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A RANDOMIZED, DOUBLE-BLIND, ACTIVE-CONTROLLED PHASE 3 STUDY EVALUATING THE EFFICACY AND SAFETY OF ABP 959 COMPARED WITH ECULIZUMAB IN ADULT SUBJECTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

Test Drug: ABP 959

Protocol Number: 20150168 **EudraCT number:** 2017-001418-27

Study Phase: 3

Date and Version: **05 March 2020**, version **4.0**

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This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) as set forth in the International Conference for Harmonisation (ICH) guidelines on GCP (ICH E6), and applicable local regulatory requirements.

CONFIDENTIAL

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NCT Number: NCT03818607
This NCT number has been applied to the document for purposes of posting on Clinicaltrials.gov

SIGNATURES

Representatives of Sponsor and Clinical Research Organization

I have read and agree to the protocol, 20150168, titled "A Randomized, Double-blind, Active-controlled Phase 3 Study Evaluating the Efficacy and Safety of ABP 959 Compared With Eculizumab in Adult Subjects With Paroxysmal Nocturnal Hemoglobinuria (PNH)." I am aware of my responsibilities under the guidelines of GCP, local regulations (as applicable), and the study protocol. I agree to conduct the study according to these responsibilities.

Accepted for the Sponsor – Amgen Inc.:

[redacted] | Medical Director, Amgen

Print Name | Title

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Signature | Date

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Approved

Investigator

I have read and agree to the protocol, 20150168, entitled "A Randomized, Double-blind, Active-controlled Phase 3 Study Evaluating the Efficacy and Safety of ABP 959 Compared With Eculizumab in Adult Subjects With Paroxysmal Nocturnal Hemoglobinuria (PNH)." I am aware of my responsibilities as an investigator under the guidelines of GCP, local regulations (as applicable), and the study protocol. I agree to conduct the study according to these responsibilities and to appropriately direct and assist the staff under my control, who will be involved in the study.

Clinical Site: _____

Site Number: _____

Site Principal Investigator:

_____ _____
Print Name Title

_____ _____
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Coordinating Investigator Signature (if applicable):

_____ _____
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2 SYNOPSIS

NAME OF SPONSOR: Amgen Inc.	**PROTOCOL No.:** 20150168
NAME OF STUDY TREATMENT: ABP 959	
TITLE OF STUDY: A Randomized, Double-blind, Active-controlled, Phase 3 Study Evaluating the Efficacy and Safety of ABP 959 Compared With Eculizumab in Adult Subjects With Paroxysmal Nocturnal Hemoglobinuria (PNH)	
STUDY CENTERS: Approximately **45** sites globally	
STUDY PERIODS: Subjects will be treated in 2 study periods. Period 1 will be 52 weeks in duration. Period 2 will be 26 weeks in duration.	**PHASE OF DEVELOPMENT:** Phase 3
PLANNED STUDY DATES: The planned duration of the clinical study is approximately **30** months (approximately **12** months for enrollment and approximately 18 months for treatment), from approximately Q1 2019 to **Q3** 2021.	
OBJECTIVES: **Primary Objective:** The primary objective for this study is to evaluate the efficacy of ABP 959 compared with that of eculizumab based on control of intravascular hemolysis. **Secondary Objective:** The secondary objective is to assess the safety, pharmacokinetics (PK), and immunogenicity of ABP 959 compared with that of eculizumab.	
STUDY DESIGN AND METHODOLOGY: This is a randomized, double-blind, active-controlled, 2-period crossover study in adult subjects with PNH. Approximately 40 subjects will be randomized (1:1) to receive each investigational product (IP) in 1 of 2 sequences, either treatment T followed by treatment R (TR) or treatment R followed by treatment T (RT). Treatment will be administered over 2 periods: Period 1 will be 52 weeks in duration; Period 2 will start at week 53 with a crossover in treatment and will be 26 weeks in duration. Randomization will occur within 8 days before the first dose of IP administration and will be stratified by red blood cell (RBC) transfusion received within the last 12 months before randomization (yes vs no). Period 1 (week 1 to week 53): Treatment T: ABP 959 at a dose of 900 mg intravenously (IV) every 14 ± 2 days for 52 weeks Treatment R: eculizumab at a dose of 900 mg IV every 14 ± 2 days for 52 weeks Period 2: (week 53 to week 79) Treatment T: ABP 959 at a dose of 900 mg IV every 14 ± 2 days for 26 weeks Treatment R: eculizumab at a dose of 900 mg IV every 14 ± 2 days for 26 weeks Subjects may require dose adjustments for IP based on signs and symptoms of intravascular hemolysis, including lactate dehydrogenase (LDH) levels. Upon investigator's determination of resolution of symptoms, subjects should resume the 900 mg dose within the recommended dosing schedule ie, every 14 ± 2 days. If a subject requires extended dose adjustments of IP indicating that the subject is no longer adequately responding to the treatment regimen, the subject will be discontinued from study. Subjects will remain in the treatment phase until 14 days after the last planned dose of IP in Period 2 (ie, at week 79). An independent data monitoring committee (DMC) will evaluate the safety data throughout the study.	

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STUDY POPULATION AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:

INCLUSION CRITERIA:

The study will enroll subjects with PNH who are stable on eculizumab treatment. Subjects cannot be enrolled or randomized before all inclusion criteria (including test results) are confirmed:

1. Men and women ≥ 18 years of age
2. Historical diagnosis of PNH by documented flow cytometry (eg, type III erythrocyte cells ≥ 10%)
3. Administration of eculizumab for ≥ 6 months and currently receiving 900 mg of eculizumab every 14 ± 2 days
4. Hemoglobin ≥ 9.0 g/dL for at least 6 weeks before randomization
5. Lactate dehydrogenase (LDH) < 1.5 × the upper limit of normal at screening
6. Platelet count ≥ 50 × 10^9/L
7. Absolute neutrophil count ≥ 0.5 x 10^9/L (500/μL)
8. Subjects must have been vaccinated against *Neisseria meningitidis*. Subjects must be vaccinated or revaccinated according to current national guidelines for vaccination use.
9. Subjects must sign an institutional review board/independent ethics committee-approved informed consent form before participation in any procedures.

EXCLUSION CRITERIA:

If any of the following apply, the subject **MUST NOT** enter the study:

1. Known or suspected hereditary complement deficiency
2. Clinically significant cardiovascular disease (including myocardial infarction, unstable angina, symptomatic congestive heart failure [New York Heart Association ≥ Class III], serious uncontrolled cardiac arrhythmia), peripheral vascular disease, cerebrovascular accident, or transient ischemic attack in the previous 6 months
3. Evidence of acute thrombosis (liver Doppler ultrasound of hepatic and portal veins)
4. Known to be positive for human immunodeficiency virus
5. Woman who is pregnant or breastfeeding
6. Woman of childbearing potential who does not consent to use a highly effective method of birth control (eg, true abstinence, sterilization, birth control pills, Depo Provera injections, or contraceptive implants) during treatment and for an additional 5 months after the last administration of protocol-specified treatment
7. Man with a partner of childbearing potential who does not consent to use a highly effective method of birth control (eg, true abstinence, vasectomy, or a condom in combination with hormonal birth control or barrier methods used by the woman) during treatment and for an additional 5 months after the last administration of protocol-specified treatment
8. Subject is currently enrolled in or has not yet completed at least 30 days since ending other investigational device or drug study(s), or subject is receiving other investigational agent(s).
9. Subject has known sensitivity to any constituent of the products to be administered during the study, including mammalian cell-derived drug products.
10. History or evidence of clinically significant disorder, condition, or disease that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion
11. History of meningococcal infection
12. Presence or suspicion of active bacterial infection, or recurrent bacterial infection
13. History of bone marrow transplantation
14. Red blood cell transfusion required within 12 weeks before randomization
15. Subject experienced ≥ 2 breakthrough events, (ie, signs and symptoms of intravascular hemolysis, that require dose and/or schedule adjustments of eculizumab) in the previous 12 months before screening.

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NUMBER OF SUBJECTS: Approximately 40 subjects will be randomized 1:1 to 1 of the 2 treatment sequences. The sample size of 40 was chosen to provide approximately 87% power to demonstrate non-inferiority (NI) at a 1-sided significance level of 0.025 on the primary endpoint of week 27 LDH for the parallel comparison, assuming an inter-subject coefficient of variation (CV) of 130% for ABP 959 and eculizumab, a true geometric mean ratio (GMR) of 1 between ABP 959 and eculizumab, a**n** NI margin of 2.873, and a 10% dropout rate. The 2.873 margin is considered appropriate to rule out a potential clinically relevant difference, as it essentially equates to a mean LDH in the ABP 959 arm of less than 1.5-fold of the mean LDH in the eculizumab arm. The sample size of 40 will also provide **greater than 95**% power to demonstrate similarity at a 2-sided significance level of 0.05 on the primary endpoint of time-adjusted area under the effect curve (AUEC) of LDH **from week 13 to week 27, from week 39 to week 53, and from week 65 to week 79** for the crossover comparison, assuming an intra-subject CV of 34%, a true GMR of 1 between ABP 959 and eculizumab, a similarity margin of (0.77, 1.30), and a 10% dropout rate. Blinded assessments of the inter-subject CV of LDH and the intra-subject CV of time-adjusted AUEC of LDH will be performed. If the aggregated intra-subject CV of AUEC is greater than **44**%, additional subjects **will** be enrolled **if feasible**. If the aggregated inter-subject CV of LDH is **greater** than 130%, the primary endpoint of parallel comparison of LDH at week 27 will be replaced by crossover comparison of LDH at week 53 and week 79.

STUDY TREATMENTS:
Test Product, Dose and Mode of Administration:
ABP 959 administered at a dose of 900 mg IV every 14 ± 2 days
Reference Therapy, Dose and Mode of Administration:
Eculizumab administered at a dose of 900 mg IV every 14 ± 2 days

DURATION OF TREATMENT: Study participation consists of a screening period of up to 4 weeks, followed by Period 1 (treatment every 14 ± 2 days for a total of 52 weeks), followed by Period 2 (treatment every 14 ± 2 days for a total of 26 weeks), and an end of study **(EOS)** visit 2 weeks (± 2 days) after the last dose of IP. The total duration of study treatment is up to 78 weeks.

STUDY EVALUATIONS:
Primary Endpoint for Parallel Comparison:
- Hemolysis, as measured by LDH at week 27

Primary Endpoint for Crossover Comparison:
- Hemolysis, as measured by the time-adjusted AUEC of LDH **from week 13 to week 27,** from week 39 to **week** 53**,** and from week 65 to **week** 79

Secondary Endpoints:
- Total complement (CH50), total hemoglobin, serum-free hemoglobin, haptoglobin, bilirubin, degree of hemoglobinuria, and type III erythrocytes at week 27, week 39, week 53, and post-crossover week 65 and week 79
- Crossover comparison of hemolysis as measured by LDH at week 53 and week 79
- Lactate dehydrogenase-time profile
- Red blood cell transfusion
- Pharmacokinetic area under the curve (AUC) of ABP 959 and eculizumab from week 13 to **week** 15, and trough PK

Safety Endpoints:
- Treatment-emergent adverse events
- Treatment-emergent serious adverse events
- Treatment-emergent events of interest (EOIs)
- Incidence of anti-drug antibodies (ADAs)

STATISTICAL METHODS:
The primary analysis of the primary endpoint of week 27 LDH for the parallel comparison will be conducted on the Full Analysis Set (FAS), consisting of all randomized subjects, with treatment as randomized in Period 1 regardless of treatment actually received. Sensitivity analyses, such as per-protocol, will also be performed.

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The clinical similarity of the week 27 LDH between treatments will be assessed by comparing the 1-sided 97.5% upper confidence interval (CI) limit for the GMR of the LDH at week 27 between ABP 959 and eculizumab treatment with an NI margin of 2.873. The point estimate of the mean difference in the log-transformed LDH and the corresponding 1-sided 97.5% upper CI limit will be estimated from a linear mixed effects model with treatment, stratification factor, week 1 LDH value, time (as a continuous variable), and treatment by time interaction term as fixed effects, and subject as a random effect. Lactate dehydrogenase values from all assessed time points from week 13 to week 27 will be included in the mixed model. The point estimate and the upper CI limit for the GMR will then be calculated by transforming back to the original scale.

The primary analysis of the primary endpoint of time-adjusted AUEC of LDH for the crossover comparison will be conducted on the Modified Full Analysis Set (mFAS), consisting of all randomized subjects who have an LDH-time profile evaluable for the time-adjusted AUEC within **at least one of the following 14-week assessment periods: week 13 to week 27,** week 39 to **week** 53**,** and week 65 to **week** 79, according to treatment per the randomized sequence regardless of treatment actually received. Sensitivity analyses, such as per-protocol, will also be performed.

The linear trapezoidal rule will be used to derive the AUEC of LDH **from week 13 to week 27,** from week 39 to **week** 53, and from week 65 to **week** 79 for each subject. The time-adjusted AUEC will be calculated by dividing the AUEC by the total duration of observed LDH data (in weeks) for each individual subject within each 14-week assessment period.

The clinical similarity of the AUEC between treatments will be assessed by comparing the 2-sided 90% CI for the GMR of the time-adjusted AUEC of LDH (**week 13 to week 27,** week 39 to **week** 53, and week 65 to **week** 79) between ABP 959 and eculizumab treatment with a similarity margin of (0.77, 1.30). The point estimate of the mean difference in the log-transformed time-adjusted AUEC and the corresponding 2-sided 90% CI will be calculated from a linear mixed effects model with treatment, stratification factor, **assessment** period, and sequence as fixed effects, and subject as a random effect. The point estimate and CI for the GMR will then be calculated by transforming back to original scale.

The analysis of secondary endpoints (except for PK) will be conducted on the **Full Analysis Set (**FAS**)**. Total complement, total hemoglobin, serum-free hemoglobin, haptoglobin, bilirubin, degree of hemoglobinuria, and type III erythrocytes (%) at weeks 27, 39, 53, 65, and 79 will be summarized descriptively. For the endpoint of RBC transfusions, summary statistics for the number of packed red cells transfused per month after week 13 will be presented. A descriptive summary of LDH at each time point through the EOS visit will be presented. Individual and mean LDH-time profile**s** through **the** EOS visit will also be presented graphically.

The secondary endpoint of crossover comparison of LDH at week 53 and week 79 will be evaluated descriptively. The point estimate of the mean difference in the log-transformed LDH between treatments and the corresponding 1-sided 97.5% upper CI limit will be calculated from a linear mixed effects model with treatment, stratification factor, period, and sequence as fixed effects, and subject as a random effect. The point estimate and 1-sided upper 97.5% CI limit for the GMR will then be calculated by transforming back to original scale.

The PK Concentration Analysis Set will be defined as the subset of subjects in the Safety Analysis Set who have at least 1 serum concentration of ABP 959 or eculizumab. Serum ABP 959 and eculizumab trough concentrations will be summarized descriptively on the PK Concentration Analysis Set for the study through the EOS visit by actual treatment (ABP 959 or eculizumab) and by visit within each period.

The PK Parameter Analysis Set will be defined as the subset of subjects in the Safety Analysis Set who have an evaluable ABP 959 or eculizumab serum concentration-time profile from week 13 to **week** 15. Pharmacokinetic AUC from week 13 to **week** 15 will be analyzed on the PK Parameter Analysis Set according to the actual treatment received with GMR and 90% CI provided descriptively.

Safety will be assessed for the study through the EOS visit in the Safety Analysis Set, consisting of all treated subjects with treatment assignment based on actual treatment received. Safety

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endpoints will be summarized descriptively. All reported adverse events will be assigned the system organ class and preferred term according to the Medical Dictionary for Regulatory Activities and graded by the National Cancer Institute (US) Common Terminology Criteria for Adverse Events, version 5.0. The number and percentage of subjects reporting adverse events (all, serious, and fatal) and EOIs will be tabulated by treatment (ABP 959 vs eculizumab) for the study through the EOS visit, for each study period, and for each **14-week assessment** period (ie, **week 13 to week 27,** week 39 to **week** 53**,** and week 65 to **week** 79). Vital signs and laboratory data will also be summarized similarly by visit and treatment. The number and percentage of subjects developing ADAs will be tabulated by visit and treatment (ABP 959 vs eculizumab) for Period 1 and by treatment sequence for the study through the EOS visit using the Safety Analysis Set.

Independent safety reviews will be performed by the DMC approximately every 6 months throughout the study. Blinded study data will also be monitored on an ongoing basis by the clinical study team.

DATE AND VERSION: 05 March 2020, version 4.0

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
ADA	anti-drug antibody
ANC	absolute neutrophil count
AUC	area under the curve
AUEC	area under the effect curve
BP	blood pressure
BUN	**blood urea nitrogen**
CFR	Code of Federal Regulations
CI	confidence interval
CRO	clinical research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DMC	data monitoring committee
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EOI	event of interest
EOS	end of study
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GMR	geometric mean ratio
HRT	hormonal replacement therapy
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
Ig	Immunoglobulin
IP	investigational product
INR	international normalized ratio
IRB	institutional review board
IV	intravenous
IXRS	interactive voice and web response system
LDH	lactate dehydrogenase

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Term	**Definition**
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified full analysis set
NCI	National Cancer Institute
NI	non-inferiority
PD	pharmacodynamic(s)
PIN	**Personal Identification Number**
PK	pharmacokinetic(s)
PNH	paroxysmal nocturnal hemoglobinuria
PPC	per-protocol (crossover comparison)
PPP	per-protocol (parallel comparison)
RBC	red blood cell
SAP	Statistical Analysis Plan
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
US/USA	United States of America
WHO	World Health Organization
WOCBP	woman of childbearing potential

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5 ETHICS

5.1 Ethics Committee

This study will be conducted in compliance with institutional review board (IRB)/independent ethics committee (IEC) and International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines - including Title 21 Part 56 of the United States (US) Code of Federal Regulations (CFR) relating to IRBs/IECs and GCP as described in the US Food and Drug Administration (FDA) CFR (21 CFR § 50, 56, 312) - in accordance with applicable ICH regulations regarding clinical safety data management (E2A, E2B[R3]), European Community directives 2001/20, 2001/83, 2003/94, and 2005/28 as enacted into local law, and with ICH guidelines regarding scientific integrity (E4, E8, E9, and E10). In addition, this study will adhere to all local regulatory requirements and requirements for data protection.

Before initiating a trial/study, the investigator/institution must have written and dated approval/favorable opinion from the IRB/IEC for the study protocol/amendment(s), a written informed consent form (ICF), any consent form updates, subject recruitment procedures (eg, advertisements), any written information to be provided to subjects, and a statement from the IRB/IEC that these materials comply with GCP requirements. The IRB/IEC approval must identify the protocol version as well as the documents reviewed.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with the Note for Guidance on GCP (ICH Harmonised Tripartite Guideline E6 (R1); FDA CFR (21 CFR § 50, 56, 312)), the general principles indicated in the Declaration of Helsinki, and all applicable regulatory requirements.

5.3 Subject Information and Consent

The investigator will explain the benefits and risks of participation in the study to each subject or the subject's legally acceptable representative and obtain written informed consent. Written informed consent must be obtained prior to the subject entering the study and before initiation of any study-related procedure (including administration of investigational product [IP]).

The sponsor will provide a sample ICF, based on the elements of informed consent in Section 17.1. The final version-dated form must be agreed to by the sponsor and the IRB/IEC and will contain all elements in the sample form, in language readily understood by the subject. Each subject's original consent form, personally signed

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and dated by the subject or by the subject's legally acceptable representative and by the person who conducted the informed consent discussion, will be retained by the investigator. The investigator will supply all enrolled subjects with a copy of their signed ICF.

The ICF may need to be revised during the study should important new information become available that may be relevant to the safety of the subject. In this instance, approval should always be given by the IRB/IEC, and existing subjects should always be informed of the changes and re-consented. This is documented in the same way as previously described.

The investigator should, with the consent of the subject, inform the subject's primary physician about participation in the clinical study as needed.

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6 INTRODUCTION

6.1 Disease Review

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, life-threatening, bone marrow disorder characterized by intravascular hemolytic anemia, bone marrow failure, and thrombo-embolic episodes, and is associated with a significant increase in mortality, development of arterial and venous thrombo-embolic episodes, visceral organ damage, and rapid deterioration in quality of life (Kelly et al, 2009; Hill et al, 2007; Hillmen et al, 2006; Rother et al, 2005). The disease is caused by the expansion of a clone of hematopoietic cells lacking glycosylphosphatidylinositol-anchored membrane proteins (eg, CD 55 and CD 59), which leads to chronic, complement-mediated intravascular hemolysis. The clinical symptoms of the chronic complement activity and hemolysis include abdominal pain, chest pain, dyspnea, and hemoglobinuria, and life-threatening complications include thromboembolism, pulmonary hypertension, and impaired renal function (Hill et al, 2007). Laboratory evidence of intravascular hemolysis includes high lactate dehydrogenase (LDH) and bilirubin, and low or undetectable serum haptoglobin. Lactate dehydrogenase is a sensitive biochemical marker of intravascular hemolysis and can be more than 25 times the normal concentration during periods of severe hemolysis (Rother et al, 2005).

6.2 Eculizumab

Eculizumab, the active ingredient in Soliris® (Alexion Pharmaceuticals), is a monoclonal antibody that specifically binds with high affinity to the complement protein C5, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9. Eculizumab inhibits terminal complement-mediated intravascular hemolysis in patients with PNH, atypical hemolytic uremic syndrome, and refractory generalized myasthenia gravis (Soliris® Summary of Product Characteristics, 2018).

6.3 Compound Review

ABP 959 is being developed as a biosimilar to Soliris® (eculizumab), for the treatment of PNH and other indications. The active ingredient of ABP 959 is an anti-C5 monoclonal antibody that has the same amino acid sequence as eculizumab and equivalent nonclinical pharmacologic function, based on comprehensive bioanalytical assays. ABP 959 has the same pharmaceutical form, dosage strength, route of administration, and dosing regimen as US- and European Union (EU)-licensed eculizumab.

Refer to the investigator's brochure for additional information.

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6.4 Study Rationale

The similarity of ABP 959 to eculizumab has been shown using bioanalytical methods and nonclinical studies (refer to the investigator's brochure for additional information). As outlined in the guideline on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010), applicants are expected to provide data on similarity of pharmacokinetics/pharmacodynamics (PK/PD), safety, and efficacy.

In the US, EU, and much of the world, laws, regulations, and guidances have been or are being put in place to increase availability of biological treatments by developing and licensing biosimilar products (CHMP/437/04 Rev 1; EMEA/CHMP/BWP/247713/2012; EMEA/CHMP/BMWP/42832/2005 Rev 1; US FDA 2012a; US FDA 2012b). A biosimilar product, generally, is one that is highly similar to a licensed biologic reference product notwithstanding minor differences in clinically inactive components, and there are no clinically relevant differences between the biosimilar and reference product in terms of safety, purity, and potency. Biosimilarity is demonstrated by the totality of the evidence, including quality, nonclinical, and clinical evidence. The quality and nonclinical data for ABP 959 and eculizumab are summarized in the investigator's brochure. The current study is designed to demonstrate that there is no clinically relevant difference between ABP 959 and eculizumab in terms of efficacy, PD, PK, safety, and immunogenicity in adult subjects with PNH.

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7 STUDY OBJECTIVES

7.1 Primary Study Objective

The primary objective for this study is to evaluate the efficacy of ABP 959 compared with that of eculizumab, based on control of intravascular hemolysis.

7.2 Secondary Study Objective

The secondary objective is to assess the safety, PK, and immunogenicity of ABP 959 compared with that of eculizumab.

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8 INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan

This is a randomized, double-blind, active-controlled, 2-period crossover study in adult subjects with PNH.

The study will be run in approximately **45** sites globally.

Approximately 40 subjects will be randomized (1:1) to 1 of the 2 treatment sequences, either treatment T followed by treatment R (TR) or treatment R followed by treatment T (RT). Treatments will be administered over 2 periods. Period 1 will be 52 weeks in duration; Period 2 will start at week 53, with a crossover in treatment, and will be 26 weeks in duration. Randomization will occur within 8 days before the first dose of IP administration **(defined as day 1)** and will be stratified by red blood cell (RBC) transfusion received within the last 12 months before randomization (yes vs no).

The treatment sequences will be as shown in Figure 1:

Sequence TR: ABP 959 for 52 weeks in Period 1 followed by eculizumab for 26 weeks in Period 2, each at a dose of 900 mg administered as an intravenous (IV) infusion every 14 ± 2 days

Sequence RT: Eculizumab for 52 weeks in Period 1 followed by ABP 959 for 26 weeks in Period 2, each at a dose of 900 mg administered as an IV infusion every 14 ± 2 days.

Subjects will remain on the treatment phase until 14 days after the last planned dose of IP in Period 2 (ie, at week 79).

An independent data monitoring committee (DMC) will perform safety reviews approximately every 6 months throughout the study (Section 12.6.8). Blinded study data will also be monitored on an ongoing basis by the clinical study team.

The study endpoints will be analyzed as described in Section 12.6.

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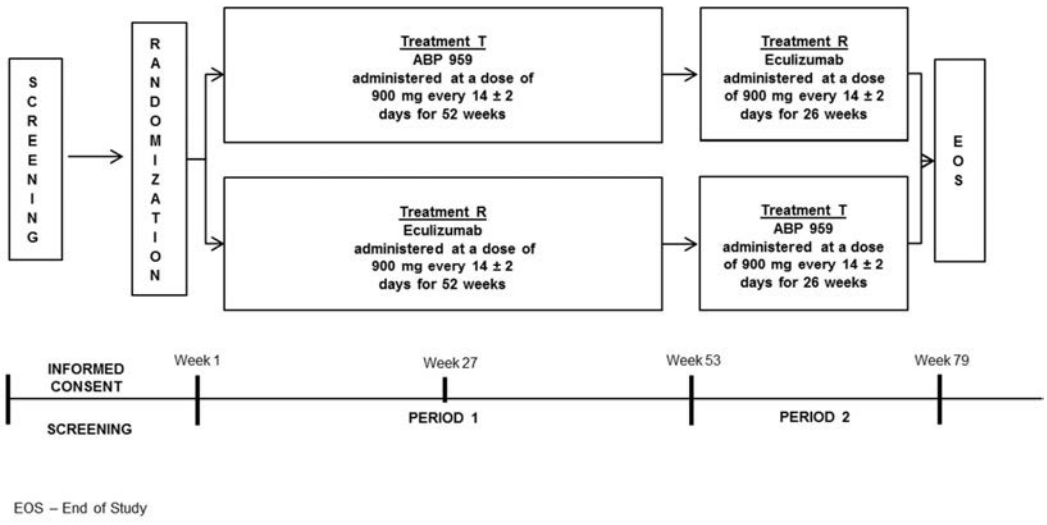
Figure 1. Study Diagram



EOS – End of Study

8.2 Discussion of Study Design

This study is randomized to prevent bias in treatment sequence allocation. The assessment of the primary endpoint for the parallel comparison of the study will be based on LDH at week 27, and the assessment of the primary endpoint for the crossover comparison will be based on **the** time-adjusted area under the effect curve (AUEC) of LDH **from week 13 to week 27,** from week 39 to **week** 53**,** and from week 65 to **week** 79. The primary analysis for the parallel comparison of the study will be performed when the last subject has completed or has had the chance to complete the week 53 evaluations. The primary analysis for the crossover comparison of the study will be performed when the last subject has completed the week 79 evaluations.

8.3 Study Duration

Study participation consists of a screening period of up to 4 weeks, followed by Period 1 (treatment every 14 ± 2 days for a total of 52 weeks), followed by Period 2 (treatment every 14 ± 2 days for a total of 26 weeks), and an end of study (EOS) visit, 2 weeks after the last dose of IP. The total duration of study treatment is up to 78 weeks.

The planned duration of the clinical study is approximately **30** months (approximately **12** months for enrollment and approximately 18 months for treatment), from approximately Q1 2019 to **Q3** 2021.

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8.3.1 End of Study Definition

The end of the study will be defined as the date the last subject completes the week 79 visit or the date of the last subject's last completed scheduled procedure.

8.4 Study Population

8.4.1 Inclusion Criteria

The study will enroll subjects with PNH who are stable on eculizumab treatment.

Subjects cannot be enrolled or randomized before all inclusion criteria (including test results) are confirmed:

1. Men and women ≥ 18 years of age
2. Historical diagnosis of PNH by documented flow cytometry (eg, type III erythrocyte cells of ≥ 10%)
3. Administration of eculizumab for ≥ 6 months and currently receiving 900 mg of eculizumab every 14 ± 2 days
4. Hemoglobin ≥ 9.0 g/dL for at least 6 weeks before randomization
5. Lactate dehydrogenase < 1.5 × the upper limit of normal at screening
6. Platelet count ≥ 50 × 10^9/L
7. Absolute neutrophil count (ANC) ≥ 0.5 x 10^9/L (500/µL)
8. Subjects must have been vaccinated against *Neisseria meningitidis*. Subjects must be vaccinated or revaccinated according to current national guidelines for vaccination use.
9. Subjects must sign an IRB/IEC-approved ICF before participation in any procedures.

8.4.2 Exclusion Criteria

If any of the following apply, the subject **MUST NOT** enter the study:

1. Known or suspected hereditary complement deficiency
2. Clinically significant cardiovascular disease (including myocardial infarction, unstable angina, symptomatic congestive heart failure [New York Heart Association ≥ Class III], serious uncontrolled cardiac arrhythmia), peripheral vascular disease, cerebrovascular accident, or transient ischemic attack in the previous 6 months
3. Evidence of acute thrombosis (liver Doppler ultrasound of hepatic and portal veins)
4. Known to be positive for human immunodeficiency virus
5. Woman who is pregnant or breastfeeding
6. Woman of childbearing potential (WOCBP) who does not consent to use a highly effective method of birth control (eg, true abstinence, sterilization, birth control pills, Depo Provera injections, or contraceptive implants) during treatment and for an additional 5 months after the last administration of protocol-specified treatment

   WOCBP is defined as a woman who is fertile, following menarche, and until becoming postmenopausal unless permanently sterile. Permanent sterilization

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methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

7. Man with a partner of childbearing potential who does not consent to use a highly effective method of birth control (eg, true abstinence, vasectomy, or a condom in combination with hormonal birth control or barrier methods used by the woman) during treatment and for an additional 5 months after the last administration of protocol-specified treatment
8. Subject is currently enrolled in or has not yet completed at least 30 days since ending other investigational device or drug study(s), or subject is receiving other investigational agent(s).
9. Subject has known sensitivity to any constituent of the products to be administered during the study, including mammalian cell-derived drug products.
10. History or evidence of clinically significant disorder, condition, or disease that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion
11. History of meningococcal infection
12. Presence or suspicion of active bacterial infection, or recurrent bacterial infection
13. History of bone marrow transplantation
14. Red blood cell transfusion required within 12 weeks before randomization
15. Subject experienced ≥ 2 breakthrough events, (ie, signs and symptoms of intravascular hemolysis, that require dose and/or schedule adjustments of eculizumab) in the previous 12 months before screening.

8.4.3 Withdrawal and Replacement of Subjects

8.4.3.1 Criteria for Subject Withdrawal

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to future medical care by the physician or at the institution.

Subjects (or a legally acceptable representative) can decline to continue receiving IP and/or other protocol-required procedures at any time during the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation of treatment with the IP. Additionally, the subject should be followed and complete the EOS visit, 2 weeks (± 2 days) after the last dose of IP and prior to starting commercial eculizumab or other PNH treatment.

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Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and, where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

Reasons for removal of a subject from the study might include:

- Worsening of PNH
- Subject request to end IP(s) administration
- Safety concern (eg, due to an adverse event, failure to follow contraception requirements, and/or noncompliance with protocol requirements)
- Pregnancy
- Withdrawal of consent to participate in study
- Meningococcal infection
- Decision by sponsor

8.4.3.2 Evaluations at Withdrawal

For any subject who is withdrawn before completing all treatment visits, the investigator should do all of the following:

- Perform all procedures scheduled for the EOS visit (ie, week 79 visit [Section 9.4.2]). These assessments will be performed 2 weeks (± 2 days) after the last dose of IP (unless the subject withdraws consent to do so).
- Complete all appropriate electronic case report form (eCRF) screens, providing the date of and explanation for the subject's withdrawal/discontinuation.
- If a subject discontinues IP and will not receive commercial eculizumab, or another PNH treatment, the subject will be monitored for at least 8 weeks to detect serious hemolysis and other reactions as detailed in Section 9.4.2.

8.4.3.3 Replacement of Subjects

Subjects who are withdrawn will not be replaced.

8.5 Treatment

8.5.1 Treatments Administered

The investigator must ensure that the IP will be used only in accordance with the protocol. ABP 959 and eculizumab will be considered the IPs.

Subjects will be randomly assigned to 1 of 2 treatment sequences in a 1:1 ratio. Treatments will be administered over 2 periods: Period 1 will be 52 weeks in duration; Period 2 will start at week 53 with a crossover in treatment and will be 26 weeks in duration. Randomization will be stratified by RBC transfusion received within the last 12 months before randomization (yes vs no).

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Investigational product will be administered after all other procedures have been completed for each visit.

Investigational product will be administered according to local practice for administration of eculizumab therapy, ie, as an IV infusion over 25 to 45 minutes. Investigational product must not be administered as an IV push or bolus.

Subjects should be monitored for 1 hour following the IP infusion. If an adverse event occurs during the administration of IP, the infusion may be slowed or stopped at the discretion of the investigator. If the infusion is slowed, the total infusion time may not exceed 2 hours.

As with all protein products, administration of IP may result in infusion reactions, including anaphylaxis or other hypersensitivity reactions. In clinical trials of eculizumab, no subjects experienced an infusion reaction that required discontinuation. Hypersensitivity reactions should be managed according to institutional guidelines.

Subjects should be educated about the signs and symptoms of meningococcal infection and strongly advised to seek immediate medical attention if any of these signs or symptoms occur. These signs and symptoms are as follows:

- Moderate to severe headache with:
  - nausea or vomiting
  - fever
  - stiff neck or stiff back
- Fever of 103°F (39.4°C) or higher
- Fever and a rash
- Confusion
- Severe muscle aches with influenza-like symptoms and eyes sensitive to light

Subjects will be provided with a Patient Safety Card, which they will be instructed to carry with them at all times. This card describes symptoms that, if experienced, should prompt the subject to immediately seek medical evaluation.

Subjects will be discontinued from the study and treated per standard of care if they develop a meningococcal infection or become pregnant.

Additionally, subjects may experience increased signs and symptoms of PNH, such as hemolysis when subjects are revaccinated against *Neisseria meningitidis*. Therefore, subjects should be closely monitored for disease symptoms after recommended vaccination.

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Refer to the investigator's brochure for ABP 959 or the package insert or Summary of Product Characteristics for eculizumab to obtain additional information regarding the IPs.

8.5.2 Study Treatment Formulation

8.5.2.1 Study Drug

The test product, ABP 959, is a humanized recombinant immunoglobulin (Ig)G2/4 monoclonal antibody that binds to the human C5 complement protein. ABP 959 has the identical amino acid sequence as eculizumab. Both ABP 959 and eculizumab are produced by recombinant DNA technology and are purified by a process that includes specific viral inactivation and filtration steps. ABP 959 is expressed in a Chinese hamster ovary cell line system and has a molecular weight of 148 kilodaltons.

ABP 959 is supplied as a sterile, clear, colorless, preservative-free 10-mg/mL solution for IV infusion in 30-mL single-use vials. Each sterile vial contains 30 mL deliverable volume of 10 mg/mL ABP 959 formulated in 10 mM acetate, 5% sorbitol, 0.01% polysorbate 80, at pH 5.2.

8.5.2.2 Comparator

Eculizumab is a genetically engineered chimeric murine/human monoclonal IgG1-kappa antibody directed against the complement protein C5. Eculizumab has an approximate molecular weight of 148 kilodaltons, is produced by murine myeloma cell culture, and is purified by standard bioprocess technology.

Eculizumab is supplied as a sterile, clear, colorless, preservative-free liquid concentrate for IV administration and is supplied at a concentration of 10 mg/mL in 30-mL single-use vials. The product is formulated at pH 7, and each vial contains 300 mg eculizumab, sodium phosphate monobasic (0.46 mg/mL), sodium phosphate dibasic (1.78 mg/mL), sodium chloride (8.77 mg/mL), polysorbate 80 (0.22 mg/mL), and Water for Injection.

8.5.3 Study Treatment Labeling and Packaging

A manual containing detailed information regarding the labeling, packaging, storage, preparation, and administration of each IP is provided separately in the Pharmacy Guide.

8.5.4 Blinding of Study Medication

This is a double-blind study. Since the IP containers are different for ABP 959 and eculizumab, IP (ABP 959 or eculizumab) will be prepared by an unblinded pharmacist, or designee, into a common IV preparation for administration to the subject. Subjects, Amgen, designated PRA, and other clinical site staff will be blinded

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to the IP allocation for each subject. Select PRA staff (eg, clinical research associate), not involved in the monitoring or the daily operations of the study, will be unblinded to subject IP allocation in order to perform IP accountability.

At randomization, randomization numbers will be assigned to each subject by the interactive voice and web response system (IXRS). ABP 959 and eculizumab will be provided for IV infusion in 30-mL single-use vials identified by codes that can only be broken in the case of emergency unblinding (Section 8.5.10).

8.5.5 Study Treatment Storage and Accountability

It is forbidden to use IP for purposes other than as defined in this protocol.

8.5.5.1 Study Treatment Storage

ABP 959 and eculizumab vials should be stored in a secure limited-access location, protected from direct sunlight at 2°C to 8°C, and according to the storage and expiration information (where required) provided on the label that is affixed to the package containing the IP. Do not freeze or shake.

8.5.5.2 Study Treatment Accountability

All supplies of IPs will be accounted for in accordance with GCP. There will be an individual study drug accountability record for each subject, and the pharmacist, or designee, should maintain accurate records of the disposition of all IP supplies received during the study. These records should include the amounts and dates clinical drug supplies were received and destroyed/returned to Amgen or its designee. If errors or damages in the clinical drug supply shipments occur, the investigator should contact Amgen or its designee immediately. The study monitor will periodically check the supplies of IP held by the investigator or pharmacist to verify accountability of the IP used. Copies of the IP accountability records will be provided by each investigator for inclusion in the Trial Master File during and at the end of the trial.

The investigator will administer the medication only to the identified subjects of this study, according to the procedures described in this study protocol. After the end of the study, all unused medication and all medication containers should be destroyed on site or returned to Amgen or its designee, as appropriate, for destruction. In either instance, complete documentation will be returned to the sponsor.

8.5.6 Dose Adjustments and Dose Escalation

Subjects may require dose adjustments for IP based on signs and symptoms of intravascular hemolysis, including LDH levels. Upon investigator's determination of resolution of symptoms, subjects should resume the 900 mg dose within the recommended dosing schedule, ie, every 14 ± 2 days. If a subject requires extended

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dose adjustments of IP indicating that the subject is no longer adequately responding to the treatment regimen, the subject will be discontinued from the study.

If any scheduled dose of IP is delayed from the scheduled visit date (by more than 2 days), then the dose will be administered as soon as possible, and subsequent doses will be adjusted accordingly to remain every 14 days (± 2 days) from the adjusted dose date.

Administration of IP (ABP 959 or eculizumab) will be withheld for any subject who experiences a Grade 3 or 4 adverse event per the National Cancer Institute (NCI; US) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, reported by the investigator as related to IP. Re-exposure to IP may occur only when the event resolves to ≤ Grade 1 or the subject's baseline and if the investigator and Amgen, or its designee, agree that subject safety will not be compromised.

Subjects are to be discontinued from the study and treated per standard of care if they develop a meningococcal infection or become pregnant.

8.5.7 Prior and Concomitant Therapy

Any experimental (biological or non-biological) therapy (within or outside a clinical study) is prohibited at any time during the study.

Excessive vitamin C intake, ie, more than 2000 mg a day, and intravenous immunoglobulin treatment are prohibited at any time during the study.

Subjects taking erythropoietin and/or immunosuppressants, corticosteroids, low molecular weight heparin, iron supplements, and/or folic acid must be on a stable dose, and the dose must be expected to remain stable during the treatment periods.

Subjects taking anticoagulants must be at a stable international normalized ratio (INR) level and are expected to maintain a stable INR level during the treatment periods.

Any non-experimental, prescribed therapy**, including prophylactic antibiotics,** that is considered necessary for the subject's welfare may be given at the discretion of the investigator.

All subjects who prematurely discontinue treatment with the IP should be offered alternative treatment if applicable. Treatment should be given according to normal clinical practice, after EOS assessments have been performed.

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8.5.8 Treatment Compliance

IP will be administered by site staff and recorded in the eCRF and subject records. No other measures of compliance are required. Records of IP used and intervals between visits will be kept during the study. Drug accountability will be noted by the study monitor during study center visits and at the completion of the study. An up-to-date treatment inventory/dispensing record must be maintained.

8.5.9 Assignment to Treatment

When subjects enter the screening period for the study, the investigator (or designee) will contact the IXRS and receive a unique 11-digit subject identification number before any study procedures are performed. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. Unique 11-digit subject identification numbers will be assigned in sequential order for each site in the format 168XXXXX###, where "168XXXXX" refers to the site number, and "###" refers to the sequential subject ordering as each subject at a site is entered into the IXRS (eg, 16812345001). Signing of the ICF establishes entry into the screening period.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed at the time of rescreening, enrollment, or randomization. This number will not necessarily be the same as the randomization number assigned for the study.

Upon completion of screening and confirmation of eligibility, the investigator (or designee) will contact the IXRS to randomize the subject centrally to 1 of the 2 treatment sequences (Figure 1). Randomization will occur within 8 days before the first dose of IP administration and will be stratified by RBC transfusion received within the last 12 months before randomization (yes vs no).

8.5.10 Unblinding Procedures

A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject. Unblinding at the study site for any other reason will be considered a protocol deviation. The investigator is strongly encouraged to contact the PRA or Amgen Medical Monitor (or designee) before unblinding any subject's treatment assignment but must do so within 1 working day after the event.

The identity of IP assigned to subject numbers or to individual boxes of IP will be available for emergency situations through the IXRS. Authorized site staff will be provided with a unique Personal Identification Number (PIN) to access the IXRS to

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obtain unblinding information. This PIN is unique to the individual and must not be shared.

8.6 Efficacy and Safety Variables

8.6.1 Efficacy and Safety Measurements Assessed

Schedules of assessments and procedures are provided in Table 1 and Table 2 for Period 1, and Table 3 for Period 2.

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Table 1. Schedule of Assessments and Procedures – Screening to Period 1 Week 25

	Screen	Baseline		Period 1 Treatment Phase [a]											
	(≤ 28 days)	Visit 1 Week 1	Visit 2 Wk 3	Visit 3 Wk 5	Visit 4 Wk 7	Visit 5 Wk 9	Visit 6 Wk 11	Visit 7 Wk 13	Visit 7a Wk 14	Visit 8 Wk 15	Visit 9 Wk 17	Visit 10 Wk 19	Visit 11 Wk 21	Visit 12 Wk 23	Visit 13 Wk 25
General Assessments															
Informed consent	X														
Medical and medication history	X														
Physical examination	X [b]														
Vital signs [c]	X	X	X	X	X	X	X	X		X	X	X	X	X	X
Concomitant medication	X [d]	X	X	X	X	X	X	X		X	X	X	X	X	X
Adverse event recording	X [e]	X	X	X	X	X	X	X		X	X	X	X	X	X
Blood transfusion data collection		X	X	X	X	X	X	X		X	X	X	X	X	X
Treatments															
ABP 959/eculizumab dose [f]		X	X	X	X	X	X	X		X	X	X	X	X	X
Laboratory Assessments															
Serum chemistry [g, h]	X	X [i]	X		X			X		X		X			X
Hematology [g, j]	X	X [i]	X		X			X		X		X			X
Hemolysis-related tests [k]		X [i]	X		X			X							
Coagulation [g,l]	X														
C-reactive protein [p]		X[p]	(X)[p]	(X)[p]	(X)[p]	(X)[p]	(X)[p]	(X)[p]	(X)[p]	(X)[p]	(X)[p]	(X)[p]	(X)[p]	(X)[p]	(X)[p]
Hemoglobinuria [m]		X [i]	X		X			X				X			X
Total complement (CH50)		X [i]	X		X			X				X			X
Pregnancy [n]	X														
Liver Doppler ultrasound	X														
Pharmacokinetic sampling [o]		X	X		X			X, X [o]	X[o]	X		X			X
Anti-drug antibodies [o]		X	X		X			X				X			X

BUN = blood urea nitrogen; IP = investigational product; Wk = week.

[a] All visits can be conducted in a ± 2-day window.

[b] Physical examination includes height and weight at screening.

[c] Vital signs include pulse, respiratory rate, temperature, and blood pressure (BP). Systolic and diastolic BP will be measured on the same arm (preferentially the left arm) after the subject has been in a supine/sitting position for 5 minutes.

[d] At the screening assessment, all concomitant medications from 3 months before the planned start of study treatment will be recorded.

[e] Only serious adverse events that occur from the time of signed informed consent until day 1 will be reported.

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[f] ABP 959/eculizumab dose to be administered after all assessments are completed for each visit. If a dose is delayed from the scheduled visit date (by > 2 days), the dose will be administered as soon as possible, and subsequent doses will be adjusted accordingly to remain every 14 ± 2 days from the adjusted dose date.

[g] Clinical laboratory and pregnancy tests will be performed at local laboratories for screening. Clinical laboratory tests will be performed at central laboratories for all visits after screening, including additional and repeat laboratory safety testing that may be performed at the discretion of the investigator.

[h] Serum chemistry will include sodium, potassium, BUN/urea, creatinine, total protein, albumin, total and direct bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, non-fasting glucose, and uric acid. Haptoglobin will also be assessed.

[i] Serum chemistry, hematology, hemolysis-related tests, hemoglobinuria, and total complement for the baseline visit can be performed up to 3 days prior to the baseline visit (visit 1, week 1).

[j] Hematology assessment will include complete blood count, which will include hemoglobin, packed cell volume, red blood cell count, white blood cell count, absolute neutrophil count, and platelet count.

[k] Hemolysis-related laboratory tests will include type III cells (erythrocytes, monocytes, and granulocytes), and serum-free hemoglobin.

[l] Coagulation assessment will include prothrombin time and international normalized ratio.

[m] Urine samples will be tested for the presence of hemoglobin. Subjects will be requested to collect the first urine void on the morning of each visit.

[n] Serum or urine pregnancy tests will be conducted only for women of childbearing potential and will be performed at local laboratories.

[o] Pharmacokinetic (PK) and anti-drug antibody (ADA) samples will be shipped to a central laboratory. Both samples should be taken immediately prior to administration of IP. Details will be provided in a laboratory manual. Subjects with positive ADA results will be assessed for neutralizing antibodies. At visit 7 (week 13) a postinfusion- PK serum sample will be collected immediately after the end of infusion, as indicated by the X. A PK serum sample will also be collected 7 days (± 2 days) **following the visit 7 (week 13)** dosing **and is noted above as** visit 7a (week 14).

[p] Collection of C-reactive protein will be completed at visit 1 and during each breakthrough event as indicated by the (X).

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Table 2. Schedule of Assessments and Procedures – Period 1 Week 27 to Week 53

	Period 1 Treatment Phase [a]													
	Visit 14 Wk 27	Visit 15 Wk 29	Visit 16 Wk 31	Visit 17 Wk 33	Visit 18 Wk 35	Visit 19 Wk 37	Visit 20 Wk 39	Visit 21 Wk 41	Visit 22 Wk 43	Visit 23 Wk 45	Visit 24 Wk 47	Visit 25 Wk 49	Visit 26 Wk 51	Visit 27 Wk 53
General Assessments														
Physical examination	X													X
Vital signs [b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood transfusion data collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Treatments														
ABP 959/eculizumab dose [c]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory Assessments														
Serum chemistry [d, e]	X	X		X			X	X	X	X	X	X	X	X
Hematology [d, f]	X	X		X			X	X	X	X	X	X	X	X
Hemolysis-related tests [g]	X						X							X
C-reactive protein [j]	(X)[j]	(X)[j]	(X)[j]	(X)[j]	(X)[j]	(X)[j]	(X)[j]	(X)[j]	(X)[j]	(X)[j]	(X)[j]	(X)[j]	(X)[j]	(X)[j]
Hemoglobinuria [h]	X			X			X			X			X	X
Total complement (CH50)	X			X			X			X			X	X
Pharmacokinetic sampling [i]	X			X			X			X			X	X
Anti-drug antibodies [i]	X			X			X			X			X	X

BUN = blood urea nitrogen; IP = investigational product; Wk = week.

[a] All visits can be conducted in a ± 2-day window.

[b] Vital signs include pulse, respiratory rate, temperature, and blood pressure (BP). Systolic and diastolic BP will be measured on the same arm (preferentially the left arm) after the subject has been in a supine/sitting position for 5 minutes.

[c] ABP 959/eculizumab dose to be administered after all assessments are completed for each visit. If any scheduled dose is delayed from the scheduled visit date (by more than 2 days), the dose will be administered as soon as possible, and subsequent doses will be adjusted accordingly to remain every 14 ± 2 days from the adjusted dose date.

[d] Clinical laboratory tests will be performed at central laboratories, including additional and repeat laboratory safety testing that may be performed at the discretion of the investigator.

[e] Serum chemistry will include sodium, potassium, BUN/urea, creatinine, total protein, albumin, total and direct bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, non-fasting glucose, and uric acid. Haptoglobin will also be assessed.

[f] Hematology assessment will include complete blood count, which will include hemoglobin, packed cell volume, red blood cell count, white blood cell count, absolute neutrophil count, and platelet count.

[g] Hemolysis-related laboratory tests will include type III cells (erythrocytes, monocytes, and granulocytes) and serum-free hemoglobin.

[h] Urine samples will be tested for the presence of hemoglobin. Subjects will be requested to collect the first urine void on the morning of each visit.

[i] Pharmacokinetic and anti-drug antibody (ADA) samples will be shipped to a central laboratory. Both samples should be taken immediately prior to administration of IP. Details will be provided in a laboratory manual. Subjects with positive ADA results will be assessed for neutralizing antibodies.

[j] Collection of C-reactive protein is to be completed during each breakthrough event as indicated by the (X).

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Table 3. Schedule of Assessments and Procedures – Period 2 Week 53 to End of Study Visit (Week 79)

	Period 2 Treatment Phase [a]													EOS[l]
	Visit 27 Wk 53	Visit 28 Wk 55	Visit 29 Wk 57	Visit 30 Wk 59	Visit 31 Wk 61	Visit 32 Wk 63	Visit 33 Wk 65	Visit 34 Wk 67	Visit 35 Wk 69	Visit 36 Wk 71	Visit 37 Wk 73	Visit 38 Wk 75	Visit 39 Wk 77	Visit 40 Wk 79
General Assessments														
Physical examination														X
Vital signs [b]		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event recording		X	X	X	X	X	X	X	X	X	X	X	X	X
Blood transfusion data collection		X	X	X	X	X	X	X	X	X	X	X	X	X
Treatments														
ABP 959/eculizumab dose[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory Assessments														
Serum chemistry [d, e]		X		X			X	X	X	X	X	X	X	X
Hematology [d, f]		X		X			X	X	X	X	X	X	X	X
Hemolysis-related tests [g]		X		X			X							X
C-reactive protein [k]		(X)[k]	(X)[k]	(X)[k]	(X)[k]	(X)[k]	(X)[k]	(X)[k]	(X)[k]	(X)[k]	(X)[k]	(X)[k]	(X)[k]	(X)[k]
Hemoglobinuria [h]		X		X			X			X			X	X
Pregnancy [j]														X
Total complement (CH50)		X		X			X			X			X	X
Pharmacokinetic sampling[i]		X		X			X			X			X	X
Anti-drug antibodies [i]		X		X			X			X			X	X

BUN = blood urea nitrogen; EOS = end of study**; IP = investigational product**; Wk = week.

[a] All visits can be conducted in a ± 2-days window.

[b] Vital signs will include pulse, respiratory rate, temperature, and blood pressure (BP). Systolic and diastolic BP will be measured on the same arm (preferentially the left arm) after the subject has been in a supine/sitting position for 5 minutes.

[c] ABP 959/eculizumab dosing to be administered after all assessments are completed for each visit. If any scheduled dose of **IP** is delayed from the scheduled visit date (by more than 2 days), then the dose will be administered as soon as possible, and subsequent doses will be adjusted accordingly to remain every 14 ± 2 days from the adjusted dose date.

[d] Clinical laboratory tests will be performed at central laboratories, including additional and repeat laboratory safety testing that may be performed at the discretion of the investigator.

[e] Serum chemistry will include sodium, potassium, BUN/urea, creatinine, total protein, albumin, total and direct bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, non-fasting glucose, and uric acid. Haptoglobin will also be assessed.

[f] Hematology assessment will include complete blood count, which will include hemoglobin, packed cell volume, red blood cell count, white blood cell count, absolute neutrophil count, and platelet count.

[g] Hemolysis-related laboratory tests will include type III cells (erythrocytes, monocytes, and granulocytes) and serum-free hemoglobin.

[h] Urine samples will be tested for the presence of hemoglobin. Subjects will be requested to collect the first urine void on the morning of each visit.

[i] Pharmacokinetic and anti-drug antibody (ADA) samples will be shipped to a central laboratory. Both samples should be taken immediately prior to administration of **IP**. Details will be provided in a laboratory manual. Subjects with positive ADA results will be assessed for neutralizing antibodies.

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[j] Serum or urine pregnancy tests will be conducted only for women of childbearing potential and will be performed at local laboratories.
[k] Collection of C-reactive protein is to be completed during each breakthrough event as indicated by the (X).
[l] If a subject discontinues IP and will not receive commercial eculizumab, or another PNH treatment after EOS, the subject will be monitored for at least 8 weeks to detect serious hemolysis and other reactions as detailed in Section 9.4.2.

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8.6.1.1 Efficacy Measurements

The primary efficacy endpoint for the parallel comparison is hemolysis as measured by LDH at week 27.

The primary efficacy endpoint for the crossover comparison is hemolysis, as measured by the time-adjusted AUEC of LDH **from week 13 to week 27,** from week 39 to week 53, and from week 65 to week 79.

The secondary efficacy endpoints are:

- Total complement, total hemoglobin, serum-free hemoglobin, haptoglobin, bilirubin, degree of hemoglobinuria, and type III erythrocytes at week 27, week 39, week 53, and post-crossover week 65 and week 79
- Crossover comparison of hemolysis as measured by LDH at week 53 and week 79
- Lactate dehydrogenase-time profile
- Red blood cell transfusion
- Pharmacokinetic area under the curve (AUC) of ABP 959 and eculizumab from week 13 to week 15, and trough PK

8.6.1.2 Safety Measurements

Safety endpoints include:

- Treatment-emergent adverse events
- Treatment-emergent serious adverse events
- Treatment-emergent events of interest (EOIs)
- Incidence of anti-drug antibodies (ADAs)

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9 STUDY EVALUATIONS BY VISIT

After the screening visit, there will be 40 additional visits: 26 visits in Period 1 and 14 visits in Period 2.

9.1 Screening (≤ 28 Days Before Randomization)

Unless otherwise stated, screening assessments/procedures will be performed within 28 days before randomization. Randomization will occur within 8 days before the first dose of IP administration and will be stratified by RBC transfusion received within the last 12 months before randomization (yes vs no).

Assessments/procedures performed as routine standard of care, prior to the subject signing informed consent, and according to the criteria outlined in Section 10, can be used for screening purposes as long as the assessments/procedures were performed within 28 days before randomization.

The following screening assessments/procedures will be performed:

- Informed consent
- Medical history (including history of PNH) and medication history
    - All concomitant medications from 3 months before the planned start of study treatment will be recorded.
- Physical examination, including evaluation of body systems, height, and weight
- Vital signs (systolic and diastolic blood pressure [BP], pulse, respiratory rate, and temperature)
- Concomitant medications
- Adverse event recording (only serious adverse events will be reported between the signing of the ICF and day 1).
    - Any adverse events occurring during the screening period will be recorded as medical history; any serious adverse events will be recorded and reported as outlined in Section 11.2.2.
- Clinical laboratory testing, including serum chemistry, hematology, and coagulation
- Serum or urine pregnancy test for women of childbearing potential
- Liver Doppler ultrasound

9.1.1 Screen Failures

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Laboratory assessments used to determine subject eligibility may be repeated during the screening period before the subject is considered a screen failure. Screen-failed subjects may be eligible for rescreening up to

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2 times at the investigator's discretion (ie, a total of 3 screens including initial screening). Rescreen subjects must first be registered as screen failures in IXRS and subsequently registered as rescreens. Once the subject is registered as rescreened, a new 28-day screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than 30 days after the original signing of the ICF, all screening procedures, including informed consent, must be repeated.

9.2 Treatment Period 1

9.2.1 Period 1 Visits

The following assessments/procedures will be performed before study treatment is administered per the schedule of assessments in Table 1 and Table 2 for Period 1 visits (± 2 days for each visit):

- Vital signs (systolic and diastolic BP, pulse, respiratory rate, and temperature)
- Any changes in concomitant medications since the last assessment
- All adverse events, including increases in severity or frequency of pre-existing conditions, will be recorded. Serious adverse events will be reported as outlined in Section 11.2.2.
- Blood transfusion data collection
- Clinical laboratory testing, including serum chemistry and hematology
- Hemolysis-related tests
- Collection of C-reactive protein to be completed at visit 1 and during each breakthrough event
- Total complement CH50
- Pretreatment PK samples
- At visit 7 (week 13), a post-infusion PK serum sample will be collected immediately after the end of infusion. A PK serum sample will also be collected 7 days (± 2 days) **following the visit 7 (week 13)** dosing**, noted in Table 1 as** visit 7a (week 14).
- Pretreatment ADA **samples**
    - Subjects with positive ADA results will be assessed for neutralizing antibodies.
- Urine testing for hemoglobinuria
- At visit 14 (week 27) study assessments will also include physical examination.

Serum chemistry, hematology, hemoglobinuria, and total complement (CH50) for the baseline visit can be performed up to 3 days prior to the baseline visit (visit 1, week 1).

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At each visit, after completion of pretreatment procedures, ABP 959 or eculizumab will be administered as an IV infusion in a double-blinded fashion.

9.3 Visit 27 (Week 53)/Crossover

For subjects who do not complete Period 1, the EOS visit will be 2 weeks (± 2 days) after the last dose of IP.

At the week 53 visit the following assessments will be performed at the study center:

- Physical examination, including evaluation of body systems
- Vital signs (systolic and diastolic BP, pulse, respiratory rate, and temperature)
- Concomitant medications since the last assessment
- Adverse events, including increases in severity or frequency of pre-existing conditions
    - For subjects who discontinue the study, any serious adverse events ongoing at the EOS visit will be followed until they resolve or are considered chronic or stable.
- Blood transfusion data collection
- Dosing with ABP 959 or eculizumab
- Clinical laboratory testing, including serum chemistry, hematology, hemolysis-related tests, and total complement (CH50)
- Urine testing for hemoglobinuria
- Pretreatment PK samples
- **Pretreatment** ADA **samples**
    - **Subjects with positive ADA results will be assessed for neutralizing antibodies.**

9.4 Treatment Period 2

9.4.1 Period 2 Visits

The following assessments/procedures will be performed prior to administration of study treatment per the schedule of assessments in Table 3 for Period 2 visits (± 2 days for each visit):

- Vital signs (systolic and diastolic BP, pulse, respiratory rate, and temperature)
- Concomitant medications since the last assessment
- Adverse events, including increases in severity or frequency of pre-existing conditions
- Blood transfusion data collection
- Clinical laboratory testing, including serum chemistry and hematology
- Hemolysis-related tests

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- Single collection of C-reactive protein to be completed during each breakthrough event
- Total complement (CH50)
- Pretreatment PK samples
- Pretreatment ADA **samples**
    - **Subjects with positive ADA results will be assessed for neutralizing antibodies.**
- Urine testing for hemoglobinuria

After completion of pretreatment procedures, ABP 959 or eculizumab will be administered as an IV infusion in a double-blinded fashion.

9.4.2 Visit 40 (Week 79)/End of Study

For subjects completing Period 2, the EOS visit will be at week 79. For subjects who do not complete Period 2, the EOS visit will be 2 weeks (± 2 days) after the last dose of IP.

At the week 79 visit or at the time of early discontinuation, the following assessments will be performed at the study site:

- Physical examination, including evaluation of body systems
- Vital signs (systolic and diastolic BP, pulse, respiratory rate, and temperature)
- Concomitant medications
- Adverse events, including increases in severity or frequency of pre-existing conditions
    - Any serious adverse events ongoing at week 79 will be followed until they resolve or are considered chronic or stable.
- Blood transfusion data collection
- Clinical laboratory testing, including serum chemistry, hematology, and hemolysis-related tests
- Urine testing for hemoglobinuria
- Serum or urine pregnancy test for WOCBP

Samples will also be collected for analyses of:

- Total complement (CH50)
- Pharmacokinetics
- Anti-drug antibodies

If a subject will not receive commercial eculizumab or another PNH treatment after EOS, the subject will enter a follow-up period to be monitored for detection of serious

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hemolysis and other reactions 8 weeks after last dose of IP. **Adverse events** and related treatments (eg, blood transfusion data, concomitant medications, procedures) will be recorded in the eCRF during the follow-up period.

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10 METHODS OF ASSESSMENT

10.1 Physical Examination

Physical examinations will be performed by a physician and will include examination of the following: general appearance, head, ears, eyes, nose, throat, neck, skin, cardiovascular system, respiratory system, abdominal system, and nervous system. Clinically significant findings will be recorded in the eCRF. Clinically significant changes from baseline will be reported as adverse events.

10.2 Vital Signs and Weight

Systolic BP and diastolic BP will be measured on the same arm (preferentially on the left arm) after the subject has been in a supine or sitting position for 5 minutes. Pulse may be recorded simultaneously with BP measurements. Respiratory rate and temperature will also be recorded.

Body weight (kg) will be measured without shoes or jacket. Height and weight will be determined at screening.

During the study, the measurement of vital signs may be repeated at the discretion of the investigator for safety reasons. Clinically significant abnormal findings will be reported as adverse events.

10.3 Medical History

The subject's medical history will be obtained prior to randomization and recorded on the eCRF. A detailed history of PNH will be obtained.

10.4 Adverse Event Assessments

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur from the day of randomization through the EOS visit or for 8 weeks after the last dose of IP for subjects that will not receive commercial eculizumab or another PNH treatment after EOS are reported using the applicable eCRF (eg, Medical History or Adverse Event Summary CRF). All serious adverse events should be followed until they resolve or are considered chronic or stable.

10.5 Concomitant Medication Assessments

Information regarding the type, date(s) taken, and dose of concomitant medications and treatments will be collected.

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10.6 Blood Transfusion Data Collection

Detailed information regarding the date, reason for blood transfusion, type, and amount transfused will be collected for each subject.

10.7 Pregnancy Test

Pregnancy will be determined by evaluation of β-human chorionic gonadotropin in serum or urine via local laboratories. Subjects who are pregnant are excluded from the study.

Any pregnancies occurring on study will be reported as indicated in Section 11.4.

10.8 Clinical Laboratory Testing

Venous blood samples will be taken for clinical laboratory tests at the time points indicated in Table 1, Table 2, and Table 3. Screening assessments will be performed locally, and all other clinical laboratory tests will be performed at the central laboratory.

The following parameters will be determined:

Hematology: Complete blood count (including hemoglobin, packed cell volume, RBC count, white blood cell count, ANC, and platelet count).

Clinical chemistry: Sodium, potassium, BUN/urea, creatinine, total protein, albumin, total and direct bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, LDH, non-fasting glucose, uric acid, and haptoglobin.

Hemolysis-related laboratory tests: Type III cells (erythrocytes, monocytes, and granulocytes) and serum-free hemoglobin.

Coagulation: Prothrombin time and INR.

C-reactive protein: Collection of C-reactive protein is to be completed at Visit 1 and during each breakthrough event.

Urine test for hemoglobinuria: A sample of urine will be tested for hemoglobinuria at the time points indicated in Table 1, Table 2, and Table 3. Subjects will be requested to collect the first urine void on the morning of each visit for shipment to the central laboratory.

Total complement (CH50) (central laboratory): Blood samples for total complement (CH50) will be collected at the time points indicated in Table 1, Table 2, and Table 3. and analyzed via the CH50 total complement assay.

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Immunology (central laboratory): Blood samples for ADA assessments will be collected at the time points indicated in Table 1, Table 2, and Table 3.

Further details of the procedures to be followed for sample collection, storage, and shipment will be documented in a laboratory manual.

Samples testing positive for binding antibodies will also be tested for neutralizing antibodies and may be further characterized. Additional blood samples may be obtained to rule out ADAs.

Sites will be notified if any subject tests positive for neutralizing antibodies to ABP 959 or eculizumab at the final scheduled study visit. If results are not provided to the sites, no neutralizing antibodies have been detected. Subjects who test positive for neutralizing antibodies to ABP 959 or eculizumab at the final scheduled study visit may be asked to return for additional follow-up testing. This testing may occur approximately every 3 months starting from when the site has been notified of the positive result, until:

- Neutralizing antibodies are no longer detectable.

OR

- The subject has been followed for a period of at least 1 year (± 4 weeks) post-administration of ABP 959 or eculizumab.

All follow-up results, both positive and negative, will be communicated to the sites. More frequent testing (eg, every month) or testing for a longer period of time may be requested in the event of safety-related concerns.

Subjects who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered potentially related to ABP 959 or eculizumab antibody response may also be asked to return for additional follow-up testing.

10.9 Blood Samples for Pharmacokinetic Analysis

During treatment, a series of predose serum samples (trough) will be taken according to the schedules in Table 1, Table 2, and Table 3. Serum concentrations of ABP 959 and eculizumab will be determined by a central PK laboratory. The exact times of blood sampling will be recorded.

Subjects will also have a post-infusion PK serum sample collected immediately after the end of infusion at visit 7 (week 13) and an additional PK serum sample collected 7 days (± 2 days) **following the visit 7 (week 13)** dosing**, noted in Table 1 as** visit 7a (week 14).

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Details of the procedures to be followed for sample collection, storage, and shipment will be documented in the laboratory manual.

10.10 Liver Doppler Ultrasound

To assess for evidence of acute thrombosis, liver Doppler ultrasonography will be conducted according to the schedule in Table 1.

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11 SAFETY DATA COLLECTION, RECORDING, AND REPORTING

11.1 Adverse Events

11.1.1 Definition of Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject is recorded in the subject's medical record as well as in the eCRF.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. In the case of worsening of a pre-existing condition, the start date of the event is the date when the first signs of worsening were observed. A pre-existing condition that has not worsened during the study or involves an intervention, such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse event.

11.1.2 Reporting Procedures for Adverse Events

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur from day 1 through the EOS visit or for 8 weeks after last dose of IP for subjects that will not receive commercial eculizumab or another PNH treatment after EOS are reported using the applicable eCRF Adverse Event Summary page. Adverse events observed by the investigator or reported by the subject that occur after signing of informed consent but before day 1 will be recorded as medical history, unless the adverse event is serious.

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms)
- Dates of onset and resolution
- Severity
- Assessment of relatedness to IP
- Action taken

Adverse events must be graded for severity according to the NCI-CTCAE (US), version 5.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

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The investigator must assess whether the adverse event is possibly related to IP. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by the IP?"

Worsening of PNH should not be reported as an adverse event. However, any specific symptoms or sequelae of the disease progression or recurrence (eg, organ failure, respiratory distress) will be considered adverse events and will be captured on the eCRF.

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value for any individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse events.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. A subject, or subject's legal guardian, can also voluntarily withdraw from treatment due to an adverse event. If the subject withdraws consent, the subject is encouraged to undergo, at a minimum, an EOS assessment.

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11.2 Serious Adverse Events

11.2.1 Definition of Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria:

- Fatal
- Life-threatening (places the subject at immediate risk of death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other medically important serious event

An adverse event would meet the criterion of "requires hospitalization" if the event necessitated an admission to a health care facility (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event." Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug-induced liver injury, or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

11.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the ICF through the EOS visit or for 8 weeks after last dose of IP for subjects that will not receive commercial eculizumab or another PNH treatment after EOS are recorded in the subject's medical record and are submitted to Amgen.

The serious adverse event must be submitted to Amgen, or its designee, within 24 hours following the investigator's knowledge of the event via the applicable eCRF.

If the electronic data capture (EDC) system is not functional, the serious adverse event can be reported by faxing a completed paper Serious Adverse Event Fax Cover Sheet and Serious Adverse Event report form or by direct telephone communication with PRA Safety Risk Management at the numbers provided below. The event must be updated electronically in the EDC by the clinical site once the EDC function resumes.

Contact information to Safety Risk Management/PRA, to the attention of:

PRA Drug Safety Center

For North America and South America Clinical Sites:
Fax: +1 888-772-6919 or
+1 434-951-3482
Phone: +1 800-772-2215 or
+1 434-951-3489
CHOSafety@prahs.com/SAOSafety@prahs.com

For Europe, Asia, and Pacific Region Clinical Sites:
Fax: +44 179-252-5720
Phone: +49 621-878-2154
MHGSafety@prahs.com

New information relating to a previously reported serious adverse event must be submitted to Amgen, or its designee. All new information for serious adverse events

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must be sent to Amgen, or its designee, within 24 hours following knowledge of the new information. The investigator may be asked to provide additional follow-up information, which may include a discharge summary or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the applicable eCRF (eg, Adverse Event Summary eCRF).

Elective hospitalizations are not considered **serious adverse events**. If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen, or its designee.

To comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Amgen, or its designee, before submission to regulatory authorities. Investigators will receive notification of related serious adverse event reports sent to regulatory authorities in accordance with local requirements.

Determination of expectedness for Amgen products will be based on the contents of the Investigator's Brochure/Development Core Safety Information for IP and the regional prescribing information for products being studied for an approved use. Expectedness assessments are to be made for all IPs (Amgen and non-Amgen) using the appropriate reference safety information per local regulatory reporting requirements. Suspected unexpected serious adverse reactions (SUSARs) reported for subjects receiving a non-Amgen IP are to be expedited according to local requirements.

Amgen, or its designee, will report serious adverse events and/or SUSARs as required to regulatory authorities, investigators/institutions, and IRBs/IECs in compliance with all reporting requirements according to local regulations and GCPs.

The investigator is to notify the appropriate IRB/IEC of serious adverse events occurring at the site and of other adverse event reports received from Amgen, in accordance with local procedures and statutes.

After the protocol-required reporting period defined above, the investigator does not need to actively monitor subjects for serious adverse events. However, if the investigator becomes aware of a serious adverse event after this protocol-required reporting period, the investigator will report the event to Amgen within 24 hours following the investigator's knowledge of the event. Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

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11.3 Events of Interest

Events of Interest for ABP 959/eculizumab will be defined in the Statistical Analysis Plan (SAP) and analyzed from the clinical database. There are no expedited reporting requirements for EOIs (other than those that meet other reporting requirements).

11.4 Pregnancy Reporting

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through end of study.
- Information will be recorded on the Pregnancy Notification Worksheet. The worksheet must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws).
- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through end of study. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.
- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.
- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject will be discontinued from the study and treated per standard of care if they become pregnant.

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Male Subjects With Partners Who Become Pregnant

In the event a male subject fathers a child during study treatment, the information will be recorded on the Pregnancy Notification Worksheet. The worksheet must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws).

- The investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

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12 DATA MANAGEMENT AND STATISTICAL ANALYSIS

The data management and statistical analysis of this study will be performed by PRA, an external clinical research organization (CRO).

12.1 Data Management

Previous and concomitant medications will be coded using the latest available World Health Organization (WHO) Drug Reference Dictionary. Coexistent diseases and adverse events will be coded using the latest available Medical Dictionary for Regulatory Activities (MedDRA).

When the database has been declared to be complete and accurate, the database will be locked.

12.2 Sample Size Estimation

Approximately 40 subjects will be randomized 1:1 to 1 of the 2 treatment sequences (TR or RT [Section 8.1]).

The sample size of 40 was chosen to provide approximately 87% power to demonstrate **non-inferiority (**NI**)** at a 1-sided significance level of 0.025 on the primary endpoint (Section 8.6.1.1) of week 27 LDH for the parallel comparison, assuming an inter-subject coefficient of variation (CV) of 130% for ABP 959 and eculizumab, a true geometric mean ratio (GMR) of 1 between ABP 959 and eculizumab, an NI margin of 2.873, and a 10% dropout rate. The 2.873 margin is considered appropriate to rule out a potential clinically relevant difference, as it essentially equates to a mean LDH in the ABP 959 arm of less than 1.5-fold of the mean LDH in the eculizumab arm.

The sample size of 40 will also provide **greater than 95**% power to demonstrate similarity at a 2-sided significance level of 0.05 on the primary endpoint of time-adjusted AUEC of LDH **from week 13 to week 27, from week 39 to week 53, and from week 65 to week 79** for the crossover comparison, assuming an intra-subject CV of 34%, a true GMR of 1 between ABP 959 and eculizumab, a similarity margin of (0.77, 1.30), and a 10% dropout rate.

Blinded assessments of the inter-subject CV of LDH and the intra-subject CV of time-adjusted AUEC of LDH will be performed. If the aggregated intra-subject CV of AUEC is greater than **44%,** additional subjects **will** be enrolled **if feasible**. If the aggregated inter-subject CV of LDH is **greater** than 130%, the primary endpoint of

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parallel comparison of LDH at week 27 will be replaced by crossover comparison of LDH at week 53 and week 79.

12.3 Statistical Analysis Plan

An SAP will be written and finalized prior to unblinding for the primary analysis of the week 27 LDH. The SAP will provide a detailed description of the statistical methods and expand on the details provided in the protocol. Additional analyses may be added. Table, listing, and figure shells will also be included.

12.4 Randomization

Subjects will be randomized 1:1 to receive ABP 959 and eculizumab in 1 of 2 treatment sequences in a 2-period crossover design. Randomization will be performed using an IXRS. Randomization will occur within 8 days before the first dose of IP administration and will be stratified by RBC transfusion received within the last 12 months before randomization (yes vs no). The randomization schedule will be prepared by a statistician not otherwise involved in the conduct of the study.

12.5 Analysis Sets

The primary analysis for the parallel comparison of week 27 LDH will be performed using the Full Analysis Set (FAS) based on the treatment as randomized in Period 1. The primary analysis for the crossover comparison of time-adjusted AUEC of LDH will be performed using the Modified Full Analysis Set (mFAS) according to treatment per the randomized sequence. The per-protocol analysis sets will be used for sensitivity analyses of the primary efficacy endpoints based on actual treatment received.

Analysis of safety endpoints will be performed using the Safety Analysis Set according to the actual treatment received. The PK Concentration Analysis Set and PK Parameter Analysis Set will be used to analyze PK concentration data and parameters, respectively, based on the actual treatment received.

12.5.1 Full Analysis Set

The FAS will consist of all randomized subjects, with treatment as randomized in Period 1 regardless of treatment actually received.

12.5.2 Modified Full Analysis Set

The mFAS will consist of all randomized subjects who have an LDH-time profile evaluable for the time-adjusted AUEC within **at least one of the following 14-week assessment periods: week 13 to week 27,** week 39 to **week** 53**,** and week 65 to **week**

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79, according to treatment per the randomized sequence regardless of treatment actually received.

12.5.3 Per-protocol Analysis Sets

12.5.3.1 Per-protocol Analysis Set for the Primary Endpoint of Lactate Dehydrogenase at Week 27 for the Parallel Comparison

The per-protocol analysis set for the primary endpoint of LDH at week 27 for the parallel comparison (PPP) is a subset of the FAS, which includes subjects who did not experience an important protocol deviation between week 13 and week 27 that affects their primary efficacy evaluation for the parallel comparison. The protocol deviations that affect primary efficacy evaluation will be determined based on a blinded data review prior to database snapshot for the primary analysis of week 27 LDH for the parallel comparison. Analyses for the PPP analysis set will be based on actual treatment received.

12.5.3.2 Per-protocol Analysis Set for the Primary Endpoint of AUEC for the Crossover Comparison

The per-protocol analysis set for the primary endpoint of time-adjusted AUEC for the crossover comparison (PPC) is a subset of the mFAS, **which includes** subjects who did not experience an important protocol deviation during **week 13 to week 27,** week 39 to **week** 53**,** and week 65 to **week** 79 that affects their primary efficacy evaluation for the crossover comparison. The protocol deviations that affect primary efficacy evaluation will be determined based on a blinded data review prior to database lock for the crossover comparison. Analyses for the PPC analysis set will be based on actual treatment received.

12.5.4 Safety Analysis Set

The Safety Analysis Set will consist of all treated subjects with treatment assignment based on actual treatment received.

12.5.4.1 Pharmacokinetic Concentration Analysis Set

The Pharmacokinetics Concentration Analysis Set will be defined as the subset of subjects in the Safety Analysis Set who have at least 1 serum concentration of ABP 959 or eculizumab.

12.5.4.2 Pharmacokinetics Parameter Analysis Set

The Pharmacokinetics Parameter Analysis Set will be defined as a subset of subjects in the Safety Analysis Set who have an evaluable ABP 959 or eculizumab serum concentration time profile from week 13 to **week** 15.

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12.6 Statistical Methods

Categorical variables will be summarized using the number and percentage of subjects falling into each category. Continuous variables will be summarized using mean, standard error or standard deviation, median, minimum, maximum, and number of subjects with observations.

12.6.1 Missing Data

Missing LDH values will not be imputed.

12.6.2 Demographic and Baseline Data

The following demographic and baseline characteristics will be summarized for each analysis set: age (in years, at time of signing informed consent), race, sex, ethnicity, height, and weight. Disease history and baseline disease characteristics will also be summarized.

12.6.3 Subject Disposition

The following information will be summarized for subject disposition and accountability:

- Number of subjects randomized will be tabulated by country and site
- Subject disposition (including number of subjects who were screened, randomized, treated with ABP 959/eculizumab, completed study, and discontinued study early with reason for discontinuation)
- Summaries of analysis populations with reason for exclusion
- Important protocol deviations
- Number and percentage of subjects on study at each visit
- Randomization list of subjects and their actual versus randomized treatment sequence

12.6.4 Primary Endpoints

12.6.4.1 Parallel Comparison

The primary endpoint for the parallel comparison is hemolysis, as measured by LDH at week 27. It will be analyzed when all subjects have completed or have had the chance to complete their week 53 visits.

The primary analysis of the primary endpoint of week 27 LDH for the parallel comparison will be conducted on the FAS. The analysis will be repeated in the PPP analysis set as a sensitivity analysis.

The clinical similarity of the week 27 LDH between treatments will be assessed by comparing the 1-sided 97.5% upper confidence interval (CI) limit for the GMR of the LDH at week 27 between ABP 959 and eculizumab treatment with a NI margin of 2.873. The

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point estimate of the mean difference in the log-transformed LDH and the corresponding 1-sided 97.5% upper CI limit will be estimated from a linear mixed effects model with treatment, stratification factor, week 1 LDH value, time (as a continuous variable), and treatment by time interaction term as fixed effects, and subject as a random effect. Lactate dehydrogenase values from all assessed time points from week 13 to week 27 will be included in the mixed model. The point estimate and the upper CI limit for the GMR will then be calculated by transforming back to the original scale.

LDH values impacted by confounding events (eg, acute infection, or trauma including surgery), unrelated to efficacy of IP that trigger dose adjustment, will be excluded from the primary comparison of LDH. The details will be described in the SAP.

12.6.4.2 Crossover Comparison

The primary endpoint for the crossover comparison is hemolysis, as measured by the time-adjusted AUEC of LDH **from week 13 to week 27,** from week 39 to week 53, and from week 65 to week 79.

The primary analysis of the primary endpoint of time-adjusted AUEC of LDH for the crossover comparison will be conducted on the mFAS. The analysis will be repeated in the PPC analysis set, as a sensitivity analysis.

The linear trapezoidal rule will be used to derive the AUEC of LDH **from week 13 to week 27,** from week 39 to **week** 53**,** and from week 65 to **week** 79 for each subject. The time-adjusted AUEC will be calculated by dividing the AUEC by the total duration of observed LDH data (in weeks) of each individual subject within each 14-week assessment period. An LDH-time profile will be considered evaluable for AUEC if it contains at least 3 LDH measurements within the 14-week assessment period. LDH values impacted by confounding events (ie, acute infection, or trauma including surgery), unrelated to efficacy of IP that trigger dose adjustment, will be excluded from the calculation of AUEC. The details will be described in the SAP.

The clinical similarity of the AUEC between treatments will be assessed by comparing the 2-sided 90% CI for the GMR of the time-adjusted AUEC of LDH (**week 13 to week 27,** week 39 to **week** 53**,** and week 65 to **week** 79) between ABP 959 and eculizumab treatment with a similarity margin of (0.77, 1.30). The point estimate of the mean difference in the log-transformed time-adjusted AUEC and the corresponding 2-sided 90% CI will be calculated from a linear mixed effects model with treatment, stratification factor, **assessment** period, and sequence as fixed effects, and subject as a random

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effect. The point estimate and CI for the GMR will then be calculated by transforming back to original scale.

12.6.5 Secondary Endpoints

The secondary endpoints of total complement, total hemoglobin, serum-free hemoglobin, haptoglobin, bilirubin, degree of hemoglobinuria, and type III erythrocytes (%) at week 27, week 39, week 53, week 65, and week 79 will be summarized descriptively by randomized treatment (ABP 959 vs eculizumab) using the FAS.

The secondary endpoint of crossover comparison of LDH at week 53 and week 79 will be evaluated descriptively. The point estimate of the mean difference in the log-transformed LDH between treatments and the corresponding 1-sided 97.5% upper CI limit will be calculated from a linear mixed effects model with treatment, stratification factor, period, and sequence as fixed effects and subject as a random effect. The point estimate and 1-sided 97.5% upper CI limit for the GMR will then be calculated by transforming back to original scale. LDH values impacted by confounding events (ie, acute infection, or trauma including surgery), unrelated to efficacy of IP that trigger dose adjustment, will be excluded from the crossover comparison of LDH. The details will be described in the SAP.

For the secondary endpoint of RBC transfusions, summary statistics for the number of packed red cells transfused per month after week 13 will be presented. A descriptive summary of LDH at each time point through the EOS visit will be presented. Individual and mean LDH-time profile through the EOS visit will also be presented graphically.

The pharmacokinetic AUC from week 13 to week 15 will be analyzed on the PK Parameter Analysis Set according to the actual treatment received with GMR and the 90% CI provided descriptively. Serum ABP 959 and eculizumab trough concentrations will be summarized descriptively on the PK Concentration Analysis Set for the study through the EOS visit by actual treatment (ABP 959 or eculizumab) and by visit within each period.

12.6.6 Safety Endpoints

The safety endpoints of the study are:

- Treatment-emergent adverse events
- Treatment-emergent serious adverse events
- Treatment-emergent EOIs
- Incidence of ADAs

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Safety will be assessed for the study through the EOS visit in the Safety Analysis Set.

Safety endpoints will be summarized descriptively.

12.6.6.1 Adverse Events

Only treatment-emergent adverse events will be summarized. Treatment-emergent events are those that begin or increase in severity or frequency at or after the time of first treatment up to the EOS visit.

All reported adverse events will be assigned the system organ class (SOC) and preferred term according to the current version of MedDRA and graded by NCI-CTCAE, version 5.0. The number and percentage of subjects reporting adverse events (all, serious, and fatal) and EOIs will be tabulated by treatment (ABP 959 vs eculizumab) for the study through the EOS visit, for each study period, and for each **14-week assessment** period (ie, **week 13 to week 27,** week 39 to **week** 53**,** and week 65 to **week** 79).

All treatment-emergent adverse events will be summarized by treatment arm and according to the current version of MedDRA SOC and preferred term. Summaries will be provided for the incidences of all treatment-emergent adverse events by severity. Additional summaries will be presented for serious adverse events, adverse events leading to discontinuation from the study, and EOIs. All adverse event data will be listed by subject, and a separate listing will include all serious adverse events, including any deaths on study.

12.6.6.2 Immunogenicity

The number and percentage of subjects developing ADAs will be tabulated by visit and treatment (ABP 959 vs eculizumab) for Period 1 and by treatment sequence for the study through the EOS visit using the Safety Analysis Set.

12.6.6.3 Investigational Product Administration

Summary statistics will be provided for the total number of doses and cumulative dose of ABP 959 and eculizumab for Period 1, Period 2, and overall for the study.

12.6.6.4 Concomitant Medications

Concomitant medications will be coded by the latest available WHO Drug Reference Dictionary and will be summarized using the number and percentage of subjects receiving each category of medication for Period 1, Period 2, and overall for the study.

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12.6.6.5 Clinical Laboratory Tests

Laboratory data will be summarized by visit and treatment.

12.6.6.6 Vital Signs and Physical Examinations

Vital signs will be summarized by visit and treatment.

Abnormal findings from physical examinations will be listed by subject and assessed for clinical significance and included in the adverse event listings and summaries.

12.6.7 Interim Analyses

Blinded assessments of the inter-subject CV of LDH and the intra-subject CV of time-adjusted AUEC of LDH will be performed.

The first blinded interim check of CV will take place **prior to the end of enrollment.** If the aggregated intra-subject CV of AUEC is greater than **44%,** additional subjects will be enrolled if feasible. The second blinded interim check of CV will take place when **approximately** all subjects complete their week 27 visit. If the aggregated inter-subject CV of LDH at week 27 is **greater** than 130%, the primary endpoint of parallel comparison of LDH at week 27 will be replaced by crossover comparison of LDH at week 53 and week 79.

Details of the interim analyses will be provided in the SAP.

12.6.8 Data Monitoring Committee

A DMC external to Amgen and PRA will be formed with members consisting of individuals chosen for their expertise in PNH. Members of the DMC will include, at a minimum, physicians external to Amgen and PRA and appropriate statistical representation external to Amgen and PRA. The primary role of this independent DMC will be to monitor safety data. Details regarding the DMC will be provided in the DMC Charter.

Independent safety reviews of unblinded safety data will be performed by the DMC approximately every 6 months (or as determined by the DMC) throughout the study, as outlined in the DMC Charter, and the DMC will communicate any major safety concerns and recommendations regarding study modification or termination to Amgen management at any time during the conduct of the study.

Records of all meetings will be archived. Selected Amgen staff, or its designee, may serve as liaisons to the external DMC but will not be voting members and will not be unblinded to the results.

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Blinded study data will also be monitored on an ongoing basis by the clinical study team.

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13 MONITORING PROCEDURES (QUALITY ASSURANCE)

Amgen has ethical, legal, and scientific obligations to conduct this study in accordance with established research principles and ICH GCP guidelines. As such, to fulfill these obligations and to maintain a current understanding of study progress, Amgen monitors (or designees) will visit the investigative sites during study conduct in addition to maintaining telephone and written communication. On-site visits, telephone calls, and regular inspection of the eCRFs will be conducted to assess subject enrollment, compliance with protocol procedures, completeness and accuracy of data entered on the eCRFs, verification of eCRF data against original source documents, and occurrence of adverse events. The investigator must provide the monitor with full access to all source and study documents.

13.1 Routine Monitoring

Monitors assigned by Amgen, or its designee, will conduct regular site visits to the investigational facilities for the purpose of monitoring various aspects of the study. The investigator must agree to personnel authorized by Amgen, or its designee, having direct access to the clinical (or associated) files and clinical study supplies (dispensing and storage areas) for all study subjects considered for study entry for the purpose of verifying entries made in the eCRF and must assist with their activities, if requested. Adequate time and space for monitoring visits should be made available by the investigator.

The site must complete the eCRFs in a timely manner and on an ongoing basis to allow regular review by the study monitor.

Whenever a subject name is revealed on a document that is to be collected for the sponsor, the name must be blacked out permanently by the site personnel, leaving the initials visible, and must be annotated with the subject number as identification.

13.2 Inspections and Auditing Procedures

Amgen, or its designee, may conduct audits at the investigative sites including, but not limited to, drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. All medical records (progress notes) must be available for audit. The investigator agrees to participate with audits conducted at a convenient time in a reasonable manner.

Government regulatory authorities may also inspect the investigation site during or after the study. The investigator or designee should contact Amgen, or its designee,

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immediately if this occurs. He/she must cooperate fully with regulatory authorities or other audits conducted at a convenient time in a reasonable manner.

The purpose of an audit is to assess whether ethics, regulatory, and quality requirements are fulfilled.

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14 STUDY MANAGEMENT AND MATERIALS

14.1 Electronic Case Report Forms

An eCRF will be used to store and transmit subject information. The file structure and format for the eCRF will be provided by the sponsor or their representative and should be handled in accordance with the instructions provided.

The eCRF must be reviewed and electronically signed and dated by the investigator.

Access to the eCRF will be strictly password protected and limited to personnel directly participating in the study. Complete data should be entered into the eCRF by examining personnel or the appropriate site staff. The eCRF must be completed as soon as possible after any subject evaluation or communication. If data are to be changed due to erroneous input or other reason, an electronic audit trail will track these changes. The eCRFs and computers that store them must be accessible to study monitors and other regulatory auditors.

14.2 Data Collection

During each study visit, a physician participating in the study will maintain progress notes in the subject's medical records to document all significant observations. At a minimum, these notes will contain:

- The date of the visit and the corresponding day or visit in the study schedule (eg, screening, day 1, week 2, etc.)
- General condition and status remarks by the subject, including any *significant* medical findings; the severity, frequency, duration, and resolution of any reported adverse event, and the investigator's assessment as to whether or not the reported adverse event is study drug-related
- Changes in concomitant medications or dosages
- A general reference to the procedures completed
- The signature or initials of all physicians making an entry in the medical record (progress notes)

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the medical record (progress notes), as described above.

Information from the medical records (progress notes) and other source documents will be promptly transcribed to the appropriate section of the eCRF.

Changes to information in the medical record (progress notes), eCRF, and other source documents will be initialed and dated on the day the change is made by the investigator

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or designee. If the reason for the change is not apparent, a brief explanation for the change will be written adjacent to the change.

14.3 Source Documents Maintenance

Source documents contain the results of original observations and activities of a clinical investigation. Source documents include, but are not limited to, medical records (progress notes), computer printouts, screening logs, and recorded data from automated instruments.

All source documents from this study will be maintained by the investigator and made available for inspection by authorized persons. The original signed ICF for each subject shall be filed with records kept by the investigator and a copy shall be given to the subject.

14.4 Record Maintenance

All data derived from the study will remain the property of Amgen Inc.

Records must be retained in accordance with the current ICH Guidelines on GCP. All essential study documents including records of subjects, source documents, eCRFs and study drug inventory must be kept on file.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the IPs. However, essential documents may be retained for a longer period if required by the applicable regulatory requirements or by agreement with the sponsor.

The investigator will not dispose of any records relevant to this study without written permission from the sponsor and will give the sponsor the opportunity to collect such records. The investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by the sponsor, its representatives, and regulatory authorities.

If an investigator moves, withdraws from an investigation, or retires, the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be given to and agreed to by the sponsor.

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14.5 Confidentiality

All information obtained during the conduct of the study with respect to the subject's state of health will be regarded as confidential. For disclosure of any such information, an agreement will be obtained in writing.

The investigator must ensure that each subject's anonymity is maintained. On eCRFs and other documents submitted to the sponsor or the CRO, subjects must not be identified by name. Instead, subjects will only be known by the unique subject number allocated to them to ensure confidentiality on all study documentation. Subjects will retain this unique number throughout the study. The investigator will keep a separate log of these codes.

To comply with government regulatory guidelines and to ensure subject safety, it may be necessary for the sponsor and its representative, the CRO personnel, the local research review board, or regulatory authorities, such as the US FDA or the European Medicines Agency (EMA), to review subjects' medical records as they relate to this study. Only the subject's unique number on the eCRFs will identify him/her, but his/her full name may be made known to a drug regulatory authority or other authorized government or health care officials, if necessary, and to personnel designated by the sponsor.

Documents that are not for submission to the sponsor or the CRO (eg, consent forms) will be maintained by the investigator in strict confidence, except to the extent necessary to allow monitoring by the sponsor and the CRO, and auditing by regulatory authorities. No documents identifying subjects by name will leave the investigative site, and subject identity will remain confidential in all publications related to the study.

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15 ADMINISTRATION PROCEDURES

15.1 Regulatory Approval

Amgen Inc., or their appointed agents, will be responsible for ensuring that appropriate regulatory authority approvals are obtained, according to local country requirements.

No subject may enter the study until this approval has been obtained. A copy of the approval (where one is provided as requested, according to local country requirements) will be provided to the investigator and to the IRB/IEC.

15.2 Protocol Amendments

In accordance with ICH Topic E6 (R1) Guideline for GCP, the investigator should not implement any deviation from or changes to the protocol without agreement by the sponsor and documented approval from the IRB/IEC of a protocol amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (eg, change in monitor[s], change of telephone number[s]).

Any change to the protocol must be handled as a protocol amendment. Any potential amendment must be approved by the sponsor. A written amendment must be submitted to the appropriate regulatory authorities and to the IRB/IEC assuming this responsibility. The investigator must await IRB/IEC approval of protocol amendments before implementing the changes, except where necessary to eliminate apparent immediate hazard to subjects. In these cases, the IRB/IEC must be notified within 5 days of the change.

All amendments to the protocol must be approved in writing by both the appropriate regulatory authorities and the IRB/IEC, except for administrative amendments, which require notification but not written approval. Once approved, the protocol amendment will be distributed to all recipients of the original protocol, with instructions to append the amendment to the protocol.

If, in the judgment of the local IRB/IEC or the investigator and/or sponsor, the protocol amendment alters the study design or procedures and/or increases the potential risk to the subject, the currently approved written ICF will require modification. The modified ICF must also be reviewed and approved by the sponsor, appropriate regulatory authorities, and the IRB/IEC. In such cases, repeat informed consent must be obtained from subjects enrolled in the study before participation continues.

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15.3 Protocol Adherence and Deviations

The protocol must be read thoroughly, and the instructions must be followed. However, exceptions will be made in emergency situations when the protection, safety, and well-being of the subject(s) requires immediate intervention based on the judgment of the investigator or a responsible, appropriately trained and credentialed professional(s) designated by the investigator as a subinvestigator.

In the event of a significant protocol deviation due to an emergency, accident, or error, the investigator or designee must contact the Medical Monitor at the earliest possible time by telephone. This allows for an early joint decision to be made as to whether or not the subject should continue in the study. The investigator, the sponsor, and the Medical Monitor will document this decision.

15.4 Publication Policy

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors), which states:

- Authorship credit is to be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; 4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors are to meet conditions 1, 2, 3, and 4.
- When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals are to fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors are to qualify for authorship, and all those who qualify are to be listed.
- Each author is to have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement between the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

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15.5 Clinical Study Report

A final clinical study report (CSR) will be prepared according to the ICH guideline on Structure and Contents of Clinical Study Reports. A final CSR will be prepared regardless of whether the study is completed or prematurely terminated.

15.6 Contractual and Financial Details

The investigator (and/or, as appropriate, the hospital administrative representative) and Amgen, or its designee, will sign a clinical study agreement prior to the start of the study, outlining overall Amgen, or its designee, and investigator responsibilities in relation to the study. Financial disclosure statements will be completed only as required by local regulations.

15.7 Compensation

Any arrangements for compensation to subjects for injuries or illnesses that arise in the study are described in the Compensation for Injury section of the ICF that is available as a separate document.

15.8 Discontinuation of the Study

This study may be terminated by Amgen at any time. In terminating the study, Amgen, the CRO (PRA), and the investigator will ensure that adequate consideration is given to the protection of the subjects' interests. Amgen will not provide ABP 959 or eculizumab for subjects after termination of the trial or upon **a subject's** discontinuation **from** the study.

Possible reasons for early termination of the study include the following:

- **New or emerging safety information that negatively affects the benefit/risk assessment of the product or trial as a whole**
- **Insufficient patient recruitment**
- **Lack of efficacy**
- **Administrative reasons**
- **Sponsor decision**

15.9 Study Center File Management

The investigator is responsible for assuring that the Study Center File is maintained. The Study Center File will contain, but will not be limited to, the information listed below:

1. Investigator's brochure
2. Current, signed version of the protocol and any previous versions of the protocol

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3. Protocol amendments (if applicable)
4. Operations manual (if applicable)
5. Current ICF (blank) and any previous versions of the ICF
6. Curricula vitae of investigator(s) and subinvestigator(s) and photocopy of their respective license(s) where required by law; Original US FDA Form 1572 (for all studies conducted under US Investigational New Drug [IND] regulations), or equivalent, signed by all principal investigators. The names of any subinvestigators must appear on this form. Investigators must also complete all regulatory documentation as required the ICH GCP and by local or national regulations.
7. Documentation of IRB/IEC approval of the protocol, the ICF, any protocol amendments, and any ICF revisions
8. All correspondence between the investigator, IRB/IEC, and the sponsor/CRO relating to study conduct
9. Lab certification(s)
10. Monitoring log
11. Study drug invoices
12. Signature list of all staff completing eCRFs
13. Signature list of all staff completing drug accountability summaries

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16 REFERENCE LIST

European Medicines Evaluation Agency (EMEA), Committee for Medicinal Products for Human Use (CHMP). Guideline on similar biological medicinal products. CHMP/437/04 Rev 1(draft).

European Medicines Evaluation Agency (EMEA), Committee for Medicinal Products for Human Use (CHMP). Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues. EMEA/CHMP/BWP/247713/2012, (Rev1) (draft).

European Medicines Evaluation Agency (EMEA), Committee for Medicinal Products for Human Use (CHMP). Guideline on similar biological medicinal products containing monoclonal antibodies: nonclinical and clinical issues. EMEA/CHMP/BMWP/403543/2010, (Rev1) (draft).

European Medicines Evaluation Agency (EMEA), Committee for Medicinal Products for Human Use (CHMP). Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Non-clinical and clinical issues. EMEA/CHMP/BMWP/42832/2005, Rev.1.(draft).

Hill A, Richards SJ, Hillmen P. Recent developments in the understanding and management of paroxysmal nocturnal haemoglobinuria. *Br J Haematol*. 2007;137:181-192.

Hillmen P, Young NS, Schubert J, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med*. 2006;355:1233-1243.

Kelly R, Richards S, Hillmen P, Hill A. The pathophysiology of paroxysmal nocturnal hemoglobinuria and treatment with eculizumab. *Ther Clin Risk Manag.* 2009;5:911-921.

Rother RP, Bell L, Hillmen P, et al. The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin: a novel mechanism of human disease. *JAMA.* 2005;293:1653-1662.

Soliris® (eculizumab) – Summary of Product Characteristics. http://www.ema.europa.eu; 2018.

United States Food and Drug Administration. Guidance for Industry: Scientific considerations in demonstrating biosimilarity to a reference product. February 2012a, US FDA (draft).

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United States Food and Drug Administration. Guidance for Industry: Quality considerations in demonstrating biosimilarity to a reference protein product. February 2012b, US FDA (draft).

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17 APPENDICES

17.1 Appendix 1: Elements of Informed Consent

ELEMENTS OF INFORMED CONSENT

Both the informed consent discussion and the written ICF and any other written information to be provided to subjects should include explanations of the following:

- That the study involves research.
- The purpose of the study.
- The study treatment(s) and the probability for random assignment to each treatment.
- The study procedures to be followed, including all invasive procedures.
- The subject's responsibilities.
- Those aspects of the study that are experimental.
- The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.
- The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
- The alternative procedure(s) or course(s) of treatment that may be available to the subject and their important potential benefits and risks.
- The compensation and/or treatment available to the subject in the event of study-related injury.
- The anticipated prorated payment, if any, to the subject for participating in the study.
- The anticipated expenses, if any, to the subject for participating in the study.
- That the subject's participation in the study is voluntary and that the subject may refuse to participate or withdraw from the study, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
    - That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written ICF, the subject or the subject's legally acceptable representative is authorizing such access.
- That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the study are published, the subject's identity will remain confidential.
- That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
- The person(s) to contact for further information regarding the study and the rights of study subjects, and who to contact in the event of study-related injury.
- The foreseeable circumstances and/or reasons under which the subject's participation in the study may be terminated.
- The expected duration of the subject's participation in the study.
- The approximate number of subjects involved in the study.

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Summary of Changes: Version 4.0

A RANDOMIZED, DOUBLE-BLIND, ACTIVE-CONTROLLED PHASE 3 STUDY EVALUATING THE EFFICACY AND SAFETY OF ABP 959 COMPARED WITH ECULIZUMAB IN ADULT SUBJECTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

Test Drug: ABP 959

Protocol Number: 20150168 **EudraCT number:** 2017-001418-27

Study Phase: 3

Date and Version: **05 March 2020;** Version **4.0**

Key Contacts:

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Clinical Research Organization (CRO):

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Phone: [redacted]
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This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) as set forth in the International Conference for Harmonisation (ICH) guidelines on GCP (ICH E6), and applicable local regulatory requirements.

CONFIDENTIAL

This document is a confidential communication of Amgen Inc. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein shall be published or disclosed without prior written approval, except that this document may be disclosed to the appropriate Institutional Review Board(s)/Independent Ethics Committee(s) under the condition that they keep it confidential.

Rationale:

This amendment is issued to make the following changes:

- To update the planned number of sites from 25 to 45.
- To update the threshold of the aggregated intra-subject CV from the first blinded interim analysis from 42% to 44% according to the modified statistical analysis after adding week 13 to week 27 data.
- To update the primary endpoint for crossover comparison to include an additional assessment period from week 13 to week 27. Appropriate statistical sections were updated as well.
- To add the End of Study definition as last subject, last visit in Section 8.3.1 (End of Study Definition).
- To amend text in Section 8.5.7 (Prior and Concomitant Therapy) to clarify that concomitant therapy may include prophylactic antibiotics.
- To update timing of the first blinded interim check of CV to take place prior to the end of enrollment rather than when approximately 20 subjects complete their week 27 visit.
- To clarify the criteria for discontinuation of the trial in Section 15.8 (Discontinuation of the Study).
- To make minor administrative updates and non-substantive grammatical and typographic corrections (changes not detailed in this summary).

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Summary of Changes:

Any changes in the synopsis that also appear in the body of the protocol will appear only once in this summary of changes document, under the section number.

Section: Cover Page, page 1

Replace:

Clinical Research Organization (CRO):

[redacted]
Project Manager
PRA Health Sciences
731 Arbor Way, Suite 100
Blue Bell, PA USA
19422
Phone:
Mobile:
Email:

With:

Clinical Research Organization (CRO):

[redacted]
Project **Director**
PRA Health Sciences
995 Research Park Blvd. Suite 300Charlottesville, VA
USA
22911
Phone:
Email:

Section: Synopsis, Study Centers, page 4

Section: 8.1 Overall Study Design and Plan, page 19

Replace:

Approximately 25 sites

With:

Approximately **45** sites

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Section: Synopsis, Planned Study Dates, page 4

Section: 8.3 Study Duration, page 20

Replace:

The planned duration of the clinical study is approximately 27 months (approximately 9 months for enrollment and approximately 18 months for treatment), from approximately Q1 2019 to Q2 2021.

With:

The planned duration of the clinical study is approximately **30** months (approximately **12** months for enrollment and approximately 18 months for treatment), from approximately Q1 2019 to **Q3** 2021.

Section: Synopsis, Number of Subjects, page 6

Section: 12.2 Sample Size Estimation, page 51-52

Replace:

The sample size of 40 was chosen to provide approximately 87% power to demonstrate non-inferiority (NI) at a 1-sided significance level of 0.025 on the primary endpoint of week 27 LDH for the parallel comparison, assuming an inter-subject coefficient of variation (CV) of 130% for ABP 959 and eculizumab, a true geometric mean ratio (GMR) of 1 between ABP 959 and eculizumab, a NI margin of 2.873, and a 10% dropout rate. The 2.873 margin is considered appropriate to rule out a potential clinically relevant difference, as it essentially equates to a mean LDH in the ABP 959 arm of less than 1.5-fold of the mean LDH in the eculizumab arm. The sample size of 40 will also provide 90% power to demonstrate similarity at a 2--sided significance level of 0.05 on the primary endpoint of time-adjusted area under the effect curve (AUEC) of LDH for the crossover comparison, assuming an intra-subject CV of 34%, a true GMR of 1 between ABP 959 and eculizumab, a similarity margin of (0.77, 1.30), and a 10% dropout rate. Blinded assessments of the inter-subject CV of LDH and the intra-subject CV of time-adjusted AUEC of LDH will be performed. If the aggregated intra-subject CV of AUEC is greater than 42%, additional subjects may be enrolled. If the aggregated inter-subject CV of LDH is larger than 130%, the primary endpoint of parallel comparison of LDH at week 27 will be replaced by crossover comparison of LDH at week 53 and week 79.

With:

The sample size of 40 was chosen to provide approximately 87% power to demonstrate non-inferiority (NI) at a 1-sided significance level of 0.025 on the primary endpoint of week 27 LDH for the parallel comparison, assuming an inter-subject coefficient of variation (CV) of 130% for ABP 959 and eculizumab, a true geometric mean ratio (GMR) of 1 between ABP 959 and eculizumab, a**n** NI margin of 2.873, and a 10% dropout rate. The 2.873 margin is considered appropriate to rule out a potential clinically relevant difference, as it essentially equates to a mean LDH in the ABP 959 arm of less than 1.5-fold of the mean LDH in the eculizumab arm. The sample size of 40 will also provide **greater than 95**% power to demonstrate similarity at a 2--sided significance level of 0.05 on the primary endpoint of time-adjusted area under the effect curve (AUEC) of LDH **from week 13 to week 27, from week 39 to week 53, and from week 65 to week 79** for the crossover comparison, assuming an intra-subject CV of 34%, a true GMR of 1 between ABP 959 and eculizumab, a

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similarity margin of (0.77, 1.30), and a 10% dropout rate. Blinded assessments of the inter-subject CV of LDH and the intra-subject CV of time-adjusted AUEC of LDH will be performed. If the aggregated intra-subject CV of AUEC is greater than **44**%, additional subjects **will** be enrolled **if feasible**. If the aggregated inter-subject CV of LDH is **greater** than 130%, the primary endpoint of parallel comparison of LDH at week 27 will be replaced by crossover comparison of LDH at week 53 and week 79.

Section: Synopsis, Duration of Treatment, page 6

Replace:

Study participation consists of a screening period of up to 4 weeks, followed by Period 1 (treatment every 14 ± 2 days for a total of 52 weeks), followed by Period 2 (treatment every 14 ± 2 days for a total of 26 weeks), and an end of study visit 2 weeks (± 2 days) after the last dose of IP. The total duration of study treatment is up to 78 weeks.

With:

Study participation consists of a screening period of up to 4 weeks, followed by Period 1 (treatment every 14 ± 2 days for a total of 52 weeks), followed by Period 2 (treatment every 14 ± 2 days for a total of 26 weeks), and an end of study **(EOS)** visit 2 weeks (± 2 days) after the last dose of IP. The total duration of study treatment is up to 78 weeks.

Section: Synopsis, Study Evaluations, page 6

Replace:

Primary Endpoint for Crossover Comparison:

- Hemolysis, as measured by the time-adjusted AUEC of LDH from week 39 to 53 and from week 65 to 79

With:

Primary Endpoint for Crossover Comparison:

- Hemolysis, as measured by the time-adjusted AUEC of LDH **from week 13 to week 27,** from week 39 to **week** 53**,** and from week 65 to **week** 79

Section: Synopsis, Study Evaluations, page 6

Replace:

Secondary Endpoints:

- Pharmacokinetic area under the curve (AUC) of ABP 959 and eculizumab from week 13 to 15, and trough PK

With:

Secondary Endpoints:

- Pharmacokinetic area under the curve (AUC) of ABP 959 and eculizumab from week 13 to **week** 15, and trough PK

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Section: Synopsis, Statistical Methods, page 7

Replace:

The primary analysis of the primary endpoint of time-adjusted AUEC of LDH for the crossover comparison will be conducted on the Modified Full Analysis Set (mFAS), consisting of all randomized subjects who have an LDH-time profile evaluable for the time-adjusted AUEC within week 39 to 53 and/or within week 65 to 79, according to treatment per the randomized sequence regardless of treatment actually received.

With:

The primary analysis of the primary endpoint of time-adjusted AUEC of LDH for the crossover comparison will be conducted on the Modified Full Analysis Set (mFAS), consisting of all randomized subjects who have an LDH-time profile evaluable for the time-adjusted AUEC within **at least one of the following 14-week assessment periods: week 13 to week 27,** week 39 to **week** 53**,** and week 65 to **week** 79, according to treatment per the randomized sequence regardless of treatment actually received.

Section: Synopsis, Statistical Methods, page 7

Section: 12.6.4.2 Crossover Comparison, page 55

Replace:

The linear trapezoidal rule will be used to derive the AUEC of LDH from week 39 to 53 and from week 65 to 79 for each subject.

With:

The linear trapezoidal rule will be used to derive the AUEC of LDH **from week 13 to week 27,** from week 39 to **week** 53**,** and from week 65 to **week** 79 for each subject.

Section: Synopsis, Statistical Methods, page 7

Section: 12.6.4.2 Crossover Comparison, page 55-56

Replace:

The clinical similarity of the AUEC between treatments will be assessed by comparing the 2-sided 90% CI for the GMR of the time-adjusted AUEC of LDH (within weeks 39 to 53 and within weeks 65 to 79) between ABP 959 and eculizumab treatment with a similarity margin of (0.77, 1.30). The point estimate of the mean difference in the log-transformed time-adjusted AUEC and the corresponding 2- sided 90% CI will be calculated from a linear mixed effects model with treatment, stratification factor, period, and sequence as fixed effects, and subject as a random effect.

With:

The clinical similarity of the AUEC between treatments will be assessed by comparing the 2-sided 90% CI for the GMR of the time-adjusted AUEC of LDH (**week 13 to week 27,** week 39 to **week** 53**,** and week 65 to **week** 79) between ABP 959 and eculizumab treatment with a similarity margin of (0.77, 1.30). The point estimate of the mean difference in the log-transformed time-adjusted AUEC and the corresponding 2--sided 90% CI will be calculated

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from a linear mixed effects model with treatment, stratification factor, **assessment** period, and sequence as fixed effects, and subject as a random effect.

Section: Synopsis, Statistical Methods, page 7

Replace:

The analysis of secondary endpoints (except for PK) will be conducted on the FAS. Total complement, total hemoglobin, serum-free hemoglobin, haptoglobin, bilirubin, degree of hemoglobinuria, and type III erythrocytes (%) at weeks 27, 39, 53, 65, and 79 will be summarized descriptively. For the endpoint of RBC transfusions, summary statistics for the number of packed red cells transfused per month after week 13 will be presented. A descriptive summary of LDH at each time point through the end of study (EOS) visit will be presented. Individual and mean LDH time profile through EOS visit will also be presented graphically.

With:

The analysis of secondary endpoints (except for PK) will be conducted on the **Full Analysis Set (**FAS**)**. Total complement, total hemoglobin, serum-free hemoglobin, haptoglobin, bilirubin, degree of hemoglobinuria, and type III erythrocytes (%) at weeks 27, 39, 53, 65, and 79 will be summarized descriptively. For the endpoint of RBC transfusions, summary statistics for the number of packed red cells transfused per month after week 13 will be presented. A descriptive summary of LDH at each time point through the EOSvisit will be presented. Individual and mean LDH time profile**s** through **the** EOS visit will also be presented graphically.

Section: Synopsis, Statistical Methods, page 7

Replace:

The PK Parameter Analysis Set will be defined as the subset of subjects in the Safety Analysis Set who have an evaluable ABP 959 or eculizumab serum concentration time profile from weeks 13 to 15. Pharmacokinetic AUC from week 13 to 15 will be analyzed on the PK Parameter Analysis Set according to the actual treatment received with GMR and 90% CI provided descriptively.

With:

The PK Parameter Analysis Set will be defined as the subset of subjects in the Safety Analysis Set who have an evaluable ABP 959 or eculizumab serum concentration-time profile from week13 to **week** 15. Pharmacokinetic AUC from week 13 to **week** 15 will be analyzed on the PK Parameter Analysis Set according to the actual treatment received with GMR and 90% CI provided descriptively.

Section: Synopsis, Statistical Methods, page 8

Section: 12.6.6.1 Adverse Events, page 57

Replace:

The number and percentage of subjects reporting adverse events (all, serious, and fatal) and EOIs will be tabulated by treatment (ABP 959 vs eculizumab) for the study through the

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EOS visit, for each study period, and for the final 14 weeks of each period (ie, weeks 39 to 53 and weeks 65 to 79).

With:

The number and percentage of subjects reporting adverse events (all, serious, and fatal) and EOIs will be tabulated by treatment (ABP 959 vs eculizumab) for the study through the EOS visit, for each study period, and for each **14-week assessment** period (ie, **week 13 to week 27,** week 39 to **week** 53**,** and week 65 to **week** 79).

Section: 4 List of Abbreviations and Definition of Terms, page 12-13

Add:

BUN blood urea nitrogen

PIN Personal Identification Number

Section: 8.1 Overall Study Design and Plan, page 19

Replace:

Randomization will occur within 8 days before the first dose of IP administration and will be stratified by red blood cell (RBC) transfusion received within the last 12 months before randomization (yes vs no).

With:

Randomization will occur within 8 days before the first dose of IP administration **(defined as day 1)** and will be stratified by red blood cell (RBC) transfusion received within the last 12 months before randomization (yes vs no).

Section: 8.2 Discussion of Study Design and Plan, page 20

Replace:

The assessment of the primary endpoint for the parallel comparison of the study will be based on LDH at week 27, and the assessment of the primary endpoint for the crossover comparison will be based on time-adjusted AUEC of LDH from week 39 to 53 and from week 65 to 79.

With:

The assessment of the primary endpoint for the parallel comparison of the study will be based on LDH at week 27, and the assessment of the primary endpoint for the crossover comparison will be based on **the** time-adjusted area under the effect curve (AUEC) of LDH **from week 13 to week 27,** from week 39 to **week** 53**,** and from week 65 to **week** 79.

New section, page 21

Add:

Section: 8.3.1 End of Study Definition

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The end of the study will be defined as the date the last subject completes the week 79 visit or the date of the last subject's last completed scheduled procedure.

Section: 8.5.7 Prior and Concomitant Therapy, page 27

Replace:

Any non-experimental, prescribed therapy that is considered necessary for the subject's welfare may be given at the discretion of the investigator.

With:

Any non-experimental, prescribed therapy**, including prophylactic antibiotics,** that is considered necessary for the subject's welfare may be given at the discretion of the investigator.

Section: 8.6.1 Table 1. Schedule of Assessments and Procedures – Screening to Period 1 Week 25, page 30-31

Add:

To row "Coagulation[g]" add footnote designation "**l**"

Replace:

- Pharmacokinetic (PK) and anti-drug antibody (ADA) samples will be shipped to a central laboratory. Both samples should be taken immediately prior to administration of IP. Details will be provided in a laboratory manual. Subjects with positive ADA results will be assessed for neutralizing antibodies. At visit 7 (week 13) a postinfusion PK serum sample will be collected immediately after the end of infusion, as indicated by the X. A PK serum sample will also be collected 7 days (± 2 days) after dosing on visit 7a (week 14).

With:

- Pharmacokinetic (PK) and anti-drug antibody (ADA) samples will be shipped to a central laboratory. Both samples should be taken immediately prior to administration of IP. Details will be provided in a laboratory manual. Subjects with positive ADA results will be assessed for neutralizing antibodies. At visit 7 (week 13) a postinfusion PK serum sample will be collected immediately after the end of infusion, as indicated by the X. A PK serum sample will also be collected 7 days (± 2 days) **following the visit 7 (week 13) dosing and is noted above as** visit 7a (week 14).

Section: 8.6.1 Table 3. Schedule of Assessments and Procedures – Period 2 Week 53 to End of Study Visit (Week 79), page 33

Add:

To table abbreviations: **IP = investigational product;**

Replace:

- ABP 959/eculizumab dosing to be administered after all assessments are completed for each visit. If any scheduled dose of investigational product is delayed from the

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scheduled visit date (by more than 2 days), then the dose will be administered as soon as possible, and subsequent doses will be adjusted accordingly to remain every 14 ± 2 days from the adjusted dose date.

[i] Pharmacokinetic and anti-drug antibody (ADA) samples will be shipped to a central laboratory. Both samples should be taken immediately prior to administration of investigational product. Details will be provided in a laboratory manual. Subjects with positive ADA results will be assessed for neutralizing antibodies

With:

[c] ABP 959/eculizumab dosing to be administered after all assessments are completed for each visit. If any scheduled dose of **IP** is delayed from the scheduled visit date (by more than 2 days), then the dose will be administered as soon as possible, and subsequent doses will be adjusted accordingly to remain every 14 ± 2 days from the adjusted dose date

[i] Pharmacokinetic and anti-drug antibody (ADA) samples will be shipped to a central laboratory. Both samples should be taken immediately prior to administration of **IP**. Details will be provided in a laboratory manual. Subjects with positive ADA results will be assessed for neutralizing antibodies

Section: 8.6.1.1 Efficacy Measurements, page 35

Replace:

The primary efficacy endpoint for the crossover comparison is hemolysis, as measured by the time-adjusted area under the effect curve (AUEC) of LDH from week 39 to week 53, and from week 65 to week 79.

With:

The primary efficacy endpoint for the crossover comparison is hemolysis, as measured by the time-adjusted AUEC of LDH **from week 13 to week 27,** from week 39 to week 53, and from week 65 to week 79.

Section: 9.2.1 Period 1 Visits, page 37

Replace:

- At visit 7 (week 13), a post-infusion PK serum sample will be collected immediately after the end of infusion. A PK serum sample will also be collected 7 days (± 2 days) after dosing on visit 7a (week 14)
- Pretreatment ADAs

With:

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- At visit 7 (week 13), a post-infusion PK serum sample will be collected immediately after the end of infusion. A PK serum sample will also be collected 7 days (± 2 days) **following the visit 7 (week 13)** dosing, **noted in Table 1 as** visit 7a (week 14).
- Pretreatment ADA **samples**

Section: 9.3 Visit 27 (Week 53)/Crossover, page 38

Replace:

- Samples for ADAs

With:

- Pretreatment ADA **samples**
  - **Subjects with positive ADA results will be assessed for neutralizing antibodies.**

Section: 9.4.1 Period 2 Visits, page 39

Replace:

- Pretreatment ADAs

With:

- Pretreatment ADA **samples**
  - **Subjects with positive ADA results will be assessed for neutralizing antibodies.**

Section: 9.4.2 Visit 40 (Week 79)/End of Study, page 40

Replace:

AEs and related treatments (eg, blood transfusion data, concomitant medications, procedures) will be recorded in the eCRF during the follow-up period.

With:

Adverse events and related treatments (eg, blood transfusion data, concomitant medications, procedures) will be recorded in the eCRF during the follow-up period.

Section: 10.9 Blood Samples for Pharmacokinetic Analysis, page 43

Replace:

Subjects will also have a post-infusion PK serum sample collected immediately after the end of infusion at visit 7 (week 13) and an additional PK serum sample collected 7 days (± 2 days) after dosing on visit 7a (week 14).

With:

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Subjects will also have a post-infusion PK serum sample collected immediately after the end of infusion at visit 7 (week 13) and an additional PK serum sample collected 7 days (± 2 days) **following the visit 7 (week 13)** dosing**, noted in Table 1 as** visit 7a (week 14).

Section: 11.2.2 Reporting Procedures for Serious Adverse Events, page 48

Replace:

Elective hospitalizations are not considered SAEs.

With:

Elective hospitalizations are not considered **serious adverse events**.

Section: 12.5.2 Modified Full Analysis Set, page 52-53

Replace:

The mFAS will consist of all randomized subjects who have an LDH-time profile evaluable for the time-adjusted AUEC within weeks 39 to 53 and/or within weeks 65 to 79, according to treatment per the randomized sequence regardless of treatment actually received.

With:

The mFAS will consist of all randomized subjects who have an LDH-time profile evaluable for the time-adjusted AUEC within **at least one of the following 14-week assessment periods: week 13 to week 27,** week 39 to **week** 53**,** and week 65 to **week** 79, according to treatment per the randomized sequence regardless of treatment actually received.

Section: 12.5.3.2 Per-protocol Analysis Set for the Primary Endpoint of AUEC for the Crossover Comparison, page 53

Replace:

The per-protocol analysis set for the primary endpoint of time-adjusted AUEC for the crossover comparison (PPC) is a subset of the mFAS, subjects who did not experience an important protocol deviation during weeks 39 to 53 and weeks 65 to 79 that affects their primary efficacy evaluation for the crossover comparison.

With:

The per-protocol analysis set for the primary endpoint of time-adjusted AUEC for the crossover comparison (PPC) is a subset of the mFAS**, which includes** subjects who did not experience an important protocol deviation during **week 13 to week 27,** week 39 to **week** 53**,** and week 65 to **week** 79 that affects their primary efficacy evaluation for the crossover comparison.

Section: 12.5.4.2 Pharmacokinetics Parameter Analysis Set, page 53

Replace:

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The Pharmacokinetics Parameter Analysis Set will be defined as a subset of subjects in the Safety Analysis Set who have an evaluable ABP 959 or eculizumab serum concentration time profile from weeks 13 to 15.

With:

The Pharmacokinetics Parameter Analysis Set will be defined as a subset of subjects in the Safety Analysis Set who have an evaluable ABP 959 or eculizumab serum concentration time profile from week 13 to **week** 15.

Section: 12.6.4.2 Crossover Comparison, page 55

Replace:

The primary endpoint for the crossover comparison is hemolysis, as measured by the time-adjusted AUEC of LDH from week 39 to week 53, and from week 65 to week 79.

With:

The primary endpoint for the crossover comparison is hemolysis, as measured by the time-adjusted AUEC of LDH **from week 13 to week 27,** from week 39 to week 53, and from week 65 to week 79.

Section: 12.6.7 Interim Analyses, page 58

Replace:

The first blinded interim check of CV will take place when approximately 20 subjects complete their week 27 visit. If the aggregated intra-subject CV of AUEC is greater than 42%, additional subjects will be enrolled if feasible. The second blinded interim check of CV will take place when all subjects complete their week 27 visit. If the aggregated inter-subject CV of LDH at week 27 is larger than 130%, the primary endpoint of parallel comparison of LDH at week 27 will be replaced by crossover comparison of LDH at week 53 and week 79.

With:

The first blinded interim check of CV will take place **prior to the end of enrollment**. If the aggregated intra-subject CV of AUEC is greater than **44**%, additional subjects will be enrolled if feasible. The second blinded interim check of CV will take place when **approximately** all subjects complete their week 27 visit. If the aggregated inter-subject CV of LDH is **greater** than 130%, the primary endpoint of parallel comparison of LDH at week 27 will be replaced by crossover comparison of LDH at week 53 and week 79.

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Section: 15.8 Discontinuation of Study, page 67

Replace:

Amgen will not provide ABP 959 or eculizumab for subjects after termination of the trial or upon discontinuation of the study.

With:

Amgen will not provide ABP 959 or eculizumab for subjects after termination of the trial or upon **a subject's** discontinuation **from** the study.

Possible reasons for early termination of the study include the following:

- **New or emerging safety information that negatively affects the benefit/risk assessment of the product or trial as a whole**
- **Insufficient patient recruitment**
- **Lack of efficacy**
- **Administrative reasons**
- **Sponsor decision**

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