiom and Achillion Pharmaceuticals, Inc (a wholly owned subsidiary of Alexion Pharmaceuticals Inc.) distribution.

Pregnancy

- Record the pregnancy into **BOTH** the CRF **AND** the Fusion eClinical Suite.

- This will trigger an email notification to the Axiom and Achillion Pharmaceuticals, Inc distribution lists.

Contact information is provided below.

SAE CONTACT
Report all SAEs and/or Pregnancies into the Axiom Fusion Electronic Data Capture (EDC) System In the event of **System failure,** or for questions about completing the forms in the EDC system contact the Axiom Real-Time Metrics Team **SAE Telephone Number and e-mail** 1-866-91-AXIOM (1-866-912-9466) ACH-SAEHelp@axiom.cc

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.

6.15.10 Investigator Reporting Requirements for SAEs

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

6.16 Concomitant Medication Assessments

Details of all concomitant medication use, including all medications administered for the treatment of AEs, will be recorded in the patient's CRF at each study visit.

6.17 Monitoring Patient Safety

The safety of patients will be monitored by Investigators and by a medical monitor (or designee) at Achillion Pharmaceuticals, Inc. on an ongoing basis while patients are receiving ACH-0144471. Additionally, a Fever Management Plan (Appendix 4) has been developed for this study to enable rapid assessment, detection and treatment of any potential serious infection.

6.18 Removal of Patients from the Trial

A patient is free to withdraw from the study at any time without jeopardizing future medical care. In addition, the PI (or designee) may decide, for reasons of medical prudence or patient noncompliance, to discontinue dosing in a patient. The PI should also stop dosing in any patient who meets an individual stopping rule (Section 3.2.3). In either case, whenever possible, the Medical Monitor should be notified immediately, and if possible, before dosing is terminated. When dosing is terminated, study participation is not necessarily also terminated. Instead, whenever possible, the patient should complete the activities for a 6 Month Visit as described in Appendix 1, complete a dosing taper as described in Section 5.2.1, and return for a Follow-up Visit 2 weeks after the last dose of study drug.

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

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree
- Unacceptable toxicity (including a clinically significant laboratory abnormality) necessitating discontinuation of study or that, in the judgment of the investigator, compromises the ability to continue study-specific procedures, or it is considered not to be in the patient's best interest to continue the study (see Section 3.2.3 for individual patient stopping rules)
- Patient request to discontinue for any reason
- A female patient becomes pregnant or wishes to become pregnant, or the female partner of a male patient becomes pregnant or wishes to become pregnant
- Patient noncompliance
- Discontinuation of the study at the request of Achillion Pharmaceuticals, Inc., regulatory agency, or EC 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.

6.19 Coronavirus Disease 2019

As a result of coronavirus disease 2019 (COVID-19) restrictions, there could be various challenges which may prevent the possibility of completing a clinic or local laboratory visit.

To ensure patient safety and treatment continuity during the COVID-19 outbreak, the following will apply:

- When patients are not able to reach the study site, and until patients are able to resume physical study visits at the site:
    - The conversion of a physical visit into a phone or videoconference will be at the Investigator's discretion and oversight, in accordance with all national, state, and local laws or regulations of the pertinent regulatory authorities and conducted by a qualified

medical professional. When performing a phone/video visit, information about AEs, concomitant medications, and PNH symptomatology should be assessed.

- All attempts to obtain safety laboratory tests should be made such as the use of home healthcare lab sampling or use of a local laboratory (or other relevant clinical facility) authorized/certified to perform such tests.

- If a patient is unable to complete a local laboratory visit, an alternative method will be attempted to obtain safety laboratory tests (e.g., use of home healthcare laboratory sampling or clinic visit).

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. There is no formal screening or eligibility visit. For each patient, the PI should make the decision whether participation in this extension study would be appropriate on or around the Day 70 visit of study ACH471-100 and communicate this decision to the Medical Monitor. Day 84 of study ACH471-100 will be Day 1 (Week 1) of this study. Data collected as part of the final visit for ACH471-100 may be entered as the Day 1 data for this study as appropriate.

During the study period, physical examinations, assessment of vital signs, ECG measurements, all required safety laboratory testing, pregnancy testing for women of childbearing potential, and collection of blood and urine samples for efficacy, PD, and PK evaluation will be performed at various time points throughout the study as specified in Appendix 1.

Dosing should be at approximately the same times each day.

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

ECG and vital signs prior to blood sampling

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

7.1.1 Clinic Visits

The procedures indicated in Appendix 1 should be followed for each visit. As part of these activities, site personnel should review with the patient the instructions for how to take their medication at home, as described in Section 5.3.

Visits may take place within a window of ±3 days relative to the specified day for the first 6 months, and then within a window of ±7 days relative to the specified day for the duration of the study.

7.1.2 Safety Follow-up at Local Laboratory

As indicated in Appendix 1 (Schedule of Assessments), after 6 months, the frequency of clinic visits will be reduced from once every 4 weeks to once every 8 weeks. Once this happens, patients will have blood drawn at a local clinical laboratory 4 weeks after clinic visits for assessment of hemoglobin, free hemoglobin, and LDH levels. These visits should occur within a window of ±7 days relative to the specified day.

7.1.3 Safety Follow-up After Escalation

As described in Section 3.2.2, the PI, in consultation with the Sponsor, may escalate dosing in increments of 50 mg to a maximum of 250 mg TID after evaluating the clinical benefit and the available safety, PD, and PK data (including laboratory test results) for a patient. Patients should have blood drawn (locally or at the clinic) 72 to 84 hours after starting the new dose for measurement of LDH and liver function tests (ALT, AST, GGT, and ALP). Patients should have a clinic visit after approximately 2 weeks at their new dose for safety evaluation and collection of samples for efficacy and predose PK

evaluation. The timing of dose escalation may be managed so this visit coincides with a scheduled clinic visit, in which case all normal activities should be performed.

7.1.4 Patient Reported Outcomes Interviews

Quality of Life interviews were conducted with patients as described in Section 6.14 after approximately and 3 and 9 months of treatment in this study (i.e., after approximately 6 and 12 months of treatment with ACH-0144471, including approximately 3 months of treatment during Study ACH471-100). As of 30 April 2019, PRO interviews were discontinued by the Sponsor.

7.1.5 Dosing Taper

It is recommended that patients who discontinue ACH-0144471 for any reason have study drug tapered over 6 days, as described in Section 5.2.1.

Patients who enter into Study ACH228-110 from this study, will not be required to follow dose tapering. ALXN2050 should be administered the morning after the last dose of ACH-0144471, thus their participation in Study ACH471-103 will be complete on their 'Day 1' Visit for Study ACH228-110 prior to first dose of ALXN2050.

The intention of the taper period in Study ACH471-103 was to slowly remove the study drug for patients who would be transitioning to no treatment. Patients able and choosing to enter Study ACH228-110 will be switching from one fD inhibitor (ACH4471) to another (ALXN2050), and thus to taper of the ACH-0144471 prior to starting ALXN2050 would create a gap in fD inhibitor exposure and is not expected to be in the patient's treatment best interest.

Patients who are eligible to participate in other ACH-0144471 (danicopan) clinical studies will also not need to have their ACH-0144471 dose tapered, as long as there is no gap in dosing before starting the next clinical study.

7.1.6 Follow-Up Visit

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

Patients who enter into Study ACH228-110 from this study, will not be required to have a follow-up visit. The decision to cancel the Follow-up Visit in Study ACH471-103 for patients entering into Study ACH228-110 was taken because the patients will be followed more closely in another study, and thus it would not compromise the overall care and follow-up of the patient and had the effect of limiting overall patient burden.

7.1.7 Unscheduled Visits

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

- Assess for compliance with protocol restrictions
- Assess for AEs and SAEs

- Record concomitant medications, including transfusions
- Conduct a physical exam and obtain resting supine vital signs (BP, HR, RR)
- Measure body temperature
- Additional tests or procedures as appropriate

PK and PD sampling may be performed in response to a drug-related safety event or clinical deterioration as determined by the Investigator and in discussion with the Medical Monitor. In this scenario, the date and time of the most recent dose should be recorded when available.

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

8 Quality Control and Assurance

8.1 Routine Monitoring

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

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

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

8.2 Site Audits

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

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

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

9 Planned Statistical Methods

9.1 General Considerations

Descriptive and exploratory statistical methods may be utilized to present results from data analysis. It should be noted that some data from study ACH471-100 will be carried over to this study for continuity in data presentation and clinical interpretation of long-term safety and efficacy.

Subject listings will be provided for all data points collected from this study. If selected data points from the primary studies are utilized to produce summary tables, these data points will also be included in the pertinent subject listings. Summary statistics may be computed for selected study parameters so that meaningful clinical interpretations can be made. Graphic presentations may also be produced for selected study parameters.

A statistical analysis plan (SAP) will be developed and finalized before enrollment of the last patient in this study.

9.2 Analysis Populations

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

9.3 Demographics and Baseline Characteristics

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

9.4 Efficacy Analysis

The following efficacy parameters will be examined to assess the long-term efficacy of ACH-0144471 in PNH patients:

- LDH levels
- Hgb levels in the absence of RBC transfusion
- Number of RBC transfusions
- Reticulocyte counts

Levels at baseline in the primary study and changes from baseline for the above efficacy parameters will be summarized for each pre-specified time point, using observed values. Longitudinal plots may be provided to display mean (or median) level versus pre-specified time points and mean (or median) change from baseline versus pre-specified time points.

Other PD biomarkers such as free Hgb, haptoglobin, PNH clone size, factor D level, AP Wieslab, and other PNH- and/or complement-related assays may be measured to monitor and evaluate the long-term effects of ACH-0144471 on PNH cells and complement AP components and function.

9.5 Safety Analysis

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

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

Data on vital signs and ECGs will be examined either through patient listings or by summary statistics of selected parameters.

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

9.6 Patient-Report Outcomes Assessments

9.6.1 Quality of Life Scales

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

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

9.6.2 Patient Interviews

De-identified transcripts of the patients' interviews will be qualitatively analyzed following a thematic analysis. The analysis of patient interviews will be based on the grounded theory approach, allowing the voice of the patient to be heard rather than apply a priori concepts or hypotheses [18]. A validated software package [19] will be used to facilitate the storage, coding, analysis, and retrieval of qualitative data.

Other analysis procedures relevant to interview data may also be explored. A separate analysis plan and/or report will be provided for the interview data if deemed feasible and clinically appropriate.

10 Administrative Considerations

10.1 Investigators and Study Administrative Structure

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

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

10.2.1 Ethical Approval

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

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

10.2.2 Regulatory Approval

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

10.2.3 Amendments

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

10.3 Ethical Conduct of the Study

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

10.4 Patient Information and Consent

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirements and should adhere to ICH GCP (E6). Each patient must be adequately informed in a language that they can understand and read of the aims, methods, anticipated benefits, potential hazards and the discomfort the study may entail, as well as their right to abstain from participating in the study and to withdraw their consent at any time without affecting their medical care. If important new

information is incorporated in the ICF and approved by the EC, all patients still actively participating in the study must be re-consented.

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

10.5 Patient Confidentiality

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

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

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

10.6 Study Monitoring

10.6.1 Access to Information for Monitoring

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

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

10.6.2 Access to Information for Auditing or Inspections

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

10.7 Case Report Forms and Study Records

10.7.1 Recording of Data

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

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

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

10.7.2 Source Documentation and Medical/Study Records

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

10.8 Data Monitoring Committee

There will be no formal data monitoring committee.

10.9 Protocol Violations/Deviations

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

10.10 Access to Source Documentation

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

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

10.11 Data Generation and Analysis

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

10.12 Retention of Data

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

- Investigator study file, and
- Patient clinical source documents.

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

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

All clinical study documents must be retained by the investigator for at least 2 years after the last approval of a marketing application in an ICH region (i.e., United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with Achillion Pharmaceuticals, Inc. The investigator (or designee) must contact Achillion Pharmaceuticals prior to destroying any records associated with the study. Achillion Pharmaceuticals, Inc. will notify the PI when the study records are no longer needed.

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

The interviews were 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 study results are considered to be confidential. The investigator agrees to use this information for purposes of conducting this study. It is understood that Achillion Pharmaceuticals, Inc. may use data derived from this study 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 study 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

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12 Appendices

Appendix 1. Schedule of Assessments

Table 5. Schedule of Assessments

	Months 1-6 (Weeks 1-25)[1]							>6 Months[2]		Taper and Follow-up[5]			Dose Esc[3]	
	1[4]	5	9	13	17	21	25	Clinic Visits	Local Labs	T3	T6	F/U	3-4 Day	~2 Wk
Enrollment Assessments														
Informed Consent	X													
Inclusion/ Exclusion Criteria	X													
Vaccination Boosters	See Section 6.2													
Urine Pregnancy Test	X	X	X	X	X	X	X	X	X			X		
Patient-Reported Outcomes Assessment Interviews[6]	Interviews will be conducted after approximately 3 and 9 months, as described in Section 7.1.4													
Dosing and Drug Distribution														
ACH-0144471 Dosing	X									X	X			
Study Drug Dispensing	X	X	X	X	X	X	X	X						
Clinical Assessments														
Physical Exam	X	X	X	X	X	X	X	X				X		
Vital Signs	X	X	X	X	X	X	X	X				X		X
Body Temperature	X	X	X	X	X	X	X	X				X		X
Weight	X	X	X	X	X	X	X	X				X		
Patient-Reported Outcome Measures Assessments (QoL Questionnaires)	X			X		X		X[6]				X		
12-Lead ECGs (single)	X			X			X	X[7]						
AEs/SAEs	X													
Concomitant Medications, including transfusions	X	X	X	X	X	X	X	X		X	X	X		X
Laboratory Assessments														
Hematology, Chemistry, and Urinalysis[8]	X	X	X	X	X	X	X	X					X[9]	X
Free Hemoglobin, Haptoglobin, D-dimer, Direct Coombs	X		X		X		X	X						X
Local Labs: Hgb, Free Hgb, LDH[10]									X				X	
PK samples[11]	X	X	X	X	X	X	X							X
PNH Clone Size[12]	X						X	X[12]						
Factor D, AP Wieslab[12]	X						X							

Table 5. Schedule of Assessments

	Months 1-6 (Weeks 1-25)[1]							>6 Months[2]		Taper and Follow-up[5]			Dose Esc[3]	
	1[4]	5	9	13	17	21	25	Clinic Visits	Local Labs	T3	T6	F/U	3-4 Day	~2 Wk
Plasma/Serum Samples for Non-genetic Biomarker Testing[11]	X	X	X	X	X	X	X	X						

AE = Adverse Event; ECG = Electrocardiogram; F/U = Follow-up Visit; Hgb = Hemoglobin; PK = Pharmacokinetic; PRO = Patient Reported Outcomes; QoL = Quality of Life; SAE = Serious Adverse Event; T3 = Day 3 of the taper; T6 = Day 6 of the taper; Wk = Weeks

1 Visits may take place within a window of ±3 days relative to the specified day.

2 Clinic visits should take place every 8 weeks, starting with Week 25 visit. Local Labs should be drawn 4 weeks after clinic visits. Both clinic visits and local lab draws may take place within a window of ±7 days relative to the specified day.

3 Measurement of LDH and liver function tests (ALT, AST, GGT, ALP), to be drawn locally or at the clinic 72-84 hours after escalation, and at a clinic visit 2 weeks after escalation, as described in Section 7.1.3.

4 Day 84 of the study ACH471-100 will be Day 1 (Week 1) of this study. Data collected as part of the final visit for ACH471-100 may be used for the Week 1 data as appropriate.

5 The follow-up visit should be ~14 days after the last dose of study drug (including taper). Patients who enter into Study ACH228-110 from this study, will not be required to have their dose tapered or the Follow-Up Visit. For these patients, the last visit in Study ACH471-103 should coincide with the Day 1 visit of Study ACH228-110. Data collection for the last visit under Study ACH471-103 will be limited to AEs, concomitant medications, and study drug accountability. For patients who discontinue from the study, these visits may be conducted at clinic or by phone. Patients who are eligible to participate in other ACH-0144471 (danicopan) clinical studies will also not need to have their ACH-0144471 dose tapered as long as there is no gap in dosing before starting the next clinical study.

6 PRO assessments should be conducted after approximately 9 months, to align with the PRO Assessment Interview, and then every 6 months for the duration of the study. PRO Interviews were no longer collected after 30 April 2019.

7 Every other visit (weeks 41, 57, 73, etc).

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

9 Liver function tests (ALT, AST, GGT, ALP) and LDH only (Section 7.1.2).

10 Only for Hgb, Free Hgb, LDH (Section 7.1.3).

11 Samples will be collected for PK analysis and potential measurement of PD biomarkers as described in Section 6.9. Upon implementation of Protocol Amendment 5.0, collection of these samples in the extension phase will no longer be required. PK and PD sampling may be performed in response to a drug-related safety event or clinical deterioration as determined by the Investigator and in discussion with the Medical Monitor, and the time of the most recent dose should be recorded when available.

12 Every 6 months for the first 2 years, and then annually for the duration of the study. Upon implementation of Protocol Amendment 5.0, collection of these samples in the extension phase will no longer be required.

Appendix 2. Quality of Life Assessments

FACIT Fatigue Scale (Version 4)

EORTC-QLQ-C30 (Version 3)

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

FACIT Fatigue Scale (Version 4)

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

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

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

English (Universal)

16 November 2007

EORTC-QLQ-C30 (Version 3)

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

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

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

During the past week:

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

Please go on to the next page

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 3. Grading the Severity of Adverse Events

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

To view or print the table, go to:

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

Appendix 4. Fever Management Plan

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

Minimum Requirements

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

A. General Management for Outpatients

All patients in this study will:

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

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

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

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

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

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

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

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

B. General Management for Any Fever Detected in the Clinic

For Any Fever, the site needs to:

1. Assess for symptoms - Consider meningococcal disease as a diagnosis. When meningococcal disease is suspected, early treatment is critical

2. Repeat and confirm all temperature measurements >38.0°C

3. Notify the PI and Sponsor for all confirmed temperature measurements >38.0°C

4. Consider if referring to an emergency medical facility is appropriate. If so, refer. Otherwise:

    a. PI or designee to perform a complete physical examination (including assessing if fever is accompanied by a severe headache, stiff neck, or other signs of meningeal irritation, shortness of breath, skin rashes, or other unusual signs or symptoms), document a plan based on her/his clinical judgment, and possibly an ID consult depending on assessment

    b. CBC (if not done in the last 12 hours) and blood culture

    c. Treat any suspicion of meningococcal infection aggressively; consider initiation of empirical antimicrobial therapy (assuming there are no other obvious sources of fever) at least until culture results become available and/or an alternative etiology is found

    d. Infectious disease consult is required once the PI or designee initiates empiric antibiotic treatment

    e. Measure temperature hourly until < 38.0°C

    f. All cases of fever will be assessed by the Investigator, regardless of apparent causality from use of the study treatment(s)

    g. All activities performed as part of the Fever Management Plan should be documented

Acute Meningococcal Disease

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

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

Appendix 5 COVID-19 Risk Assessment

Paroxysmal nocturnal hemoglobinuria can cause irreversible morbidity and even mortality, if untreated. As such, and due to the limited number of available treatment options, the benefit a participant may receive from joining an investigational study with a therapeutic treatment is potentially significant. Given that treatment for PNH does involve immunosuppression, there is a theoretical concern that the risk for infection may be higher than in patients not receiving immunosuppressants. However, there is no specific data to further inform this risk. The Investigator will therefore balance the risk/benefit considerations in the patient taking these factors into account.

The potential risks identified and mitigation measures put in place in light of the COVID-19 pandemic are provided in Table 6.

Table 6: Potential Risks and Mitigation Measures due to COVID-19

Risks Category	Summary of Data/ Rationale for Risk	Mitigation Strategy
Potential risks		
Healthcare institution availability for non-COVID-19 related activities	COVID-19 pandemic may impact the workload of healthcare institutions globally and may reduce staff availability to perform non-urgent activities and non-COVID-19 related activities.	During the time that the COVID-19 pandemic is active, Alexion will not open study sites or enroll new patients at sites unless the sites have the resourcing and capabilities to implement the study per protocol.
Data quality and integrity	Lack of availability of site personnel to perform study assessments and capture study-specific data in a timely manner and to maintain adequate quality standards. Lack of availability of site personnel to ensure adequate and continuous chain of custody, storage conditions, and monitoring for investigational product and biological samples. Inability of study monitors and quality personnel to conduct in-person visits to exercise adequate oversight of study execution at investigational sites. Missing data (COVID-19 pandemic may impact study visit schedules and increase missed visits and/or participant study discontinuations inadvertently resulting in missing data [eg, for protocol-specified procedures]).	During the time that the COVID-19 pandemic is active, Alexion will only open study sites that report enough personnel capacity to sufficiently conduct clinical study-related activities. During this timeframe, site capacity will be reviewed by the site Investigator and the study Medical Monitor prior to Screening. Each site is also evaluated for the capacity to perform remote monitoring visits and remote source data verification. During the time that the COVID-19 pandemic is active, it will be important to capture specific information in the eCRF that explains the reason the data is missing (eg, missed study visits or patient study discontinuations due to COVID-19).

Abbreviations: COVID19 = coronavirus disease 2019; eCRF = electronic case report form