Clinical Study Protocol

AN OPEN-LABEL, SINGLE ARM STUDY TO EVALUATE THE EFFICACY AND SAFETY OF REGN3918 IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) WHO ARE COMPLEMENT INHIBITOR-NAIVE OR HAVE NOT RECENTLY RECEIVED COMPLEMENT INHIBITOR THERAPY

Compound:	REGN3918
Clinical Phase:	2
Protocol Number:	R3918-PNH-1852
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AMENDMENT HISTORY

Amendment 2

The following changes were made in this amendment:

Change and Rationale for Change	Section Changed
Removed Sponsor as a responsible party in the confirmation of a breakthrough hemolysis event. In this study, breakthrough hemolysis events as defined by symptoms or signs of PNH concomitant with lactate dehydrogenase level ≥2 × ULN will be ascertained based on the investigator's judgment.	Section 3.2.2 Rationale for Key Secondary Endpoints
Added language to clarify that blood collection should occur if a breakthrough hemolysis event is suspected. Breakthrough hemolysis is defined by LDH ≥2 × ULN concomitant with symptoms. If a breakthrough hemolysis event is suspected based on clinical symptoms, blood will be collected for the analysis of LDH, drug concentration, ADA, total C5, and CH50.	Table 1 Schedule of Events Section 8.1.3 Unscheduled Visits Section 8.2.4.4 Laboratory Testing
Updated the duration of the open-label extension study.	Section 5.1 Study Description and Duration Figure 1 Study Flow Diagram Section 7.5 Post-Study Treatment Access
Clarified the weekly subcutaneous dose (800 mg SC QW) that will be used for the initial cohort A patients.	Section 5.1 Study Description and Duration Section 7.2 Drug Administration
Revised with clarifications related to data analysis to specify (where applicable): • Inclusion of baseline data in the week 8 analysis • Inclusion of an absence of breakthrough hemolysis in the assessment of adequate control at week 26 • Use of t-statistic vs z-statistic in analyses	Clinical Study Protocol Synopsis: Statistical Plan Section 5.1.1 Description of Study Cohorts Section 10.4.3.1 Primary Efficacy Analysis Section 10.4.3.2 Secondary Efficacy Analysis
Removed irrelevant information related to blinding for the interim analysis. This is an open-label study.	Section 5.2 Planned Interim Analysis
Revised exclusion requirement for peripheral blood absolute neutrophil count to <500/µL.	Section 6.2.2 Exclusion Criteria (Criterion #5)
Revised study drug description to remove details that are more appropriately addressed in the pharmacy manual. Amended exclusion criterion #21 to exclude patients with known hypersensitivity to components of the drug product.	Section 6.2.2 Exclusion Criteria (Criterion #21) Section 7.1 Investigational Treatment Section 7.11.1 Packaging, Labeling, and Storage Section 8.1.1 Footnotes for the Schedule of Events Table

Change and Rationale for Change	Section Changed
Revised description of PNH erythrocytes and granulocytes to reflect typical laboratory output for these analytes. Updated inclusion criterion #3 to specify PNH granulocytes that are denoted as polymorphonuclear (PMN).	Clinical Study Protocol Synopsis: Population Section 4.2.3 Exploratory Endpoints Section 6.2.1 Inclusion Criteria (Criterion #3) Table 1 Schedule of Events Section 8.2.8 Pharmacodynamic and Exploratory Biomarker Procedures
Revised language for mandatory meningococcal vaccinations to allow flexibility on the timing of the administration per local practice.	Section 7.4.1 Meningococcal Vaccinations Table 1 Schedule of Events
Clarified that risk assessment and mitigation for Neisseria gonorrhea begin at screening.	Section 5.1 Study Description and Duration Section 7.8 Risk Management of Neisseria Gonorrhea Table 1 Schedule of Events Section 8.2.1 Procedures Performed Only at the Screening/Baseline Visit
Added blood sample collection for PK and immunogenicity assessment in the event of a suspected hypersensitivity reaction.	Section 8.1.3 Unscheduled Visits Section 8.2.4.4 Laboratory Testing
Reduced number of exploratory biomarkers.	Section 4.5 Exploratory Biomarker Variables Table 1 Schedule of Events Section 8.2.8 Pharmacodynamic and Exploratory Biomarker Procedures
Clarified that the hepatitis B and C screening test (to be performed as need per local practice) may be analyzed at the central laboratory.	Table 1 Schedule of Events Section 8.2.1 Procedures Performed Only at the Screening/Baseline Visit
Updated the background information on paroxysmal nocturnal hemoglobinuria to include information on newly approved ravulizumab.	Section 1.1 Background on Paroxysmal Nocturnal Hemoglobinuria
Updated the descriptions and timing of clinical outcome assessments used in this study. The PNH Symptom-Specific Questionnaire will be completed daily by the patient.	Section 4.2.3 Exploratory Endpoints Section 8.1 Schedule of Events Table 1 Schedule of Events Section 8.2.3.6 Clinical Outcome Assessments Section 8.2.7 Clinical Outcome Assessments Section 8.2.7.1 Patient-Reported Outcome Assessments Section 22 References
Added time points for the collection of blood samples for optional research.	Table 1 Schedule of Events

Change and Rationale for Change	Section Changed
Corrected numbering of study days and updated Schedule of Events to reflect changes made in this amendment. Clarified timing of endpoints based on these changes.	Clinical Study Protocol Synopsis: Objectives, Study Duration, Endpoints, Statistical Plan Section 2.1 Primary Objectives Section 3.2.1 Rationale for Study Design Section 3.2.1.2 Rationale for the Co-Primary Endpoints Section 4.2.1 Primary Endpoints Section 4.2.2 Secondary Endpoints Section 4.2.3 Exploratory Endpoints Section 5.1.1 Description of Study Cohorts Section 5.2 Planned Interim Analysis Section 6.4 Replacement of Patients Section 7.2 Drug Administration Section 7.10.1 Method of Treatment Assignment Table 1 Schedule of Events Section 8.1.2 Premature Discontinuation and Follow-up Section 10.2 Justification of Sample Size Section 10.4.3.2 Secondary Efficacy Analysis Section 10.5 Interim Analysis
Clarified that additional screening visits can be added within the screening period. Updated the list of historical parameters that will be collected as part of medical history.	Section 8.2.1 Procedures Performed Only at the Screening/Baseline Visit
Added references to procedures and recommendations related to study drug administration described elsewhere in the protocol.	Section 5.1 Study Description and Duration Section 8.2.2 Study Drug Administration (section added)
Revised the language related to the analysis of immunogenicity data to provide clarification to sites.	Section 4.4 Immunogenicity Variables Section 10.3.4 Immunogenicity Analysis Sets Section 10.4.6 Analysis of Immunogenicity Data
Replaced safety definitions, reporting, and monitoring section with updated Sponsor protocol template language for consistency with current processes.	Section 9 Safety Evaluation and Reporting (entire section, including subsections)
Added section on data transparency for consistency with updated Sponsor protocol template language and processes.	Section 14.5 Clinical Study Data Transparency (section added)

Change and Rationale for Change	Section Changed
Clarifications and corrections.	Title page Section 1.2 Background on REGN3918 Section 2.2 Secondary Objectives Section 2.3 Exploratory Objectives Section 3.2.3 Rationale for Dose Selection Section 5.1 Study Description and Duration Section 6.1 Number of Patients Planned Table 1 Schedule of Events Section 8.2.3.2 Transfusion Record Update Section 8.2.5 Drug Concentration and Measurements Section 10.3.3 Pharmacokinetic Analysis Sets Section 10.3.4 Immunogenicity Sets Section 10.3.5.1 Exploratory Biomarker Endpoint Analysis Set Section 10.3.5.2 Exploratory Clinical Outcome Assessment Analysis Set Section 10.4.4.2 Other Safety Section 12.3 Case Report Form Requirements Section 22 References
Minor editorial changes	Throughout the document

Amendment 1

Changes were made to address comments following the European Union (EU) regulatory review. The following table outlines the changes made to the protocol and the affected sections:

Change and Rationale for Change	Section Changed
Study phase changed from phase 3 to phase 2	Title page
Clarified that safety is part of the decision to progress from cohort A to cohort B	Section 5.1.1 Description of Study Cohorts
Revised exclusion criterion #7 to exclude patients with active or latent tuberculosis infection	Section 6.2.2 Exclusion Criteria (Criterion #7) Section 8.1 – Table 1 Schedule of Events Section 8.2.1 Procedures Performed Only at Screening/ Baseline Visit Section 8.2.4.4 Laboratory Testing
Added exclusion criteria to exclude patients with known chronic infection with hepatitis B or C and patients with pre-existing or acute liver disease	Section 6.2.2 Exclusion Criteria (Criterion #14 and #29)
Extended the recommended contraception use period and safety follow-up period to 21 weeks	Section 6.2.2 Exclusion Criteria (Criterion #28) Section 7.4.2 Oral Antibiotics Section 8.1.2 Premature Discontinuation and Follow-up Section 9.4.2 Serious Adverse Events Section 9.4.3 Other Events that Require Accelerated Reporting to Sponsor Section 10.4.4.1 Adverse Events
Specified that a maximum of 6 patients may be replaced in cohort A	Section 6.4 Replacement of Patients
Added language to emphasize that the administration, duration, and choice of concomitant antibiotics are at the discretion of the investigator	Section 7.4.2 Oral Antibiotics
Revised language regarding risk assessment and risk management of Neisseria gonorrhea	Section 7.8 Risk Management of Neisseria Gonorrhea
Clarified in the statistical methods that the cohorts will be analyzed separately if there is a change in dosing regimen between cohort A and cohort B, and that cohort B will be the primary analysis cohort in this situation	Section 10.4 Statistical Methods
Revised with details of the analysis of secondary endpoints	Section 10.4.3.2 Secondary Efficacy Analysis
Minor editorial/formatting corrections	Various

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	An Open-Label, Single Arm Study to Evaluate the Efficacy and Safety of REGN3918 in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) who are Complement Inhibitor-Naive or Have Not Recently Received Complement Inhibitor Therapy
Site Location(s)	Multiple Global Sites
Coordinating Investigator	Anita Hill, MBChB (Hons), MRCP, FRCPath, Ph.D. Consultant Haematologist for Leeds Teaching Hospitals NHS Trust, UK, and Honorary Senior Lecturer at the University of Leeds
Objectives	The primary objective of the study is to demonstrate a reduction in intravascular hemolysis by REGN3918 over 26 weeks of treatment (assessed at week 26) in patients with active PNH who are treatment-naive to complement inhibitor therapy or have not recently received complement inhibitor therapy. The secondary objectives of the study are: • To evaluate the safety and tolerability of REGN3918 • To evaluate the effect of REGN3918 on parameters of intravascular hemolysis • To assess the concentrations of total REGN3918 in serum • To evaluate the incidence of treatment-emergent anti-drug antibodies to REGN3918 over time • To evaluate the effect of REGN3918 on patient-reported outcomes (PROs) measuring fatigue and health-related quality of life
Study Design	This is an open-label, single arm, 26-week treatment study in patients with confirmed diagnosis of PNH and active signs and symptoms who either are complement inhibitor naive or have received prior treatment with a complement inhibitor, but not within 6 months prior to screening visit. In this study, there will be two cohorts, one for dose confirmation (cohort A) and one for dose expansion (cohort B). Dose confirmation will be made at the interim analysis. The inclusion and exclusion criteria and schedule of events are the same for cohort A and cohort B. During the assessment of data from cohort A, recruitment into the study will continue, with patients recruited being assigned subsequently as follows: if a decision is made to expand cohort A, they will be assigned to cohort A. If a decision is made to progress to cohort B, they will be assigned to cohort B. Patients will be given a single loading dose of REGN3918 30 mg/kg intravenous (IV) on day 1, then a dose not greater than 800 mg subcutaneous (SC) once weekly (QW; ± 1 day) to week 26.

Study Duration	The duration of the study for a patient is approximately 27 weeks, excluding the screening period. The study consists of a screening period (up to 4 weeks), 26-week treatment period, and an end-of-study visit one week after the last study drug administration. After completion of the 26-week treatment period, patients may enroll into a separate open-label extension study, which will provide uninterrupted treatment with REGN3918. Patients who discontinue treatment will have a minimum of a 21-week follow-up period.
End of Study Definition	At a study level, the end of study is defined as the last visit of the last patient.
Population	
Sample Size:	Approximately 30 to 42 adults (men and women) are planned to be enrolled.
Target Population:	The study population will consist of adult male and female patients with confirmed diagnosis of PNH and active signs and symptoms who either are complement inhibitor-naive or have received prior treatment with a complement inhibitor, but not within 6 months prior to screening visit. Key Inclusion Criteria: • Male or female ≥ 18 years of age or legal age of majority at screening, whichever is greater • Diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) confirmed by high-sensitivity flow cytometry • Active disease, as defined by the presence of 1 or more PNH-related signs or symptoms or history of red blood cell (RBC) transfusion due to PNH within 3 months of screening. • Lactate dehydrogenase (LDH) level ≥ 2 × upper limit of normal (ULN) at screening visit. • PNH granulocytes (denoted as polymorphonuclear [PMN]) >10% at screening visit. Key Exclusion Criteria: • Prior treatment with a complement inhibitor either within 6 months prior to screening visit or at any time where the patient was refractory to complement inhibitor therapy, in the opinion of the investigator (with the exception of eculizumab refractory patients due to the C5 variant R885H/C)
Treatment	
Study Drug	REGN3918
Dose/Route/Schedule:	Patients will be given a single loading dose of REGN3918 30 mg/kg IV on day 1, then a dose no greater than 800 mg SC QW

Endpoints

Primary:

The co-primary endpoints are:

- The proportion of patients achieving adequate control of their intravascular hemolysis, defined as LDH ≤ 1.5 x ULN at every scheduled time point between week 4 and week 26, inclusive
- The proportion of patients achieving transfusion avoidance defined as no post baseline transfusion of RBCs per protocol through week 26

Secondary:

The secondary endpoints are:

- The rate of breakthrough hemolysis through week 26, defined as the measurement of LDH ≥ 2 x ULN concomitant with associated signs or symptoms at any time subsequent to an initial achievement of disease control (ie, LDH ≤ 1.5 x ULN)
- The proportion of patients achieving normalization of their intravascular hemolysis, defined as LDH ≤ 1.0 x ULN at every scheduled time point between week 4 through week 26, inclusive
- Time to first LDH ≤ 1.5 x ULN
- Percentage of days with LDH ≤ 1.5 x ULN between week 4 and week 26, inclusive
- Change and percent change in LDH levels from baseline to week 26
- The rate and number of units of transfusion with RBCs through week 26
- Change in RBC hemoglobin levels from baseline to week 26
- Change in free hemoglobin levels from baseline to week 26
- Change and percent change in total complement hemolytic activity assay (CH50) from baseline to week 26
- Change in patient-reported outcomes (fatigue as measured by the FACIT-Fatigue and health-related quality of life as measured by the European Organization for Research and Treatment of Cancer [EORTC]-QLQ-30 and EQ-5D-3L) from baseline to week 26
- Incidence and severity of treatment-emergent adverse events (TEAEs) and other safety variables through week 26
- Concentrations of total REGN3918 in serum assessed throughout the study
- Incidence of treatment-emergent anti-drug antibodies (ADA) to REGN3918 in patients over time

Procedures and Assessments

Procedures and Assessments are detailed in the protocol body

Statistical Plan

This is a single-arm open-label study, and a formal power calculation for comparison with a control is not intended. A sample size of 30-42 patients will provide sufficient precision for estimation of the co-primary endpoints. For cohort A, a sample size of 6 is standard in assessing safety and tolerability of a drug dose first tested in patients. Also, it was assessed that sufficient assurance of efficacy with the initial dosing regimen will be provided for a decision to progress from cohort A to cohort B if all 6 cohort A patients achieve an LDH $\leq$ 1.5 x ULN at week 8.

The full analysis set (FAS) includes all enrolled patients who received any study drug.

For the co-primary endpoint of the proportion of patients achieving adequate control of their intravascular hemolysis, defined as LDH $\leq$ 1.5 x ULN at every scheduled time point between week 4 and week 26, inclusive, the analysis set will consist of all FAS patients. Patients who have one or more of the following will be considered as not achieving adequate control of their intravascular hemolysis:

- Discontinue from study treatment early
- Have 3 consecutive missing values of the scheduled LDH measurements between week 4 and week 26
- Have 50% or more missing values of the scheduled LDH measurements between week 4 and week 26
- Experience breakthrough hemolysis event (as defined in the secondary endpoint) while on treatment through week 26.

Patients who complete study treatment, have no more than 2 consecutive missing values of the scheduled LDH measurements between week 4 and week 26, have fewer than 50% missing values of the scheduled LDH measurements between week 4 and week 26, and have no breakthrough hemolysis while on treatment will be evaluated based on their non-missing LDH measurements.

The proportion of patients achieving adequate control of their intravascular hemolysis will be calculated, along with a 95% confidence interval, by approximation of a one-sample z-statistic, as primary analysis and by exact methods as sensitivity analysis. A sensitivity analysis by multiple imputation of missing LDH measurements will also be performed. Multiple imputation methods to be applied will be detailed in the statistical analysis plan (SAP).

For the co-primary endpoint of the proportion of patients achieving transfusion avoidance, the analysis set will consist of all FAS patients. A transfusion will be counted only if the transfusion follows the predefined transfusion algorithm. A time-to-first-event analysis will be used to estimate the proportion of patients achieving transfusion avoidance at week 26 and a 95% confidence interval.

Sensitivity analyses of the co primary endpoints will also be conducted for subgroups of FAS patients, including all complement inhibitor naive patients (no prior complement inhibitor therapy) in cohort A and cohort B, all patients in cohort B, and all complement inhibitor naive patients in cohort B.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
AH50	Alternative pathway hemolytic activity assay
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BID	Twice a day
CH50	Total Complement hemolytic activity assay
CRF	Case report form (electronic or paper)
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
EORTC	European Organization for Research and Treatment of Cancer
EoS	End of study
eGFR	Estimated glomerular filtration rate
F1+2	D-dimer and N-terminal prothrombin fragments
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full analysis set
FIH	First-in-human
GCP	Good Clinical Practice
GPI	Glycophosphatidylinositol
HRQoL	Health-related quality of life
HSC	Hematopoietic stem cells
ICF	Informed consent form
ICH	International Council for Harmonisation
IgG4^{P}	Human monoclonal immunoglobulin G4^{P}
Ig	Immunoglobulin
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
LDH	Lactate dehydrogenase

LLOQ	Lower limit of quantification
MAC	Membrane attack complex
MAVE	Major adverse vascular event
MMRM	Mixed-effect model for repeated measures
NAb	Neutralizing Antibody
NOAEL	No observable adverse effect level
OLE	Open-label extension
PD	Pharmacodynamic
PIGA	Phosphatidylinositol glycan anchor biosynthesis class A
PGIC	Patient global impression of change
PGIS	Patient global impression of severity
PK	Pharmacokinetic
PMN	Polymorphonuclear
PNH	Paroxysmal nocturnal hemoglobinuria
PRO	Patient reported outcome
PT	Preferred term
Q2W	Every 2 weeks
QLQ-C30	Quality of life questionnaire-core 30
QW	Once weekly
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SC	Subcutaneous
SOC	System organ class
TEAE	Treatment-emergent adverse event
TFPI	Tissue Factor Pathway Inhibitor
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	Upper limit of normal
WBC	White blood cell

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1. INTRODUCTION

1.1. Background on Paroxysmal Nocturnal Hemoglobinuria

Paroxysmal nocturnal hemoglobinuria (PNH) is a chronic, progressive, life-threatening, and rare multisystem disease. It is characterized by uncontrolled complement activation on red blood cells (RBCs), resulting in intravascular hemolysis (Sahin, 2016), and on white blood cells (WBCs) and platelets, resulting in an increased risk of thrombosis. The estimated incidence of PNH is 1.3 cases per million individuals per year, and the estimated prevalence is 15.9 cases per million individuals per year (Preis, 2014).

Paroxysmal nocturnal hemoglobinuria originates from a multipotent, hematopoietic stem cell (HSC) that acquires a mutation of the phosphatidylinositol glycan anchor biosynthesis class A (PIGA) gene. The PIGA gene product is required for the biosynthesis of the glycophosphatidylinositol (GPI) anchor, a glycolipid moiety that attaches dozens of proteins to the plasma membrane of cells. Consequently, the PNH stem cell and all of its progeny have a reduction or absence of GPI-anchored proteins. The mature blood cells derived from the hematopoietic clone can have a complete deficiency (type III) or a partial deficiency (type II) of GPI-linked proteins (Hillmen, 2004). Two of the proteins that are affected by the absence of GPI anchors are CD55 and CD59, complement regulatory proteins. CD55 regulates complement activation by inhibiting complement component 3 (C3) convertases, whereas CD59 inhibits the assembly of the membrane-attack complex (MAC) C5b–C9 by interacting with C8 and C9 (Brodsky, 2009). Their absence renders PNH erythrocytes susceptible to complement-mediated intravascular hemolysis. This intravascular hemolysis in patients with PNH causes anemia (frequently requiring blood transfusion) and hemoglobinuria. Complications of PNH include thrombosis, abdominal pain, dysphagia, erectile dysfunction, and pulmonary hypertension (Hillmen, 2006). Thromboembolism is the most common cause of mortality in patients with PNH and accounts for approximately 40% to 67% of attributable deaths. Potential mechanisms for thromboembolism include platelet activation, toxicity of free hemoglobin, nitric oxide depletion, absence of other GPI-linked proteins, and endothelial dysfunction (Hill, 2013). PNH frequently occurs with autoimmune aplastic anemia (Luzzatto, 2018). Evidence suggests that loss of PIGA provides protection for the PNH clone against HSC loss (by removing a putative GPI-anchored autoantigen serving as a target for an autoimmune response against the HSC).

The diagnosis of PNH is established using the internationally accepted definition of presence of PNH granulocyte clone size of >10% measured in peripheral blood by flow cytometry. An accepted definition of active disease is the presence of 1 or more of the following PNH-related signs or symptoms within 3 months: fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), anemia (hemoglobin <10 g/dL), history of a major adverse vascular event (MAVE; including thrombosis), dysphagia, or erectile dysfunction. Alternatively, activity can be established by a history of RBC transfusion due to PNH within 3 months.

Eculizumab, approved for the treatment of PNH in many countries worldwide, including the United States (US) and European Union (EU) member states, is a humanized monoclonal antibody directed against the terminal complement protein C5. It blocks the formation of the MAC - C5b-9, thus protecting PNH RBCs from complement-mediated intravascular hemolysis. The basis for approval of eculizumab has been its effectiveness in PNH, as evidenced by the

initial reduction of lactate dehydrogenase (LDH) levels and by the long-term reduction in the need for blood transfusions; decrease in the incidence of thrombosis; improvement in anemia; and improvement in quality of life (Griffin, 2017).

However, not all patients receive optimal therapeutic benefit. For example, 25% of patients still need recurrent, albeit less frequent, blood transfusions. Up to 20% of patients on eculizumab therapy require significant increases in dose or dose frequency due to breakthrough hemolysis secondary to incomplete inhibition of C5 (Nakayama, 2016) (Hill, 2013) (Peffault de Latour, 2015). While the regulatory approval of ravulizumab (Ultomiris™) in the US in December 2018 has improved convenience with a dosing frequency of every 8 weeks, it is not available in most of the world and patients still experience some hemolytic breakthrough. In addition, it does not offer the significant convenience and reduced burden of subcutaneous (SC) self-administration. In rare instances, eculizumab, and presumably ravulizumab, is ineffective due to polymorphic variation in the gene encoding C5 such that the protein is not recognized by eculizumab (Nishimura, 2014). The heterogeneity in these hematological responses may be related to underlying aplastic anemia, C3b-mediated extravascular hemolysis, or incomplete pharmacologic blockade of C5, and rare polymorphisms in the gene coding for C5 (Al-Ani, 2016). Eculizumab administration every 2 weeks (Q2W) by intravenous (IV) infusion has been described as burdensome for patients.

Thus, unmet needs for patients include better control of breakthrough hemolysis by providing maximal and durable inhibition of C5 throughout the dosing interval, improving the dosing regimen, binding to the polymorphic variant C5 protein which renders eculizumab ineffective, and development of a convenient subcutaneous (SC) formulation.

1.2. Background on REGN3918

REGN3918 is a fully human monoclonal immunoglobulin $G4^P$ ($IgG4^P$) antibody directed against the terminal complement protein C5, which inhibits terminal complement activation by preventing C5 cleavage by C5 convertase into C5a (anaphylatoxin) and C5b, thereby blocking the formation of the MAC – C5b-9, a structure mediating cell lysis. REGN3918 is being developed for the treatment of PNH and other diseases in which tissue damage is mediated by terminal complement pathway activity. REGN3918 can be administered by IV or SC administration. Additionally, REGN3918 binds to polymorphic variations in C5 that are not recognized by eculizumab.

REGN3918 was well-tolerated in a toxicology study in cynomolgus monkeys at doses up to 100 mg/kg/week following IV administration for 26 weeks, with a 13-week recovery period. The no observable adverse effect level (NOAEL) based on the results of this toxicology study was determined to be 100 mg/kg, the highest dose tested. REGN3918 was demonstrated to have low potential for cytokine release in cell-based, in vitro experiments. Complexes of REGN3918 and C5 did not result in the formation of immune complexes capable of binding to complement C1q.

REGN3918 has been evaluated in a randomized, placebo-controlled, double-blind study (R3918-HV-1659) in 56 healthy subjects in 7 dose cohorts (N=8, randomized 6:2 REGN3918:placebo for each cohort). REGN3918 was found to be generally well tolerated in ascending single-doses of 1, 3, 10, 30 mg/kg IV, and 300 and 600 mg SC. The seventh cohort, a multiple-dose cohort of 4 QW SC doses of 400 mg following a 15 mg/kg IV loading dose, resulted in one resolved serious adverse event (SAE) in the study, an episode of salpingitis of undetermined microbial etiology. Utilizing the gold standard sheep RBC hemolysis assay (sRBC total complement hemolytic activity assay [CH50]), dose-dependent, complete complement inhibition was demonstrated for the single-dose cohorts. The multiple-dose cohort demonstrated complete complement inhibition throughout the dosing period. Additional background information on the study drug and development program can be found in the Investigator's Brochure.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to demonstrate a reduction in intravascular hemolysis by REGN3918 over 26 weeks of treatment (assessed at week 26) in patients with active PNH who are treatment-naive to complement inhibitor therapy or have not recently received complement inhibitor therapy.

2.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the safety and tolerability of REGN3918
- To evaluate the effect of REGN3918 on parameters of intravascular hemolysis
- To assess the concentrations of total REGN3918 in serum
- To evaluate the incidence of treatment-emergent anti-drug antibodies to REGN3918 over time
- To evaluate the effect of REGN3918 on patient-reported outcomes (PROs) measuring fatigue and health-related quality of life

2.3. Exploratory Objectives

The exploratory objectives of the study are:

- To explore the effect on clinical thrombosis events
- To explore the effect on renal function and renal injury biomarkers
- To explore the effect of REGN3918 on complement activation and intravascular hemolysis relevant to PNH and other related diseases
- To explore the effect of REGN3918 on the level of total C5 protein
- To explore the effect of REGN3918 on PNH clone size
- To explore the effect of REGN3918 on treatment satisfaction and a novel PRO measuring PNH-specific symptoms
- To explore factors contributing to changes in well-being such as fatigue or quality of life in a subset of patients at participating sites (ie, sub-study)
- To study REGN3918 mechanism of action (including relationship to safety and efficacy), complement pathway biology, PNH, and related complement-mediated diseases
- To collect whole blood DNA and RNA from consented patients in order to explore whether potential differences in patient efficacy and safety are associated with genotype and gene expression, and to further study C5, PNH, or other conditions associated with complement-mediated injury

3. HYPOTHESIS AND RATIONALE

3.1. Hypothesis

The clinical hypothesis of the study is that REGN3918 will reduce complement-mediated intravascular hemolysis as measured by reduction in LDH and reduce the requirement for transfusion with RBCs in patients with active PNH who are complement inhibitor-naive or have not recently received complement inhibitor therapy.

3.2. Rationale

3.2.1. Rationale for Study Design

The study is a single-arm study and thus patients and the investigator will be aware of treatment allocation. This is deemed acceptable as 1 of the 2 co-primary endpoints of the study is an objective, laboratory-based parameter (ie, LDH) that is less likely to be biased by knowledge of treatment assignment. The other co-primary endpoint is transfusion avoidance, and the study protocol includes a transfusion algorithm that will standardize the decision to transfuse and thus minimize bias from knowledge of treatment assignment.

The study does not include a placebo control, because there is an approved treatment for PNH (ie, eculizumab), and not treating patients with active PNH increases the risk of serious or irreversible harm from sequelae of the disease.

In this study, there will be two cohorts, one for dose confirmation (cohort A) and one for dose expansion (cohort B). Cohort A will comprise of patients whose data will contribute to an initial evaluation at week 8, after 8 weeks of therapy, the purpose of which is the confirmation of the adequacy of the selected dose regimen (Section 5.1).

3.2.1.1. Rationale for Study Population

The study population will consist of adult male and female patients with confirmed diagnosis of PNH and active signs and symptoms, who either are complement inhibitor-naive or have received prior treatment with a complement inhibitor, but not within 6 months prior to screening visit. Active signs and symptoms are defined as: The presence of PNH-related signs or symptoms in the 3 months prior to screening, or having received at least one RBC transfusion within 3 months of screening along with LDH ≥2 x upper limit of normal (ULN).

The complement inhibitor-naive population was selected because these patients are known to benefit from complement therapy, as demonstrated by effectiveness of eculizumab. The effectiveness of eculizumab has been shown to be directly related to its ability to completely inhibit complement-mediated hemolysis. Finally, the inhibition of complement-mediated intravascular hemolysis in patients with active PNH can readily be measured in vivo by a rapid reduction in serum LDH levels.

Patients with PNH who had previously received complement inhibitor therapy could benefit from an alternative treatment with REGN3918. These patients discontinued prior complement inhibitor therapy for a number of reasons, and the fact that they have active PNH is an indication for reinitiating anti-C5 therapy unless the patient was refractory to complement inhibitory therapy, with the exception of eculizumab-refractory patients due to the C5 variant R885H/C.

3.2.1.2. Rationale for the Co-Primary Endpoints

The choice of a co-primary endpoint of LDH reduction and transfusion avoidance combines the accepted objective laboratory measure of control of intravascular hemolysis with a clinical measure of reduced disease activity: transfusion avoidance. Additionally, these measures have several important precedents and disease-specific rationale for their use as co-primary endpoints.

The assessment of intravascular hemolysis, as measured by LDH, is central to the clinical monitoring of PNH (Rother, 2005), as demonstrated in eculizumab studies. Pivotal eculizumab studies, subsequent studies using eculizumab as a comparator to ravulizumab (ALXN1210, a humanized monoclonal antibody to C5 engineered from the parent molecule eculizumab), to provide extended half-life, and the PNH Registry have shown that the active PNH population has LDH elevated in the range of 6-8 x ULN (Roth, 2018). Upon treatment with anti-C5 antibody, LDH levels fall rapidly in all patients with the clinical goal of achieving an LDH of ≤1.5 x ULN.

An LDH of 1.5 x ULN is a clinically meaningful threshold for disease activity: greater than 1.5 x ULN, along with related clinical symptoms, is considered as an indication for treatment with eculizumab (Sahin, 2016) (Soliris®, 2019). Although not included as an endpoint in the efficacy section of the US Prescribing Information (USPI), reductions in LDH below the 1.5 x ULN threshold with eculizumab therapy have been shown to be correlated with improvement in patient's symptoms, quality of life measures, and transfusion requirements (Brodsky, 2008). Furthermore, in the ravulizumab treatment study in patients with PNH who are naive to complement inhibitor therapy (ravulizumab vs eculizumab) (Roth, 2018), the mean LDH at baseline was >6 x ULN and was reduced by >76% to a mean LDH between 1.0 to 1.3 x ULN at each timepoint from day 29 through day 183 of the study.

Transfusion avoidance is utilized in combination with LDH reduction as co-primary endpoints because transfusion is a clinical measure disease activity. In the eculizumab pivotal studies of patients with PNH who were treatment-naive, TRIUMPH (Sahin, 2016) and SHEPHERD (Roth, 2018), 0% of patients were transfusion-independent at enrollment, with 51% and 56% achieving transfusion avoidance during the studies, respectively. Similarly, the more recent study evaluating ravulizumab vs. eculizumab in PNH naive patients reported 18% and 17%, respectively, transfusion independence in the year prior to the study with 73.6% and 66.1%, respectively, transfusion avoidance through week 26. A predefined algorithm for transfusion allows for standardization in the current study and captures a clinically meaningful event related to complement-mediated intravascular hemolysis.

3.2.2. Rationale for Key Secondary Endpoints

Breakthrough intravascular hemolysis and a return of PNH symptoms occur in approximately 25% of patients with PNH treated with the approved dose of eculizumab, and may result in direct clinical consequences for patients. In this study, breakthrough hemolysis is a key secondary endpoint, defined by the measurement of LDH ≥ 2 x ULN concomitant with associated signs or symptoms at any time subsequent to an initial achievement of disease control (ie, LDH ≤ 1.5 x ULN) (Roth, 2018) as determined by the investigator. Examples of signs or symptoms include the following: new onset or worsening fatigue, headache, dyspnea, hemoglobinuria, abdominal pain, scleral icterus, erectile dysfunction, chest pain, confusion, dysphagia, anemia (hemoglobin value significantly lower as compared to patient's known baseline hemoglobin values), and thrombotic event.

In addition to the co-primary endpoint of the proportion of patients reaching an LDH ≤ 1.5 x ULN, a more stringent criterion of LDH normalization will be analyzed; however, an additional clinical benefit of more stringent LDH control has not been fully established. Aside from achievement of normalization of LDH (as defined by LDH ≤ 1.0 x ULN), LDH will be reported using change and percent change from baseline. It should be noted that the degree of change from baseline has not been correlated, to date, with any clinically meaningful disease control parameters. While this continuous outcome measure is efficient at showing a drug effect on hemolysis with very few patients, it does not allow for an assessment of likelihood of clinical disease control.

Hemoglobin levels in patients with PNH can be measured as RBC hemoglobin or as free hemoglobin. RBC hemoglobin levels are correlated with symptoms and are used to guide decisions on the need for transfusion. Intravascular hemolysis releases free hemoglobin into the plasma. Free plasma hemoglobin scavenges nitric oxide, and depletion of nitric oxide at the tissue level contributes to numerous PNH manifestations, including esophageal spasm, male erectile dysfunction, renal insufficiency, and thrombosis. Thus, free hemoglobin levels are a useful clinical parameter in patients with PNH.

3.2.3. Rationale for Dose Selection

A single loading dose of REGN3918 30 mg/kg IV on day 1, then 800 mg SC once weekly (QW), has been initially selected based on safety and pharmacokinetic (PK)/pharmacodynamic (PD) data from the first-in-human (FIH) study R3918-HV-1659 in healthy volunteers, as well as toxicology data in cynomolgus monkeys. Total complement hemolytic activity assay (CH50) was used as the principal PD marker and total C5 concentration in plasma was used as a secondary PD marker (ie, Section 1.2).

Descriptive and model-based PK/PD analyses were performed to facilitate dose selection for the current study. These analyses indicate that on average, a minimum concentration of 100 mg/L REGN3918 is required to maximally suppress C5 activity across the treated population. The dosing regimen was selected to achieve higher concentrations than this for three reasons:

- To ensure that all patients achieve this threshold in spite of uncertainty in the population PK/PD model and variability in PK and response among patients
- To ensure that the REGN3918 serum concentration remains above this threshold despite any increases in C5 production, which may occur during intercurrent illnesses, such as infections
- A single dose of 30 mg/kg IV was well tolerated in study R3918-HV-1659.

The loading dose of 30 mg/kg IV will help to quickly achieve the steady-state trough concentration required for sustained maximal CH50 inhibition.

At the proposed ≤800 mg SC QW regimen, the steady-state weekly area under the curve (AUC) (AUC_{tau}) in patients is predicted to be well below the cumulative AUC observed in monkeys at NOAEL dose. Also, it is expected that the peak concentration (C_{max}) in this study will not exceed that in the FIH study. Therefore, the proposed dose is expected to be tolerated.

[redacted].

3.3. Risk-Benefit

Benefit of blocking C5 complement activity in PNH has been clearly established by eculizumab. REGN3918 offers potential additional benefits of better control of breakthrough hemolysis by providing maximal and durable inhibition of C5 throughout the dosing interval, improving the dosing regimen, binding to the polymorphic variant C5 protein which renders eculizumab ineffective, and development of a convenient subcutaneous (SC) formulation.

An established risk of blocking C5 complement activity is an increased susceptibility to infections, specifically to encapsulated organisms, the most potentially severe of which is infection with Neisseria meningitidis (Figueroa, 1991). Experience with eculizumab suggests that pretreatment with appropriate vaccinations covering multiple serotypes and concurrent therapy with oral antibiotics is effective at mitigating this risk (Hillmen, 2013) (Soliris®, 2019). Current treatment guidelines for PNH and the eculizumab package insert recommend such vaccination prior to dosing. In various disease settings such as asplenia in sickle cell disease, and with terminal complement deficiency, use of long-term prophylactic antibiotics has been safely implemented for the prevention of encapsulated organisms including N. meningitidis (Gaston, 1986) (Wedzicha, 2008). Because vaccination does not provide 100% coverage to all strains and there are no proven titer levels associated with 100% protection, prophylactic oral antibiotics are also commonly given to patients with genetic or pharmacologic deficiency in terminal complement activity. Therefore, vaccination prior to administration (or at the time of administration, based on local practice, Section 7.4.1) will sufficiently mitigate the risk of single

and multiple doses of REGN3918 in patients to a level that has been considered acceptable in other anti-C5 clinical development programs. In addition, concurrent therapy with oral antibiotics is recommended (Section 7.4.2).

Recently, serious infections with Neisseria species (other than N. meningitidis), including disseminated gonococcal infections, have been reported during eculizumab treatment (Soliris®, 2019). Counseling about Neisseria gonorrhea prevention, testing, and treatment is to be performed in accordance with local practice/national guidelines (see Section 7.8).

A risk-benefit statement for REGN3918 is provided in the Investigator's Brochure.

4. STUDY VARIABLES

4.1. Demographic and Baseline Characteristics

Baseline characteristics (as allowed to be collected per local regulations) will include standard demographic information (eg, age, race, weight, height, etc), disease characteristics, medical history, and medication history for each patient.

4.2. Endpoints

4.2.1. Primary Endpoints

The co-primary endpoints are:

- The proportion of patients achieving adequate control of their intravascular hemolysis, defined as LDH ≤ 1.5 x ULN at every scheduled time point between week 4 and week 26, inclusive
- The proportion of patients achieving transfusion avoidance defined as no post-baseline transfusion of RBCs per protocol through week 26

4.2.2. Secondary Endpoints

The secondary endpoints are:

- The rate of breakthrough hemolysis through week 26, defined as the measurement of LDH ≥ 2 x ULN concomitant with associated signs or symptoms at any time subsequent to an initial achievement of disease control (ie, LDH ≤ 1.5 x ULN)
- The proportion of patients achieving normalization of their intravascular hemolysis, defined as LDH ≤ 1.0 x ULN at every scheduled time point between week 4 through week 26, inclusive
- Time to first LDH ≤ 1.5 x ULN
- Percentage of days with LDH ≤ 1.5 x ULN between week 4 and week 26, inclusive.
- Change and percent change in LDH levels from baseline to week 26
- The rate and number of units of transfusion with RBCs through week 26
- Change in RBC hemoglobin levels from baseline to week 26
- Change in free hemoglobin levels from baseline to week 26
- Change and percent change in CH50 from baseline to week 26.
- Change in patient-reported outcomes (FACIT-Fatigue, European Organization for Research and Treatment of Cancer [EORTC]-QLQ-30, and EQ-5D-3L) from baseline to week 26
- Incidence and severity of treatment-emergent adverse events (TEAEs) and other safety variables through week 26
- Concentrations of total REGN3918 in serum assessed throughout the study
- Incidence of treatment-emergent anti-drug antibodies (ADA) to REGN3918 in patients over time

4.2.3. Exploratory Endpoints

The exploratory endpoints are:

- Incidence of MAVE through week 26
- Change in renal function as measured by estimated glomerular filtration rate (eGFR) from baseline to week 26
- Treatment satisfaction as measured by the Treatment Satisfaction Questionnaire for Medication (TSQM) at week 26
- Change in PNH symptoms as measured by the de novo PNH symptom-specific questionnaire at week 26
- Change in haptoglobin from baseline to week 26
- Change in bilirubin from baseline to week 26
- Change in reticulocyte count from baseline to week 26
- Change and percent change in alternative pathway hemolytic activity assay (AH50) from baseline to week 26
- Change in Total C5 from baseline to week 26
- Change in PNH erythrocytes and granulocytes from baseline to week 26
- Change in metrics recorded by wearable activity tracker through week 12 in a subset of patients at participating sites.

4.3. Pharmacokinetic Variables

The PK variable is the concentration of total REGN3918 at each time point. The sampling time points are specified in Table 1.

4.4. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, neutralizing antibody (NAb) status, and time point/visit. Samples in this study will be collected at the clinic visits specified in Table 1.

4.5. Exploratory Biomarker Variables

Exploratory variables may include, but are not limited to, the following:

- Markers for renal injury, eg, clusterin (CLU), Cystatin-C (CysC), Kidney Injury Molecule-1 (KIM-1), Nacetyl-beta-D-glucosaminidase (NAG), Neutrophil Gelatinase-Associated Lipocalin (NGAL), and osteopontin (OPN)
- Markers for pulmonary arterial hypertension, eg, NT-proBNP
- Markers of thrombosis (D-dimer, N-terminal prothrombin fragments [F1+2], tissue Factor Pathway Inhibitor (TFPI), and inflammation (interleukin 6 [IL-6])
- Additional exploratory biomarkers (PD, predictive, and prognostic) potentially related to REGN3918 treatment exposure, clinical activity, or underlying disease may be investigated

5. STUDY DESIGN

5.1. Study Description and Duration

This is an open-label, single arm, 26-week treatment study in patients with confirmed diagnosis of PNH and active signs and symptoms who either are complement inhibitor-naive or have received prior treatment with a complement inhibitor, but not within 6 months prior to screening visit.

Patients will be given a single loading dose of REGN3918 30 mg/kg IV on day 1, then a dose no greater than 800 mg SC QW (± 1 day) over the treatment period. The weekly subcutaneous dose is 800 mg SC QW (±1 day) for the initial cohort A patients.

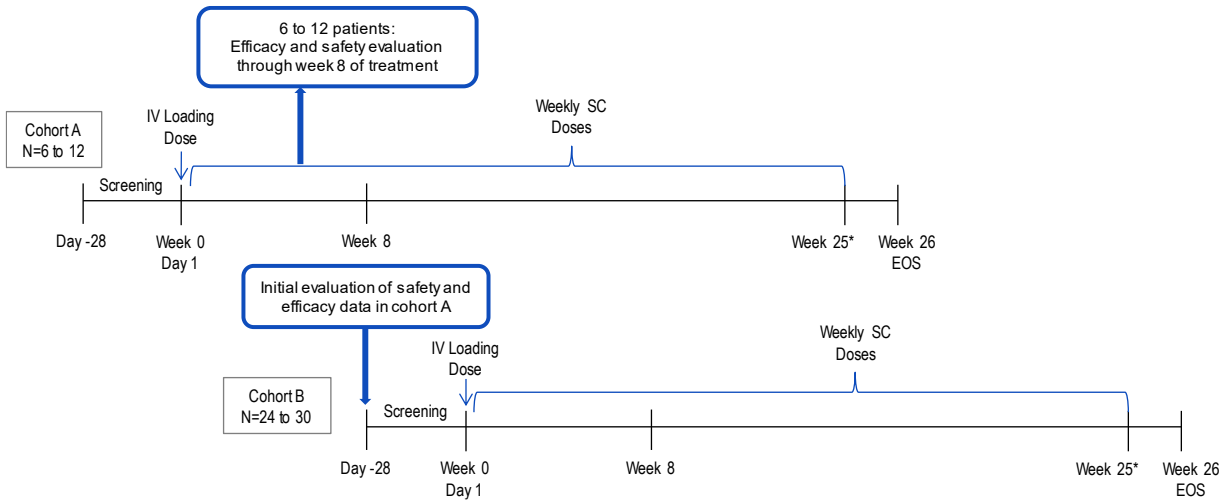
The study consists of a screening period (up to 4 weeks) followed by a 26-week treatment period (from week 0 to week 25), and an end-of-study visit one week after the last study drug administration (at week 26). After completion of the 26-week treatment period, patients may enroll into a separate open-label extension (OLE) study, which will extend treatment with REGN3918 for an additional 2 years, with the possibility of continuation for suitable patients (Section 7.5). Patients who discontinue treatment (including those who decline enrollment into the optional OLE study) will have a minimum of a 21-week follow-up period (Section 8.1.2).

As part of risk mitigation for this study, patients should receive updated meningococcal vaccination (Section 7.4.1), and are recommended to receive daily oral antibiotic prophylaxis (Section 7.4.2) and counseling regarding potential risk of Neisseria gonorrhea (Section 7.8), as applicable. In addition, blood transfusions should proceed according to the algorithm in Section 7.3. Breakthrough hemolysis is defined in Section 3.2.2.

5.1.1. Description of Study Cohorts

In this study, there will be two cohorts, one for dose confirmation (cohort A) and one for dose expansion (cohort B). Dose confirmation will be made at the interim analysis (Section 5.2). The inclusion and exclusion criteria and schedule of events are the same for cohort A and cohort B. During the assessment of data from cohort A, recruitment into the study will continue, with patients recruited being assigned subsequently as follows: If a decision is made to expand cohort A, they will be assigned to cohort A. If a decision is made to progress to cohort B, they will be assigned to cohort B.

Figure 1: Study Flow Diagram



EOS=end of study; IV=intravenous; SC=subcutaneous

* Total treatment duration is 26 weeks, from first dose at week 0 to last dose at week 25. Data analysis occurs one week after the last dose of study drug, at week 26.

At the time of the decision, other relevant available data may be considered as part of the decision-making process, including clinical data, REGN3918 PK (as available), CH50, total C5, the LDH level achieved in those not achieving ≤ 1.5 x ULN, and safety.

The decision to progress from cohort A to cohort B will be made by the Sponsor in conjunction with the global principal investigator based on the achievement of LDH reduction to ≤ 1.5 x ULN and safety at week 8, as follows:

- If all 6 out of 6 cohort A patients achieve an LDH ≤ 1.5 x ULN at week 8 and the dosing regimen is considered well tolerated, then either the dose regimen will be confirmed and the study will progress to cohort B, or the dosing regimen will be altered, with a lower dose and/or longer dosing interval being tested in an expanded cohort A (up to a further 6 subjects). These revisions would not be considered substantial and therefore would not require a formal protocol amendment.
- If one or more patients fails to achieve LDH ≤ 1.5 x ULN at week 8, then after consideration of all data (including clinical and safety data, REGN3918 PK, CH50, total C5, baseline LDH, and the LDH level achieved), a decision will be made to either:
  - Confirm the dosing regimen and progress to cohort B, or
  - Continue with the selected dosing regimen and expand cohort A up to a maximum of 12 patients, or
  - Increase dose and/or reduce dose interval and re-assess cohort A. This option will require a substantial protocol amendment.

After the first administration of REGN3918 at the study site, subsequent administrations may either be continued at the clinical site, or by the site personnel or another healthcare professional at patient's home (if possible), or self-administered/administered by the patient or designated person, respectively.

5.1.2. End of Study Definition

At a study level, the end of study is defined as the last visit of the last patient.

5.2. Planned Interim Analysis

There will not be a formal interim analysis of efficacy data.

There will be an interim analysis of the data from cohort A at week 8, the purpose of which is the confirmation of the adequacy of the selected dose regimen (Section 5.1.1).

The interim analysis will be performed by a team from the Sponsor consisting of those from the following functions: Sample Management, Bioanalytical Sciences, Clinical Pharmacology and Quantitative Pharmacology, Regeneron Senior Physicians, Program Director, Precision Medicine, and Biostatistics.

6. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

6.1. Number of Patients Planned

Approximately 30 to 42 adults (men and women) are planned to be enrolled in 2 cohorts:

- Cohort A: 6 to 12 patients
- Cohort B: Approximately 24 to 30 patients

This study will be conducted at multiple global sites.

6.2. Study Population

The study population will consist of adult male and female patients with confirmed diagnosis of PNH and active signs and symptoms who either are complement inhibitor naive or have received prior treatment with a complement inhibitor, but not within 6 months prior to screening visit. Active signs and symptoms are defined as: The presence of PNH-related signs or symptoms in the 3 months prior to screening or having received at least one RBC transfusion within 3 months of screening, along with LDH ≥ 2 x ULN.

6.2.1. Inclusion Criteria

A patient must meet the following criteria to be eligible for inclusion in the study:

1. Male or female ≥ 18 years of age or legal age of majority at screening, whichever is greater
2. Diagnosis of PNH confirmed by high-sensitivity flow cytometry
3. PNH granulocytes (denoted as polymorphonuclear [PMN]) > 10% at screening visit
4. Active disease, as defined by the presence of 1 or more PNH-related signs or symptoms (eg, fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin <10 g/dL], history of a MAVE [including thrombosis], dysphagia, or erectile dysfunction) or history of RBC transfusion due to PNH within 3 months of screening
5. LDH level ≥ 2 × ULN at screening visit
6. Willing and able to comply with clinic visits and study-related procedures
7. Provide informed consent signed by study patient
8. Able to understand and complete study-related questionnaires

6.2.2. Exclusion Criteria

A patient who meets any of the following criteria will be excluded from the study:

1. Prior treatment with a complement inhibitor either within 6 months prior to screening visit or at any time where the patient was refractory to complement inhibitor therapy, in the opinion of the investigator (with the exception of eculizumab refractory patients due to the C5 variant R885H/C)
2. History of bone marrow transplantation
3. Body weight < 40 kilograms at screening visit
4. Planned modification (initiation, discontinuation, or dose / dosing interval change) to the following background concomitant medications, as applicable, during screening and treatment periods: erythropoietin, immunosuppressive drugs, corticosteroids, anti-thrombotic agents, anticoagulants, iron supplements, and folic acid
5. Peripheral blood absolute neutrophil count (ANC) <500/μL [<1.0 x 10^9/L] or peripheral blood platelet count <50,000/μL
6. No documented meningococcal vaccination within 3 years prior to screening and patient unwillingness to undergo vaccination during the study
7. Documented history of systemic fungal disease or unresolved tuberculosis, or evidence of active or latent tuberculosis infection (LTBI) during screening period. Assessment for active TB and LTBI should accord with local practice or guidelines, including those pertaining to risk assessment, and the use of tuberculin skin test or T-cell interferon-gamma release assay
8. Any contraindication for receiving Neisseria meningitidis vaccination and antibiotic prophylaxis therapy as recommended in the study
9. Any active, ongoing infection within 2 weeks of screening or during the screening period
10. A recent infection requiring ongoing systemic treatment with antibiotics, antivirals, or antifungals within 2 weeks of screening or during the screening period
11. Immunization with a live-attenuated vaccine 1 month prior to REGN3918 administration
12. Known hereditary complement deficiency
13. Documented history of active, ongoing systemic autoimmune diseases
14. Documented history of liver cirrhosis, or patients with liver disease unrelated to PNH with ALT or AST greater than 3× ULN at the screening visit
15. Patients with an eGFR of < 30 mL/min/1.73m^2 (according to Chronic Kidney Disease - Epidemiology Collaboration equation 2009) at screening visit
16. Recent, unstable medical conditions, excluding PNH and PNH-related complications, within the past 3 months prior to screening visit (eg, myocardial infarction, congestive heart failure with New York Heart Association Class ≥ III, serious uncontrolled cardiac arrhythmia, cerebrovascular accident, active gastrointestinal bleed)

17. Anticipated need for major surgery during the study
18. Coexisting, chronic anemia unrelated to PNH
19. History of cancer within the past 5 years, except for adequately treated basal cell skin cancer, squamous cell skin cancer, or in situ cervical cancer
20. Participation in another interventional clinical study or use of any experimental therapy within 30 days before screening visit or within 5 half-lives of that investigational product, whichever is greater, with the exception of complement inhibitors (see Section 6.2.1)
21. Known sensitivity to doxycycline or to any of the components of the REGN3918 formulation and drug product
22. History of significant multiple and/or severe allergies (including latex gloves) or has had an anaphylactic reaction or significant intolerability to prescription or nonprescription drugs
23. Any clinically significant abnormality identified at the time of screening that in the judgment of the Investigator or any sub-Investigator would preclude safe completion of the study or constrain endpoints assessment such as major systemic diseases, or patients with short life expectancy
24. Considered by the Investigator or any sub-Investigator as inappropriate for this study for any reason, eg:
    - Deemed unable to meet specific protocol requirements, such as scheduled visits
    - Deemed unable to tolerate long-term injections as per the patient, the investigator, sub-Investigator, pharmacist, study coordinator, other study staff, or relative thereof directly involved in the conduct of the protocol, etc.
    - Presence of any other conditions (eg, geographic, social, etc), actual or anticipated, that the investigator feels would restrict or limit the patient's participation for the duration of the study
25. Women who are pregnant, breastfeeding, or who have a positive pregnancy test at screening visit or day 1
26. Patients who are committed to an institution by virtue of an order issued either by the judicial or the administrative authorities
27. Pregnant or breastfeeding women
28. Women of childbearing potential* who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 21 weeks after the last dose. Highly effective contraceptive measures include:
    a. stable use of combined (estrogen and progestogen-containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening
    b. intrauterine device (IUD); intrauterine hormone-releasing system (IUS)

c. bilateral tubal ligation
d. vasectomized partner
e. and/or sexual abstinence†, ‡.

* Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

† Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

‡ Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

29. Known chronic infection with hepatitis B or C, defined as a testing history showing a currently positive status for hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), hepatitis B virus DNA, or hepatitis C virus RNA (HCV RNA).

6.3. Premature Withdrawal from the Study

A patient has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator and/or sponsor have the right to withdraw a patient from the study if it is no longer in the interest of the patient to continue in the study, or if the patient's continuation in the study places the scientific outcome of the study at risk (eg, if a patient does not or cannot follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

Patients who are withdrawn prematurely from the study will be asked to complete study assessments, as described in Section 8.1.2.

Rules for discontinuation of study treatment (permanent or temporary) are discussed in Section 7.6.1.

6.4. Replacement of Patients

Patients prematurely withdrawn from the study/study drug in cohort A can be replaced, if needed, to ensure an adequate number of evaluable patients (ie, completing week 8 procedures). The Medical/Study Director, in cooperation with the Study Biostatistician, will decide whether or not to replace a withdrawn patient. There will be a maximum of 6 patients that may be replaced.

Patients prematurely withdrawn from the study/study drug in cohort B may not be replaced.

Enrollment procedures for replacement of patients are provided in Section 7.10.1.

7. STUDY TREATMENTS

7.1. Investigational Treatments

REGN3918 drug product will be provided in a sterile, single-use glass vial for either IV or SC administration and will be supplied by the sponsor.

IVRS/IWRS will be contacted according to Table 1.

Detailed information about the drug product and dose preparation is provided in the pharmacy manual.

7.2. Drug Administration

Patients will be given a single loading dose of REGN3918 30 mg/kg IV on day 1, then a dose no greater than 800 mg SC QW (±1 day) over the treatment period. The weekly subcutaneous dose is 800 mg SC QW (±1 day) for the initial cohort A patients.

For cohort A, after the IV loading dose administration of REGN3918 at the study site, subsequent SC administrations may either be continued at the clinical site by the site personnel or at the patient's home by another healthcare professional. After week 8, self-administration/ administration by the patient or designated person may occur.

For cohort B, subsequent administrations may be continued at the clinic site, at the patient's home by another healthcare professional, or by the patient/designated person.

The location and administration options for SC route of administration will depend on the preference of the investigator and patient (eg, abdomen, thigh, or upper arm), the availability of clinical supply, and home healthcare visiting professional. Clinic visits for SC administration may or may not be needed.

If self-administration/administration by patient/designated person is allowed locally, then sufficient injection training at the scheduled injection with REGN3918 will be provided. After training, observation of self-administration/administration by patient/designated person will be conducted by clinical site personnel or visiting healthcare professional. Once this observation is considered satisfactory, then the study drug can be subsequently administered independently by patient/designated person for the remainder of the study.

In addition, a patient diary will be provided prior to initiation of self-administration (ie, week 8 for cohort A and week 4 for cohort B). The diary should be completed upon each the study drug administration. A study drug kit will be dispensed at clinical site visit, using a direct-to-patient (DTP) service provider, or transported by a healthcare professional, as applicable.

Detailed information about study drug administration is provided in the pharmacy manual.

7.3. Transfusion Algorithm

Transfusions with RBCs during the study should proceed according to the following predefined criteria that will trigger a transfusion; however, the actual number of units to be transfused is at the discretion of the investigator:

- Transfuse with RBC(s) if the post-baseline hemoglobin level is <9 g/dL with symptoms resulting from anemia or
- Transfuse with RBC(s) if the post-baseline hemoglobin level is <7 g/dL.

7.4. Pretreatments

Enrolled patients will require evidence of meningococcal immunization or administration of vaccination during the screening period and oral antibiotics are recommended during the treatment period, according to local practice.

7.4.1. Meningococcal Vaccinations

Enrolled patients will require immunization with meningococcal vaccinations. Administration of vaccination should occur preferably at least 2 weeks prior to initiation of REGN3918, or at another time point according to local practice or national guidelines. If available, it is suggested that patients undergo vaccination for serotypes A, C, Y, W and serotype B. Patients who have had previous documented vaccination for meningococcus will be re-immunized based on local practice. Patients should be closely monitored for early signs and symptoms of meningococcal infection and evaluated immediately if an infection is suspected. Patients will be provided with a patient safety card describing signs and symptoms of meningococcal infection, along with instructions in case of a potential meningococcal infection, as well as information for the non-investigator healthcare provider. The vaccinations will be sourced locally by the investigator or designee and reimbursed by the sponsor.

7.4.2. Oral Antibiotics

It is recommended that daily oral antibiotic prophylaxis commence on the day of first dosing, unless the risks outweigh the benefits or it is inconsistent with local practice, and continue for the duration of the study. It is recommended that patients who prematurely discontinue REGN3918 receive at least 21 weeks of oral antibiotic prophylaxis after discontinuing REGN3918 or a duration consistent with local guidelines, whichever is longer (Section 8.1.2). It is suggested that antibiotic prophylaxis be penicillin V 500 mg twice a day (BID). In the case of penicillin allergy, Erythromycin® 500 mg BID may be used at the discretion of the investigator. Ultimately, the decision to administer prophylaxis with oral antibiotics, the duration of prophylaxis, the choice and dosage regimen of antibiotics will be at the discretion of the investigator. The oral antibiotics will be sourced locally by the investigator or designee and reimbursed by the sponsor.

7.5. Post-Study Treatment Access

All patients who complete the study without discontinuing treatment due to an adverse event (AE) thought to be related to the study drug will be offered to enroll in another study, a long-term OLE clinical trial with REGN3918.

The duration of the OLE is 2 years, with the option of extending treatment beyond the OLE treatment period for suitable patients. The transition of treatment with REGN3918 from the current study to the OLE is planned to be uninterrupted, whereby the day 1 visit of the OLE will correspond to the week 26 visit in the current study.

7.6. Dose Modification and Study Treatment Discontinuation Rules

7.6.1. Study Drug Discontinuation

Patients who permanently discontinue from study drug and who do not withdraw from the study will be asked to return to the clinic for all remaining study visits, per Section 8.1.2.

Patients who permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete study assessments, per Section 8.1.2.

7.6.1.1. Reasons for Permanent Discontinuation of Study Drug

Study drug dosing will be permanently stopped in the event of:

- Evidence of pregnancy
- Serious or severe allergic reactions considered related to study drug
- Liver impairment as evidenced by one or more of the following criteria:
  - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 8 x ULN or
  - ALT or AST > 5 x ULN for more than 2 weeks or
  - ALT or AST > 3 x ULN and total bilirubin > 2 x ULN (or international normalized ratio (INR) > 1.5) and no other reason can be found to explain the combination of increased AST/ALT and total bilirubin, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury
- Patient withdrawal of consent
- Patient non-compliance (eg, not complying with protocol-required visits, assessments, and/or dosing instructions)
- Investigator's clinical judgment that it is in the best interest of the patient

7.6.1.2. Reasons for Temporary Discontinuation of Study Drug

Temporary discontinuation may be considered by the Investigator because of suspected AEs. The investigator can reinitiate treatment with study drug under close and appropriate clinical and/or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the study drug in the occurrence of the concerned event was unlikely.

7.7. Management of Acute Reactions

7.7.1. Acute Intravenous Infusion Reactions

Patients should be observed for 30 minutes after the infusion.

Emergency equipment and medication for the treatment of infusion reactions must be available for immediate use. All infusion reactions must be reported as AEs (as defined in Section 9.2.4) and graded using the grading scales as instructed in Section 9.2.5.

7.7.1.1. Interruption of the Intravenous Infusion

The infusion should be interrupted if any of the following AEs are observed:

- Cough
- Rigors/chills
- Rash, pruritus (itching)
- Urticaria (hives, welts, wheals)
- Diaphoresis (sweating)
- Hypotension
- Dyspnea (shortness of breath)
- Vomiting
- Flushing

The reaction(s) should be treated symptomatically, and the infusion may be restarted at 50% of the original rate.

If investigators feel there is a medical need for treatment or discontinuation of the infusion other than described above, they should use clinical judgment to provide the appropriate response according to typical clinical practice.

7.7.1.2. Termination of the Intravenous Infusion

The infusion should be terminated and NOT restarted if any of the following AEs occur:

- Anaphylaxis*
- Laryngeal/pharyngeal edema
- Severe bronchospasm
- Chest pain
- Seizure
- Severe hypotension
- Other neurological symptoms (confusion, loss of consciousness, paresthesia, paralysis, etc)
- Any other symptom or sign that, in the opinion of the investigator, warrants termination of the IV infusion

*Consider anaphylaxis if the following is observed (Sampson, 2006): acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING:

- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
- Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

7.7.2. Acute Injection Reactions

7.7.2.1. Systemic Injection Reactions

Patients should be observed for 30 minutes after the first SC injection.

Emergency equipment and medication for the treatment of systemic reactions must be available for immediate use at the site. All injection reactions must be reported as AEs and graded using the grading scales as instructed in Section 9.2.5.

Acute systemic reactions following injection of study drug (SC) should be treated using clinical judgment to determine the appropriate response according to typical clinical practice.

7.7.2.2. Local Injection Site Reactions

Local injection site reactions must be reported as AEs and graded according to Section 9.2.5.

7.8. Risk Management of Neisseria Gonorrhea

Patients should be counseled about Neisseria gonorrhea prevention and regular testing should be advised for at-risk patients.

A risk factor assessment should be based on local practice or national guidelines. The investigator should make his/her own assessment of risk (and if needed, consultation with other healthcare provider) to determine if the patient is at risk, which would lead to further management on prevention, testing, and treatment of Neisseria gonorrhea.

Testing and treatment should be in accordance with local practice/national guidelines. Patients may be re-screened if they meet the exclusion criteria "A recent infection requiring ongoing systemic treatment with antibiotics, antivirals, or antifungals within 2 weeks of screening or during the screening period" (Section 6.2.2) with successful resolution of the infection.

General preventive measures include abstinence and use of a condom. Additional preventive measures should be considered based on local practice or national guidelines.

7.9. Dose Modification

Dose modification for an individual patient is not allowed.

7.10. Measures to Reduce Bias

7.10.1. Method of Treatment Assignment

All patients who sign the informed consent form (ICF) will be assigned a patient number. Treatment assignment will be performed in an unblinded fashion. Patients will be enrolled sequentially in order of confirmed eligibility.

Recruitment will be continuous, and cohort assignment to cohort A or B after the completion of week 8 procedures for the first 6 patients will be based on analysis of the available data. For patients recruited after the first 6 patients' week 8 data are available, and before a decision on progression to cohort B has been made, they will be categorized for analysis as follows:

- In the event that a decision is made to progress to cohort B, they will be considered as part of cohort B.
- In the event that a decision is made to expand cohort A, they will be considered as part of cohort A.

7.10.2. Blinding

This is an open-label study.

7.11. Treatment Logistics and Accountability

7.11.1. Packaging, Labeling, and Storage

REGN3918 for injection will be provided as open-label supplies packaged in carton boxes. Each carton box will contain 1 labeled vial. Carton box and vial will be labeled with a booklet label indicating the protocol number, product identity and strength, medication/reference number, batch number, directions for use, route of administration, expiry date, sponsor information, and storage conditions, and will correspond to all regulatory requirements.

Study drug will be stored at the site at a temperature of 2ºC to 8ºC; storage instructions will be provided in the pharmacy manual.

7.11.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2ºC to 8ºC to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be destroyed on-site or at a destruction depot after accountability and reconciliation.

7.11.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication:

- Dispensed to each patient,
- Returned from each patient (if applicable), and
- Disposed of at the site or returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

7.11.4. Treatment Compliance

All drug compliance records must be kept current and made available for inspection by the sponsor and regulatory agency inspectors.

7.12. Concomitant Medications

Any treatment administered from the time of informed consent to the end of final study visit will be considered concomitant medication. This includes medications that were started before the study and are ongoing during the study.

7.12.1. Prohibited Medications

The following medications are prohibited, with the exception of those listed in Section 7.12.2, as described below:

- Within 24 hours prior to each clinic visit when blood is drawn, patients should not consume any alcohol.
- Beginning on day 1 and continuing throughout the study, while the patient is continuing REGN3918, the patient should not take any other complement inhibitor therapy.

7.12.2. Permitted Medications

The following medications and procedures will be permitted, under the following conditions:

- Any medication required to treat an AE, including systemic corticosteroids, at the discretion of the investigator
- Meningococcal vaccination, as described in Section 7.4.1
- Oral antibiotic prophylaxis, as described in Section 7.4.2
- Oral contraceptives and hormone-replacement therapy may continue
- Acetaminophen/paracetamol, aspirin, or ibuprofen at the recommended dose per the local label
- Erythropoietin, immunosuppressive drugs, corticosteroids, anti-thrombotic agents, anticoagulants, iron supplements, and folic acid are permitted and if possible, should be kept constant throughout the study; any changes to these concomitant medications will be at the discretion of the investigator and consistent with practice prior to enrollment
- Any medication required for the treatment of patient's background medical conditions

8. STUDY SCHEDULE OF EVENTS AND PROCEDURES

8.1. Schedule of Events

Study assessments and procedures are presented by study period and visit in Table 1.

When multiple procedures are scheduled for the same visit/time point, the following guidance should be followed:

- PRO assessments should be completed prior to all other assessments and/or discussions about patient's health
- Electrocardiograms (ECGs) should be performed prior to blood draws and dosing
- PK/ADA sampling should be performed as soon as possible after an ECG and prior to study drug administration
- Collect safety and efficacy blood samples pre-dose prior to biomarker samples

Patients will be provided the following:

- Device for completing study questionnaires and other patient-reported assessments
- Patient diary

  A patient diary will be provided to patients who self-administer the study drug to collect relevant information
- Wearable device (see Section 8.2.7.2) in a subset of patients at participating sites
- Patient safety card for Neisseria meningitidis (see Section 7.4.1)

Table 1: Schedule of Events

Study Period	**Screening**	**Treatment**											**EoS**	**Notes**
Study Week	**up to -4**	**0**		**1**	**2**	**3**	**Week 4 to 23**				**24**	**25**	**26**	
							(W4, 8, 12, 16, 20)	**(W5, 9, 13, 17, 21)**	**(W6, 10, 14, 18, 22)**	**(W7, 11, 15, 19, 23)**				
Study Day (W0 to W26 ± 1D)	**up to -28**	**1**	**3**	**8**	**15**	**22**	**29, 57, 85, 113, 141**	**36, 64, 92, 120, 148**	**43, 71, 99, 127, 155**	**50, 78, 106, 134, 162**	**169**	**176**	**183**	
Visit Location:														
Clinic Visit	X	X	X	X	X	X	X				X		X	Mandatory clinic visit
Clinic, Home Healthcare, or Phone Call Visit[1]								X	X[2]	X		X[2]		Cohort A: Clinic visit mandatory for first visits up to and including week 8. Section 7.2.
Screening:														
Informed Consent	X													Including optional sub-studies
Inclusion/Exclusion	X	X												May re-screen once, as described in Section 8.2.1
Medical History	X	X												Section 8.2.1
Demographics	X													
Prior Concomitant Medications	X													
Historical Lab Parameters for Hemolysis	X													If possible, 2 yr history. Section 8.2.1
Neisseria Meningitidis Vaccination History	X													
TB history and assessment	X													Section 8.2.1
Testing history for hepatitis B and C	X													Testing may be performed by the central lab as needed per local practice. Section 8.2.1
Risk assessment for Neisseria gonorrhea	X													Section 7.8
Height	X													
Enrollment		X												

Study Period	**Screening**	**Treatment**											**EoS**	**Notes**
Study Week	**up to -4**	**0**		**1**	**2**	**3**	**Week 4 to 23**				**24**	**25**	**26**	
							(W4, 8, 12, 16, 20)	**(W5, 9, 13, 17, 21)**	**(W6, 10, 14, 18, 22)**	**(W7, 11, 15, 19, 23)**				
Study Day (W0 to W26 ± 1D)	**up to -28**	**1**	**3**	**8**	**15**	**22**	**29, 57, 85, 113, 141**	**36, 64, 92, 120, 148**	**43, 71, 99, 127, 155**	**50, 78, 106, 134, 162**	**169**	**176**	**183**	
Treatment:														
R3918 IV Administration		X												Patients should be observed for at least 30 minutes post-infusion. Section 7.2
R3918 SC Administration				X	X	X	X	X	X	X	X	X		Cohort A: Only W9-25 may be self-administered. Section 7.2
Oral Antibiotics		X	X	X	X	X	X	X	X	X	X	X	X	Per local practice. Section 7.4.2
Meningococcal Vaccine	X	X												Per local practice. Section 7.4.1
IVRS/IWRS Contact	X	X	X	X	X	X	X	X	X	X	X	X	X	
Patient Diary								X	X	X		X		For self-administration. Section 7.2
Efficacy (central):														
Serum LDH	X	X	X	X	X	X	X		X		X	X	X	Samples not required if blood chem. samples are taken. Section 8.2.3.1
Transfusion Data	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.2.3.2
Complement Hemolytic Assay (serum CH50)	X	X	X	X	X	X	X						X	Day 1, pre-dose and end of the IV infusion. Pre-dose at all other visits. Section 8.2.3.3
FACIT-Fatigue		X			X		X						X	Section 8.2.3.6
EORTC-QLQ-30		X			X		X						X	Section 8.2.3.6
EQ-5D-3L		X					X						X	Section 8.2.3.6
PGIS		X			X		X						X	Section 8.2.3.6
PGIC					X		X						X	Section 8.2.3.6

Study Period	**Screening**	**Treatment**											**EoS**	**Notes**
Study Week	**up to -4**	**0**		**1**	**2**	**3**	**Week 4 to 23**				**24**	**25**	**26**	
							(W4, 8, 12, 16, 20)	**(W5, 9, 13, 17, 21)**	**(W6, 10, 14, 18, 22)**	**(W7, 11, 15, 19, 23)**				
Study Day (W0 to W26 ± 1D)	**up to -28**	**1**	**3**	**8**	**15**	**22**	**29, 57, 85, 113, 141**	**36, 64, 92, 120, 148**	**43, 71, 99, 127, 155**	**50, 78, 106, 134, 162**	**169**	**176**	**183**	
Safety:														
Vital Signs	X	X	X	X	X	X	X		X				X	Section 8.2.4.1
Physical Examination	X	X	X	X			X						X	Section 8.2.4.2
Body Weight	X	X					X						X	Section 8.2.4.2
Electrocardiogram	X												X	Section 8.2.4.3
Adverse Events	< ----------x ---------- >													If breakthrough hemolysis is suspected, blood samples will be collected for LDH and other assessments. Blood may also be collected in the event of drug hypersensitivity. Section 8.1.3 Procedures for AEs, Section 9.
Concomitant Meds & Tx	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 7.12
Patient Safety Card		X												For Neisseria meningitidis
Laboratory Testing: (Central):														
Hematology	X	X			X		X						X	Includes RBC and free hemoglobin See Section 8.2.4.4 for analytes
Blood Chemistry	X	X			X		X						X	Includes serum lactate dehydrogenase See Section 8.2.4.4 for analytes
Pregnancy Test	X	X			X		X						X	Serum at screening Urine at all other visits
Urinalysis	X	X			X		X						X	See Section 8.2.4.4 for analytes
C-Reactive Protein	X	X	X	X	X	X	X						X	
Direct Antiglobulin Test	X	X					X						X	DAT or Coombs

Study Period	**Screening**	**Treatment**											**EoS**	**Notes**
Study Week	**up to -4**	**0**		**1**	**2**	**3**	**Week 4 to 23**				**24**	**25**	**26**	
							(W4, 8, 12, 16, 20)	**(W5, 9, 13, 17, 21)**	**(W6, 10, 14, 18, 22)**	**(W7, 11, 15, 19, 23)**				
Study Day (W0 to W26 ± 1D)	**up to -28**	**1**	**3**	**8**	**15**	**22**	**29, 57, 85, 113, 141**	**36, 64, 92, 120, 148**	**43, 71, 99, 127, 155**	**50, 78, 106, 134, 162**	**169**	**176**	**183**	
PK and ADA Samples:														
PK Sample		X	X	X			X						X	Day 1, sample pre-dose and end of the IV infusion. Pre-dose at all other visits. Section 8.2.5
ADA Sample		X					X (W12)						X	Pre-dose. Section 8.2.6
Exploratory PD/Biomarkers:														Pre-dose, unless otherwise specified
Haptoglobin	X	X					X						X	Section 8.2.8
Reticulocyte Count	X	X					X						X	
Complement Hemolytic Assay (serum AH50)	X	X	X	X	X	X	X						X	Day 1, sample pre-dose and end of the IV infusion. Pre-dose at all other visits.
Total Complement Levels	X	X					X						X	
Total C5 (plasma)	X	X	X				X						X	Day 1, sample pre-dose and end of the IV infusion. Pre-dose at all other visits.
C5a (plasma and urine)	X	X					X						X	
sC5b-9 (plasma)	X	X	X	X	X	X	X						X	
PNH Erythrocyte Cells	X	X					X (W8, W16)						X	
PNH Granulocyte Cells	X	X					X (W8, W16)						X	
NT-proBNP	X	X					X						X	
Biomarkers of Thrombosis and Inflammation	X	X					X						X	May include D-dimer, F1+2, TFPI, and IL-6
Renal Injury Markers	X	X					X						X	

Study Period	**Screening**	**Treatment**											**EoS**	**Notes**
Study Week	**up to -4**	**0**		**1**	**2**	**3**	**Week 4 to 23**				**24**	**25**	**26**	
							(W4, 8, 12, 16, 20)	**(W5, 9, 13, 17, 21)**	**(W6, 10, 14, 18, 22)**	**(W7, 11, 15, 19, 23)**				
Study Day (W0 to W26 ± 1D)	**up to -28**	**1**	**3**	**8**	**15**	**22**	**29, 57, 85, 113, 141**	**36, 64, 92, 120, 148**	**43, 71, 99, 127, 155**	**50, 78, 106, 134, 162**	**169**	**176**	**183**	
Optional Samples:														
Future Biomedical Research Serum/Plasma (optional)		X					X						X	As permitted by local regulatory policies. Section 8.2.9
Whole Blood for DNA Isolation (optional)		X												Section 8.2.9.1
Whole Blood for RNA Isolation (optional)		X		X									X	Section 8.2.9.1
Clinical Outcome Assessments														
PNH Symptom-Specific Questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X	To be completed daily by patient. Patient will complete daily PNH Symptom-Specific Questionnaire on a device at least 7 days prior to day 1 visit. Section 8.2.7.1 Cohort A: Optional Cohort B: Mandatory when available
TSQM							X (W4, W16)						X	Section 8.2.7.1 Cohort A: Optional Cohort B: Mandatory when available
Wearable Device		< ---------- W0 to W12 ---------- >												Should be worn according to the schedule set out in the study manual Section 8.2.7.2

8.1.1. Footnotes for the Schedule of Events Table

1. Clinic visit may or may not be needed for these visits (see Section 7.2). In lieu of a clinic visit, any additional study procedures required for this visit may also be done by a healthcare professional at the patient's home or, if the patient is self-administering the study drug, via a phone call from the site to the patient.
2. If the patient is self-administering the study drug, a health care professional will visit the patient's home to draw the scheduled blood samples.

8.1.2. Premature Discontinuation and Follow-up

Patients who discontinue treatment and do not withdraw from study should continue all study visits as scheduled. If the week 26 visit does not include at least 21 weeks of follow-up, then patient should continue with monthly site visits until 21 weeks after last dose of IMP. Each of these monthly visits will consist of the safety assessments, including laboratory tests (Section 8.2.4.4), listed for week 26 visit in Table 1.

Patients who discontinue treatment and study should be requested to have an early termination visit consisting of assessments listed for week 26 visit (Table 1). If the patient agrees to a follow-up safety phone visit, then a follow-up phone call will be scheduled for 21 weeks after last IMP dose.

Patients who complete the study treatment and study but do not want to enroll in the OLE (Section 7.5) should have monthly visits until 21 weeks after last dose of IMP. These visits will consist of the safety assessments, including laboratory tests (Section 8.2.4.4) listed for week 26 visit in Table 1.

8.1.3. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted.

In case of suspected breakthrough hemolysis as defined in Section 3.2.2, unscheduled blood samples (at either scheduled or unscheduled site visits) will be collected for the assessment of LDH, drug concentration (PK), ADA, total C5, and CH50 at or near the time of the event.

In case of suspected systemic hypersensitivity and anaphylaxis, unscheduled blood samples may be collected for the assessment of drug concentration and ADA at or near the time of the event.

8.2. Study Procedures

8.2.1. Procedures Performed Only at the Screening/Baseline Visit

The following procedures will be performed for the sole purpose of determining study eligibility or characterizing the baseline population:

- Medical history, including history of transfusions for the past 12 months, breakthrough hemolysis for the past 12 months, and MAVE
- Demographics
- Prior concomitant medications (see Section 7.12)
- Historical laboratory parameters for measurement of hemolysis

  If possible, obtain parameters (eg, LDH, hemoglobin, free hemoglobin, PNH granulocytes, and PNH erythrocytes) for the past 2 years from the patient's medical history.
- Neisseria meningitidis vaccination history (see Section 7.4.1)
- Height
- Risk assessment for Neisseria gonorrhea (see Section 7.8)
- Testing history for hepatitis B and C. Testing may be performed by the central lab if needed per local practice
- Tuberculosis history and assessment. Screening by tuberculin skin test or T-cell interferon-gamma release assay may be performed according to local practice or guidelines at the discretion of the investigator

For screening purposes, one retest of laboratory testing is permitted for non-clinically significant abnormality. At the discretion of the investigator, additional visits during the screening period may be scheduled as needed to complete screening procedures: for example, sample collection for laboratory re-test or 7-day baseline data collection for the PNH Symptom-Specific Questionnaire (Section 8.2.7.1).

8.2.2. Study Drug Administration

Study drug will be administered as described in Section 7.2. Immunization with meningococcal vaccines are to be performed according to local practice (Section 7.4.1). Daily oral antibiotic prophylaxis is recommended (Section 7.4.2).

Compliance with study drug administration may be monitored with a patient diary according to Table 1.

8.2.3. Efficacy Procedures

8.2.3.1. Serum Lactate Dehydrogenase

Samples for LDH testing will be collected at visits according to Table 1.

Serum LDH levels will the measured in a central lab. On days when Blood Chemistry is run (see Section 8.2.4.4), then LDH will be included in the panel which will also be run in a central lab.

For patients who self-administer, samples may be drawn at home by the visiting nurse when scheduled on non-clinic visits.

8.2.3.2. Transfusion Record Update

Patients will be requested to provide updated information about the history of transfusions received 1 year prior to the time of screening. During the study, the rate and number of units of transfusion with RBCs will be recorded in the case report form (CRF) according to Table 1. Transfusions with RBCs during the study should follow the algorithm described in Section 7.3.

The rate and number of units of transfusion with RBCs will be recorded in the CRF. Hemoglobin levels pre- and post-transfusion will be obtained (including local values).

8.2.3.3. Total Hemolytic Complement Activity

Samples for CH50 testing will be collected at visits according to Table 1.

Serum CH50 levels will the measured in a central lab.

For patients who self-administer, samples may be drawn at home by the visiting nurse when scheduled on non-clinic visits.

8.2.3.4. Red Blood Cell Hemoglobin

Red blood cell hemoglobin testing will be measured in the safety hematology panel (see Section 8.2.4.4) collected at visits according to Table 1 and will be run in a central lab.

8.2.3.5. Free Hemoglobin

Free hemoglobin testing will be measured in the safety hematology panel (see Section 8.2.4.4) collected at visits according to Table 1 and will be run in a central lab.

8.2.3.6. Clinical Outcome Assessments

The COAs are patient self-reported and will be completed according to Table 1.

Clinical outcome assessments (COAs) will include the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) and 2 health-related quality of life (HRQoL) questionnaires (EORTC quality of life questionnaire-core 30 [QLQ-C30] and the EQ-5D-3L) and Patient Global Impression of Severity (PGIS)/Patient Global Impression of Change (PGIC).

The **FACIT-Fatigue** is a 13-item, self-reported PRO measure assessing an individual's level of fatigue during their usual daily activities over the past week. This questionnaire is part of the FACIT measurement system, a compilation of questions measuring health-related QoL in patients with cancer and other chronic illnesses. The FACIT-Fatigue assesses the level of fatigue using a 4-point Likert scale ranging from 0 (not at all) to 4 (very much). Scores range from 0 to 52, with higher scores indicating greater fatigue. Although the FACIT-Fatigue was originally developed to assess fatigue in patients with cancer, it has been used in trials evaluating the efficacy of eculizumab (Brodsky, 2008) (Hillmen, 2006). The FACIT-Fatigue has demonstrated content validity among patients with PNH (Weitz, 2013).

The **EORTC QLQ-C30** is a 30-item, generic questionnaire commonly used to assess HRQoL in patients with cancer (Stead, 1999) (Cocks, 2007). The EORTC QLQ-C30 assesses HRQoL across multiple domains, including global health status, global quality of life, functioning (physical, role, emotional, cognitive, and social functioning), symptom scales (fatigue, nausea and vomiting, pain, appetite loss), and single items (dyspnea, insomnia, constipation, diarrhea, sleep, financial impact). Although the EORTC-QLQ-30 was originally developed to assess HRQoL in patients with cancer, it has been used in trials evaluating the efficacy of eculizumab (Brodsky, 2008) (Hillmen, 2006). The EORTC-QLQ also has demonstrated content validity among patients with PNH (Weitz, 2013).

The **EQ-5D-3L** is a self-administered, generic standardized health status measure, consisting of 6 questions. The EQ-5D-3L descriptive system assesses 5 dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a 3-level scale: no problems, some problems, and extreme problems. The EQ visual analog scale component is a vertical, visual analog scale used by patients to rate their health.

Patient Global Impression of Severity/Patient Global Impression of Change:

Patient Global Impression of Severity consists of 3 self-administered PRO questions assessing the patient's perception of the overall severity of the symptoms of their disease and/or of a specific symptom of their disease. At study visits, patients will be asked to rate the severity of their PNH symptoms on a 6-point Likert scale ranging from "I am not experiencing PNH symptoms" to "very severe"; the impact their PNH symptoms have on their ability to perform usual daily activities on a 5-point Likert scale ranging from "not at all impacted" to "extremely impacted"; and their overall fatigue on a 5-point Likert scale ranging from "not fatigued" to "extremely fatigued".

Patient Global Impression of Change consists of 3 self-administered PRO questions assessing the patient's perception of the change in overall severity of the symptoms of their disease and/or of a specific symptom of their disease compared to the start of the study. At key time points during the study, patients will be asked to rate the change in PNH symptoms, in their ability to perform usual daily activities, and in overall fatigue compared to before the start of the study on a 7-point Likert scale ranging from "much better" to "no change" to "much worse".

PGIS and PGIC questions are developed for this trial and allow for the interpretation of PRO findings and the investigation of a responder definition. The answers on the PGIS and PGIC items serve as "anchors" to help interpret the mean change in disease-specific PRO measures over time and to estimate responder definitions. This empirical anchor-based approach is the primary FDA-recommended approach for defining a responder and analyzing responder-based PRO results.

Additional COAs (not assessed as part of efficacy) are described in Section 8.2.7.

8.2.4. Safety Procedures

8.2.4.1. Vital Signs

Vital signs, including temperature, sitting blood pressure, and pulse, will be collected pre-dose at time points according to Table 1.

Vital signs will be obtained after subject has been sitting quietly for at least approximately 5 minutes. At the first visit, blood pressure should be measured from both arms. The arm with the higher diastolic pressure will be selected for measurement throughout the study.

8.2.4.2. Physical Examination and Body Weight

A thorough and complete physical examination will be performed at time points according to Table 1. Each physical examination will include an evaluation of head and neck, lungs, heart, abdomen, extremities, and skin. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

Body weight will be measured at time points according to Table 1. Body weight should be obtained with the patient wearing undergarments or very light clothing and no shoes. The same type/model of scale should be used throughout the study.

8.2.4.3. Electrocardiogram

A standard 12-lead ECG will be performed locally at time points according to Table 1.

Twelve-lead ECGs will be systematically recorded after the subject has been in the supine position for at least 10 minutes. The electrodes should be positioned in the same location, as much as possible, for each ECG recording.

The ECG will be interpreted locally by the investigator. Any new and/or clinically significant changes in ECG parameters should be immediately rechecked for confirmation before making any decision for the concerned patient. Any clinically significant abnormality should be documented as an AE/SAE as applicable.

Heart rate will be recorded from the ventricular rate, and the PR, QRS, RR, QT intervals, and QTcF will be recorded. The ECG strips or reports will be retained with the source.

8.2.4.4. Laboratory Testing

Samples for laboratory testing will be collected at visits according to Table 1.

Hematology, chemistry (except Total C5, CH50, and AH50), urinalysis, and pregnancy testing samples may be analyzed by a local/central laboratory.

Other testing will be done by a central or specialized laboratory as outlined in the sample management plan.

Detailed instructions for blood sample collection are in the sample management plan provided to study sites.

Blood Chemistry

Sodium	Total protein, serum	Total bilirubin
Potassium	Creatinine	Total cholesterol*
Chloride	Blood urea nitrogen (BUN)	Triglycerides
Carbon dioxide	Aspartate aminotransferase (AST)	Uric acid
Calcium	Alanine aminotransferase (ALT)	Creatine kinase (CK)
Glucose	Alkaline phosphatase	
Albumin	Lactate dehydrogenase (LDH)	

*(low-density lipoprotein [LDL] and high-density lipoprotein [HDL])

Blood chemistry should be performed after the patients have fasted for at least approximately 8 hours at the following visits defined in the schedule of events.

Hematology

Hemoglobin	Differential:
Free Hemoglobin	Neutrophils
Hematocrit	Lymphocytes
Red blood cells (RBCs)	Monocytes
White blood cells (WBCs)	Basophils
Red cell indices	Eosinophils
Platelet count	Reticulocytes

Urinalysis

pH	Glucose	Note: If macroscopy is abnormal then reflex to microscopy.
Specific gravity	Bilirubin	
Ketones	Leukocytes	
Protein	Nitrite	

Other Laboratory Tests

Other laboratory tests include:

- Pregnancy testing: serum human chorionic gonadotrophin pregnancy testing, urine pregnancy testing
- C-Reactive protein
- Direct Antiglobulin Test (DAT or Coombs)
- PD and Exploratory Biomarker Procedures (Section 8.2.8)
- Unscheduled blood collection for suspected breakthrough hemolysis events or drug hypersensitivity events (Section 8.1.3)

Abnormal Laboratory Values and Laboratory Adverse Events

All laboratory values must be reviewed by the investigator or authorized designee.

Significantly abnormal test results that occur after start of treatment must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the Medical/Study Director must be consulted.

The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in Section 9.1.

8.2.5. Drug Concentration and Measurements

Samples for drug concentration will be collected at visits listed in Table 1 for PK analysis. The exact sampling time must be recorded, as allowed per local regulation.

Any unused samples may be used for exploratory research, as allowed per local regulation.

8.2.6. Anti-Drug Antibody Measurements and Samples

Blood samples for ADA assessment in serum will be collected prior to drug administration at time points listed in Table 1.

Detailed instructions for blood sample collection are included in the laboratory manual provided to study sites.

Any unused samples may be used for exploratory research, as allowed per local regulation.

8.2.7. Clinical Outcome Assessments

The following additional patient-reported outcome assessments will be collected according to time points listed in Table 1.

8.2.7.1. Patient-Reported Outcome Assessments

A de novo PNH symptom-specific questionnaire will collect daily information on PNH symptoms including: fatigue, shortness of breath, muscle weakness, headache, abdominal pain, pain in back/legs, chest discomfort, difficulty sleeping, difficulty thinking clearly, and difficulty swallowing. Patient will complete daily PNH Symptom-Specific Questionnaire on a device at least 7 days prior to day 1 visit. The site has the option of giving the device to the patient at the screening visit or at an interim visit between screening visit and at least 7 days prior to day 1. The instrument was developed by conducting a literature review, consulting with clinical expert input, and through patient interviews assessing comprehensiveness of symptoms collected and the patient's ability to read, understand, and respond to the questionnaire. The questionnaire was developed in accordance with regulatory guidelines (FDA, 2009) and scientific best practices (Patrick, 2011).

Treatment Satisfaction Questionnaire for Medication is a generic measure that assesses patients' satisfaction with their medication (Atkinson, 2004) (Atkinson, 2005). The TSQM is an 11-question, self-administered, patient-reported outcome measure which assesses 3 domains of satisfaction: effectiveness (2 items), side effects (4 items), convenience (3 items), and global satisfaction (2 items). For each question, the patient rates their satisfaction either on a 7-point Likert scale (ranging from extremely dissatisfied to extremely satisfied) or a 5-point Likert scale (ranging from extremely dissatisfied to not dissatisfied at all) with higher scores representing greater satisfaction. The instrument was developed using patient input and has evidence of psychometric validity.

8.2.7.2. Wearable Activity Tracker

A wearable device (eg, a watch-like device on wrist, etc) for daily activity tracking will be provided and should be worn according to Table 1.

Parameters may include sleep, heart rate, and activity.

8.2.8. Pharmacodynamic and Exploratory Biomarker Procedures

Samples will be collected at time points according to Table 1.

Biomarker measurements will be performed in specified matrix to determine effects of REGN3918 on relevant physiological and pathogenic processes.

The biomarker studied will be ones believed to be relevant to the understanding of efficacy, pathophysiology of indication target engagement, mechanism of action and possible toxicities of REGN3918.

Biomarkers studied may include but need not be limited to:

- Parameters of intravascular hemolysis: ie, haptoglobin, reticulocyte count, and bilirubin
- Intravascular hemolysis mediated through the alternative complement pathway: ie, measured by AH50 (serum), and total complement level (serum)
- Total C5 protein (plasma)
- Complement activation markers: ie, C5a (plasma and urine) and sC5b-9 (plasma)
- PNH clone size: ie, PNH erythrocytes and granulocytes
- Biomarkers of pulmonary hypertension: ie, NT-proBNP
  - NT-proBNP has been shown to be associated with increased intravascular hemolysis (measured by LDH) in some patients with PNH. REGN3918 is expected to reduce NT-proBNP significantly, similar to what has been reported for Eculizumab
- Biomarkers of thrombosis and inflammation: ie, D-dimer, N-terminal prothrombin fragments (F1+2), Tissue Factor Pathway Inhibitor (TFPI), and IL-6
  - Levels of these markers were significantly elevated in PNH, including those with no history of clinical thrombosis. REGN3918 is expected to significantly reduce the levels of these markers in patients with PNH, similar to what has been reported for eculizumab (Helley, 2010)

- Urinary biomarkers of renal injury: ie, clusterin (CLU), Cystatin-C (CysC), Kidney Injury Molecule-1 (KIM-1), Nacetyl-beta-D-glucosaminidase (NAG), Neutrophil Gelatinase-Associated Lipocalin (NGAL), and osteopontin (OPN)
  - Renal diseases including acute renal failure have been reported in PNH patients (Ballarin, 2011). Effects of R3918 on renal injury biomarkers will be assessed in this study.

The list may be altered or expanded, as it is recognized that more relevant or novel biomarkers may be discovered during the process of this study.

The results of analyses performed on these samples will be presented in the CSR.

8.2.9. Future Biomedical Research (Optional)

Patients who agree to participate in the future biomedical research sub-study will be required to consent to this optional sub-study before collection of the serum and plasma samples. The unused biomarker samples for study-related research, as well as unused PK and ADA samples, will be stored for up to 15 years after the final date of the database lock. The unused samples may be utilized for future biomedical research of REGN3918, the complement pathway, PNH, and related diseases. Additional samples will be collected for future biomedical research according to Schedule of Events in Table 1. After 15 years, any residual samples will be destroyed. The results of these future biomedical research analyses will not be presented in the CSR.

8.2.9.1. Pharmacogenomic Analysis (Optional)

Patients who agree to participate in the genomics sub-study will be required to consent to this optional sub-study before collection of the samples. Whole blood samples for DNA extraction should be collected on day 1 (predose) but can be collected at a later study visit. Whole blood samples for RNA extraction will be collected at time points according to Table 1.

DNA and RNA samples will be collected for pharmacogenomics analyses. These samples will be single-coded as defined by the International Council for Harmonisation (ICH) guideline E15. Samples will be stored for up to 15 years after the final date of the database lock. If there are specific site or country requirements involving the pharmacogenomic analyses with which the sponsor is unable to comply, samples will not be collected at those sites.

The purpose of the pharmacogenomic analyses is to identify genomic associations with clinical (safety or efficacy) or biomarker response to REGN3918, the complement pathway, PNH and related complement-mediated diseases, clinical outcome measures, and possible AEs. In addition, associations between genomic variants and prognosis or progression of PNH and related complement-mediated diseases may also be studied. These data may be used or combined with data collected from other studies to identify and validate genomic markers related to the study drug, target pathway, or PNH and related diseases.

Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Other methods, including whole-exome sequencing, whole-genome sequencing, DNA copy number variation, transcriptome sequencing (or other methods for quantitating RNA expression), and methods for quantifying epigenetic modifications may also be performed. The list of methods may be expanded to include novel methodology that may be developed during the course of this study or sample storage period.

Results from the genomic analyses will not be reported in the CSR.

9. SAFETY EVALUATION AND REPORTING

9.1. Recording and Reporting Adverse Events

9.1.1. General Guidelines

The investigator must promptly record all clinical events occurring during the study data collection period (see Section 9.1.2). Medical conditions that existed or were diagnosed prior to the signing of the Informed Consent will be recorded as part of medical history. Abnormal laboratory values and vital signs observed at the time of Informed Consent should also be recorded as medical history. Any subsequent worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug should also be recorded as an AE.

At each visit, the investigator will determine whether any AEs have occurred by evaluating the patient. Adverse events may be directly observed, reported spontaneously by the patient, or by questioning the patient at each study visit. Patients should be questioned in a general way, without asking about the occurrence of any specific symptoms. The investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 9.2. The investigator's assessment must be clearly documented in the site's source documentation with the investigator's signature. The investigator should follow up on SAEs (and AESIs) until they have resolved or are considered clinically stable; AEs should be followed until they are resolved or last study visit, whichever comes first.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

Laboratory results, vital signs, and other diagnostic results or findings should be appraised by the investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or other diagnostic findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation, lead to dose reduction, require corrective treatment, or constitute an AE in the investigator's clinical judgment.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the serious adverse event (SAE; diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the ICF) procedures, treatments requiring hospitalization for pre-existing conditions that do not worsen in severity, and admission for palliative or social care should not be reported as SAEs (see Section 9.2 for definition).

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any SAE that may occur subsequent to the reporting period (end of the follow-up) that the investigator assesses as related to study drug should also be reported.

All AEs, SAEs, AESIs, and pregnancy reports are to be reported according to the procedures in Section 9.1.4.

9.1.2. Data Collection Period

The investigator will record all events, serious and non-serious, that occur from the time of signing the informed consent and for 21 weeks after the last dose of study drug (ie, the follow-up period). The follow-up period applies to all patients who complete the study or terminate early (excludes those who withdraw consent).

9.1.3. Reporting Procedure

All events (serious and non-serious) must be reported with investigator's assessment of the event's seriousness, severity, and causality to the study drug. For SAEs and AESIs, a detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome, should be provided on the AE CRF. Specific or estimated dates of event onset, treatment, and resolution should be included when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed, and include the results if available. Information not available at the time of the initial report must be documented in a follow-up report. Source documents (including hospital or medical records, diagnostic reports, etc.) will be summarized in the narrative on the AE CRF, and retained at the study center and available upon request.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

9.1.4. Events that Require Expedited Reporting to Sponsor

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

- **SAEs**.
- **Adverse Events of Special Interest** (AESI; serious and non-serious)**:** Adverse events of special interest for this study include the following:
  - Moderate or severe infusion reactions
  - Confirmed Neisseria infection
  - Any thrombotic or embolic event
- **Pregnancy:** Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female or female partner of a male, during the study or within 21 weeks of the last dose of study drug. Any complication of pregnancy affecting a female study patient or female partner of a male study patient, and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

9.2. Definitions

9.2.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug (ICH, 1994).

9.2.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that, had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as admission to a hospital or an emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

Criteria for reporting SAEs must be followed for these events.

9.2.3. Adverse Events of Special Interest

An adverse event of special interest (AESI; serious or non-serious) is one of scientific and medical interest specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

Adverse events of special interest for this study are listed in Section 9.1.4.

9.2.4. Infusion Reactions

Infusion reactions are defined as any relevant AE that occurs during the infusion or within 2 hours (up to 24 hours) after the infusion is completed.

9.2.5. Severity

The severity of AEs will be graded according to the following scale:

Mild: Does not interfere in a significant manner with the patient's normal functioning level. It may be an annoyance. Prescription drugs are not ordinarily needed for relief of symptoms, but may be given because of personality of the patient.

Moderate: Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptom may be needed.

Severe: Produces significant impairment of functioning or incapacitation and is a definite hazard to the patient's health. Treatment for symptom may be given and/or patient hospitalized.

If a laboratory value is considered an AE, its severity should be based on the degree of physiological impairment the value indicates.

Infusion Reactions

The severity of infusion reactions will be graded according to the following scale (semi-colon indicates "or" within description of the grade):

Mild: Mild transient reaction; infusion interruption not indicated; intervention not indicated.

Moderate: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours.

Severe: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae; life-threatening consequences; urgent intervention indicated; death.

Injection Site Reactions

The severity of injection site reactions will be graded according to the following scale (semi-colon indicates "or" within description of grade):

Mild: Pain that does not interfere with activity; mild discomfort to touch; <5 cm of erythema or induration that does not interfere with activity

Moderate: Pain that requires repeated use of non-narcotic pain reliever >24 hours or interferes with activity; discomfort with movement; 5.1 cm to 10 cm erythema or induration or induration that interferes with activity

Severe: Pain that requires any use of narcotic pain reliever or that prevents daily activity; significant discomfort at rest; >10 cm erythema or induration; prevents daily activity; requires ER visit or hospitalization; necrosis or exfoliative dermatitis

9.2.6. Causality

The investigator must provide causality assessment as whether or not there is a reasonable possibility that the drug caused the AE, based on evidence or facts, his/her clinical judgment, and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

The following factors should be considered when assessing causality:

- Temporal relationship: time to onset vs time drug was administered
- Nature of the reactions: immediate vs. long term
- Clinical and pathological features of the events
- Existing information about the drug & same class of drugs
- Concomitant medications
- Underlying and concurrent illnesses
- Response to dechallenge (drug discontinuation) or dose reduction
- Response to rechallenge (re-introduction of the drug) or dose increase, when applicable
- Patient's medical and social history

Causality to the study drug (including study drug administration):

- Related:
  - The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the nature of the reaction, patient's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.

  or

  - The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its class of drugs, or is predicted by known pharmacology.
- Not Related:
  - The AE does not follow a reasonable sequence from study drug administration, or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

Causality to the study conduct (protocol specified procedure):

- Related:
  - The AE follows a reasonable temporal sequence from a protocol specified procedure, and cannot be reasonably explained by the nature of the reaction, patient's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.
- Not Related:
  - The AE does not follow a reasonable sequence from a protocol specified procedure, or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

9.3. Safety Monitoring

The investigator will monitor the safety of study patient at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The Medical/Study Director will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, Pharmacovigilance; Risk Management; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

9.4. Notifying Health Authorities, Institutional Review Board/Ethics Committee, and Investigators

During the study, the sponsor and/or the CRO will inform health authorities, Institutional Review Board (IRBs)/ Ethics Committees (ECs), and the participating investigators of any SUSARs (Suspected Unexpected Serious Adverse Reactions) occurring in other study centers or other studies of the active study drug (REGN3918), as appropriate per local reporting requirements. In addition, the sponsor and/or CRO will comply with any additional local safety reporting requirements.

Upon receipt of the sponsor's notification of a SUSAR that occurred with the study drug, the investigator will inform the IRB/EC unless delegated to the sponsor.

Event expectedness for study drug (REGN3918) is assessed against the Reference Safety Information section of the current Investigator's Brochure.

At the completion of the study, the sponsor will report all safety observations made during the conduct of the trial in the Clinical Study Report to health authorities and IRB/EC as appropriate.

10. STATISTICAL PLAN

This section provides the basis for the statistical analysis plan (SAP) for the study. The SAP may be revised during the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the database is locked.

Analysis variables are listed in Section 4.

10.1. Statistical Hypothesis

The primary objective of the study is to demonstrate a reduction in intravascular hemolysis by REGN3918 over 26 weeks of treatment in patients with active PNH who are treatment-naive to a complement inhibitor or have not recently received complement inhibitor therapy. The co-primary endpoints for the study are the proportion of patients achieving adequate control of their intravascular hemolysis, defined as LDH $\leq$ 1.5 x ULN at every scheduled time point between week 4 and week 26, inclusive, and the proportion of patients achieving transfusion avoidance defined as no post-baseline transfusions of RBCs per protocol. The proportions of the co-primary endpoints will be calculated, along with their 95% confidence intervals.

10.2. Justification of Sample Size

[redacted]

10.3. Analysis Sets

10.3.1. Efficacy Analysis Sets

The full analysis set (FAS) includes all enrolled patients who received any study drug. Efficacy endpoints will be analyzed using the FAS analysis set, unless otherwise specified (see Section 10.4.3.1 and Section 10.4.3.2).

10.3.2. Safety Analysis Set

The safety analysis set (SAF) includes all enrolled patients who received any study drug. Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

10.3.3. Pharmacokinetic Analysis Sets

The PK analysis set includes all patients who received any study drug and who had at least 1 non-missing result for concentration of REGN3918 following the first dose of study drug.

10.3.4. Immunogenicity Sets

The ADA analysis set will consist of all patients who received any study drug and who had at least one non-missing ADA result after first dose of the study drug.

ADA positive samples will be further characterized for the presence of neutralizing activity.

The neutralizing antibody (NAb) analysis set includes all patients who received any study drug and who are negative in the ADA assay or with at least 1 non-missing result in the NAb assay. Patients who are ADA negative will be set to negative in the NAb analysis set.

10.3.5. Exploratory Analysis Sets

10.3.5.1. Exploratory Biomarker Endpoint Analysis Set

The PD analysis sets include all subjects who received any study drug and who had at least 1 non-missing analyte measurement following the first dose of study drug.

10.3.5.2. Exploratory Clinical Outcome Assessment Analysis Set

The COA analysis sets include all subjects who received any study drug and who had a baseline measurement and at least 1 non-missing COA measurement following the first dose of study drug.

10.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, median, standard deviation, minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

In addition to summary statistics, data will be plotted whenever needed.

If there is no change in dosing regimen for cohort B, patients of cohort A and cohort B will be pooled for both safety and efficacy analysis. If the dosing regimen is changed, cohort A and cohort B will be analyzed separately, and cohort B will be the primary analysis cohort.

10.4.1. Patient Disposition

The following will be provided:

- The total number of screened patients who met the inclusion criteria regarding the target indication and signed the ICF
- The total number of enrolled patients
- The total number of patients in each analysis set (eg, provided in Section 10.3.1)
- The total number of patients who discontinued the study, and the reasons for discontinuation
- A listing of patients enrolled but not treated
- A listing of patients prematurely discontinued from treatment, along with reasons for discontinuation

10.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively.

10.4.3. Efficacy Analyses

10.4.3.1. Primary Efficacy Analysis

For the co-primary endpoint of the proportion of patients achieving adequate control of their intravascular hemolysis, defined as LDH ≤1.5 x ULN at every scheduled time point between week 4 and week 26, inclusive, the analysis set will consist of all FAS patients. Patients who have one or more of the following will be considered as not achieving adequate control of their intravascular hemolysis:

- Discontinue from study treatment early
- Have 3 consecutive missing values of the scheduled LDH measurements between week 4 and week 26
- Have 50% or more missing values of the scheduled LDH measurements between week 4 and week 26
- Experience breakthrough hemolysis event (as defined in the secondary endpoint) while on treatment through week 26

Patients who complete study treatment, have no more than 2 consecutive missing values of the scheduled LDH measurements between week 4 and week 26, have fewer than 50% missing values of the scheduled LDH measurements between week 4 and week 26, and have no breakthrough hemolysis while on treatment will be evaluated based on their non-missing LDH measurements.

The proportion of patients achieving adequate control of their intravascular hemolysis will be calculated, along with a 95% confidence interval, by approximation of a one-sample z-statistic as primary analysis and by exact methods as sensitivity analysis. A sensitivity analysis by multiple imputation of missing LDH measurements will also be performed. Multiple imputation methods to be applied will be detailed in the SAP.

For the co-primary endpoint of the proportion of patients achieving transfusion avoidance, the analysis set will consist of all FAS patients. A transfusion will be counted only if the transfusion follows the predefined transfusion algorithm. A time-to-first-event analysis will be used to estimate the proportion of patients achieving transfusion avoidance at 26 weeks and a 95% confidence interval.

Sensitivity analyses of the co-primary endpoints will also be conducted for subgroups of FAS patients, including all complement inhibitor-naive patients (no prior complement inhibitor therapy) in cohort A and cohort B, all patients in cohort B, and all complement inhibitor-naive patients in cohort B.

10.4.3.2. Secondary Efficacy Analysis

For secondary endpoints that are defined by dichotomy of multiple measurements of a variable through a period of time, such as the proportion of patients achieving normalization of their intravascular hemolysis, defined as LDH ≤ 1.0 x ULN at every scheduled time point between week 4 through week 26, inclusive, the analysis set consists of all FAS patients. For this category of secondary endpoints, analysis (including the handling of early discontinuation and missing data) will follow the same approach employed for the co-primary endpoint of the proportion of patients achieving normalization of their intravascular hemolysis, defined as LDH ≤ 1.5 x ULN at every schedule time point between week 4 through week 26.

For secondary endpoints that are defined by a change and percent change from baseline to a time point in a variable, the analysis set will consist of all FAS patients who have a non-missing baseline measurement of the variable, such as:

- Change in LDH levels from baseline to week 26
- Change in RBC hemoglobin levels from baseline to week 26
- Change in free hemoglobin levels from baseline to week 26
- Change in patient reported outcomes (FACIT-Fatigue, EORTC-QLQ-30, and EQ-5D-3L) from baseline to week 26

Means and 95% confidence intervals by a one-sample t-statistic as primary analysis will be reported. The method to be used for imputing missing data for this category of secondary endpoints variables will be described in the SAP. Means and 95% confidence intervals derived from sensitivity analysis, such as mixed-effect model for repeated measures (MMRM) analysis without imputation for missing data, will also be reported.

For secondary endpoints that are defined by any occurrence of a defined event during a period, such as the rate of breakthrough hemolysis through week 26, the FAS will be used. Means and 95% confidence intervals by approximation of a one-sample z-statistic as primary analysis and by exact methods as sensitivity analysis will be calculated for this category of secondary endpoints.

For time-to-event endpoints, such as the time to first LDH ≤ 1.5 x ULN, the analysis set will consist of all FAS patients. Survival analysis of data with censoring through time will be applied to analyze time-to-event endpoints.

For the rate and number of units of transfusion with RBCs through week 26, the analysis set consists of the FAS. The rate of units of transfusion for a patient will be calculated based on the duration of treatment exposure of the patient. Means and 95% confidence intervals by a one-sample t-statistic as primary analysis will be reported.

For the percentage of days with LDH ≤ 1.5 x ULN between week 4 and week 26, the analysis set will consist of all FAS patients. Means and 95% confidence intervals by a one-sample t-statistic as primary analysis will be reported. The method to be used for imputing missing data will be described in the SAP.

10.4.4. Safety Analysis

10.4.4.1. Adverse Events

Definitions

For safety variables, 3 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The treatment period is defined as either the first dose of study drug to last dose of study drug + 21 weeks or from first dose of study drug until first dose in OLE study (Section 7.5).
- The posttreatment period is defined as the time after the treatment period.

Treatment-emergent adverse events are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the on-treatment period.

Analysis

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). Coding will be to lowest level terms. The verbatim text, the preferred term (PT), and the primary system organ class (SOC) will be listed.

Summaries of all TEAEs by treatment group will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 9.2.5), presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT
- Treatment-emergent AESIs (defined with a PT or a prespecified grouping)

Deaths and other SAEs will be listed and summarized by treatment group.

Treatment-emergent adverse events leading to permanent treatment discontinuation will be listed and summarized by treatment group.

10.4.4.2. Other Safety

Vital Signs

Vital signs (temperature, pulse, and blood pressure) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Laboratory Tests

Laboratory test results will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Number and percentage of patients with a potentially clinically significant value (PCSV) at any post-randomization time point will be summarized for each clinical laboratory test.

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory tests of interest.

Listings will be provided with flags indicating the out-of-laboratory range values.

10.4.4.3. Treatment Exposure

The observation period (defined as the time between the date of first study drug administration and the date of the end of study visit for the patient), rather than the treatment exposure, will be presented.

10.4.4.4. Treatment Compliance

Analysis of treatment compliance will be described in the SAP.

10.4.5. Pharmacokinetics

10.4.5.1. Analysis of Drug Concentration Data

The PK endpoint is concentration of total REGN3918 in serum over time.

Summary of total drug concentrations and total C5 will be presented by nominal time point (ie, the time points specified in the protocol). Individual data will be presented by actual time. Plots of the concentrations of REGN3918 and total C5 will be presented over time (linear and log scales). When the scale is linear, concentrations below the lower limit of quantification (LLOQ) will be set to zero. In the log-scaled figures, concentrations below the LLOQ will be imputed as LLOQ/2. Summary statistics of concentrations of total REGN3918 and total C5 may include, but are not limited to arithmetic mean, standard deviation, standard error of the mean, coefficient of variation (in %), minimum, Q1, median, Q3, and maximum.

No formal statistical analysis will be performed.

10.4.6. Analysis of Immunogenicity Data

Immunogenicity will be characterized by the ADA response observed:

Anti-drug antibodies response categories and titer categories that will be assessed are as follows:

- Pre-existing immunoreactivity
- Treatment-emergent response
- Treatment-boosted response
- NAb response in ADA positive patients
- Titer value category (titer range)
  - Low (titer <1,000)
  - Moderate (1,000 ≤ titer ≤ 10,000)
  - High (titer >10,000)

Listings of ADA positivity, treatment-emergent ADA, NAbs, and titers presented by patient, time point, and dose cohort/group will be provided. Incidence of treatment-emergent ADA and NAbs will be assessed as absolute occurrence (N) and percent of patients (%), grouped by study cohorts and ADA titer level.

Plots of drug concentrations will be examined and the influence of ADAs and NAbs on individual PK profiles evaluated. Assessment of impact of ADA and NAbs on safety and efficacy may be provided.

10.4.7. Analysis of Exploratory Pharmacodynamic and Biomarker Data

Analysis of biomarker data is defined in the SAP.

10.4.8. Analysis of Exploratory Clinical Outcome Assessment Data

Analysis of COA data is defined in the SAP.

10.5. Interim Analysis

There will not be a formal interim analysis of the efficacy data. There will be an interim analysis of cohort A patient data after week 8, the purpose of which is the confirmation of the adequacy of the selected dose regimen, as described in Section 5.2.

10.6. Additional Statistical Data Handling Conventions

The following analysis and data conventions will be followed:

- Definition of baseline:
  - Unless otherwise specified, the baseline assessment is programmatically defined as the latest available measurement taken before first administration of study treatment. For patients enrolled but not treated, the baseline will be the last available measurement before enrollment.
- General rules for handling missing data:
  - Rules for handling missing data for assessment (other than efficacy)
  - If the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the intake of study medication, except if an incomplete date (eg, month and year) clearly indicates that the event started prior to treatment. If the partial date indicates the same month or year of the intake of study medication date, then the start date by the study medication intake date will be imputed; otherwise, the missing day or month by the first day or the first month will be imputed.
  - No imputations for missing laboratory data, ECG data, vital sign data, or physical examination data will be made.
- Visit windows:
  - Assessments taken outside of protocol-allowable windows will be displayed according to the case CRF assessment recorded by the investigator.

- Unscheduled assessments:
  - Extra assessments (laboratory data or vital signs associated with nonprotocol clinical visits or obtained in the course of investigating or managing AEs) will be included in listings, but not summaries. If more than 1 laboratory value is available for a given visit, the first observation will be used in summaries and all observations will be presented in listings.

10.7. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in Section 16.1.

11. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

11.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation [quality-checking], cleaning, correcting, releasing) will be maintained and stored at Regeneron (Sponsor).

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, baseline findings, medication, medical history) will be done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected with an electronic data capture (EDC) tool.

11.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study will include the following:

- IVRS/IWRS (interactive voice response system/interactive web response system) – randomization, study drug supply
- EDC system – data capture
- Statistical analysis system (SAS) – statistical review and analysis
- Pharmacovigilance safety database
- eCOA system – capture COA

12. STUDY MONITORING

12.1. Monitoring of Study Sites

The study monitor and/or designee (eg, contract research organization [CRO] monitor) will visit each site prior to enrollment of the first patient, and periodically during the study. This study will use the principles of risk-based monitoring (ICH E6 R2). This means that the number of visits for any given site may vary based on site risk indicators. The investigator must allow study-related monitoring.

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current, approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements.

12.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents).

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an electronic CRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

12.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic Case Report Forms (eCRFs) within the EDC system by trained site personnel. All required CRFs must be completed for each and every patient enrolled in the study. The investigator must ensure the accuracy, completeness, and timeliness of the data reported to the sponsor in the CRFs. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each patient CRF casebook is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

Corrections to the CRF will be entered in the CRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the EDC system. For corrections made via data queries, a reason for any alteration must be provided.

13. AUDITS AND INSPECTIONS

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

14.2. Informed Consent

The principles of informed consent are described in ICH guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB/EC. A copy of the IRB/EC-approved ICF and documentation of approval must be provided to the sponsor before the study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written, informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in language that he/she can understand. The ICF should be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Patients who can understand but who can neither write nor read will have the ICF read to them in the presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the patient.

If new safety information results in significant changes in the risk/benefit assessment, the ICF must be reviewed and updated appropriately. All study patients must be informed of the new information and provide their written consent if they wish to continue in the study. The original, signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient.

14.3. Patients Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study patient will be maintained. Patients should be identified by a patient identification number only, on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF) must be kept in strict confidence.

The patient's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

14.4. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/EC, as described in ICH guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the patients (eg, advertising) before any patient may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patient, in which case the IRB/EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB/EC should be informed of any event likely to affect the safety of patients or the continued conduct of the clinical study.

A copy of the IRB/EC approval letter with a current list of the IRB/EC members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB/EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

14.5. Clinical Study Data Transparency

Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations.

15. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design of the protocol or ICF without an IRB/EC-approved amendment. Regulatory approval will also be sought where required, in accordance with local procedures.

16. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

16.1. Premature Termination of the Study

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

16.2. Close-out of a Site

The sponsor and the investigator have the right to close-out a site prematurely.

Investigator's Decision

The investigator must notify the sponsor of a desire to close out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study but has not enrolled any patient within a reasonable period of time.
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines.
- The total number of patients required for the study are enrolled earlier than expected.

In all cases, the appropriate IRB/EC and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the patients' interests.

17. STUDY DOCUMENTATION

17.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the CRF/eCRF must be signed electronically by the investigator. This signed declaration accompanies each set of patient final CRFs/eCRFs that will be provided to the sponsor.

17.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer, if a longer period is required by relevant regulatory authorities. The investigator must obtain written approval from the sponsor before discarding or destroying any essential study documents during the retention period following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor (written notification) and the relevant records will be transferred to a mutually agreed-upon destination.

18. DATA QUALITY ASSURANCE

In accordance with ICH E6, the sponsor is responsible for quality assurance to ensure that the study is conducted, and the data generated, recorded, and reported in compliance with the protocol, GCP, and any applicable regulatory requirement(s). The planned quality assurance and quality control procedures for the study are summarized.

Data Management

The sponsor is responsible for the data management of this study including quality checking of the data (Section 11.1).

Study Monitoring

The investigator must allow study-related monitoring, IRB/EC review, audits, and inspections from relevant health regulatory authorities, and provide direct access to source data documents (Section 12.1, Section 12.2, and Section 13)

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements (Section 12.1).

All patient data collected during the study will be recorded on paper or electronic CRF unless the data are transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for affirming that data entries in the CRF are accurate and correct by electronically signing a declaration that accompanies each set of patient final CRFs (Section 12.3 and Section 17.1).

Study Documentation

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF (Section 12.2).

The investigator will retain all records and documents, including signed ICFs, pertaining to the conduct of this study for at least 15 years after study completion, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor (Section 17.2).

19. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

20. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

21. PUBLICATION POLICY

Publication rights and procedures will be outlined in a separate clinical study agreement.

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23. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: AN OPEN-LABEL, SINGLE ARM STUDY TO EVALUATE THE EFFICACY AND SAFETY OF REGN3918 IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) WHO ARE COMPLEMENT INHIBITOR-NAIVE OR HAVE NOT RECENTLY RECEIVED COMPLEMENT INHIBITOR THERAPY and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Medical/Study Director, Regulatory Representative, Clinical Study Team Lead, and Biostatistician)

To the best of my knowledge, this report accurately describes the conduct of the study.

Study Title: AN OPEN-LABEL, SINGLE ARM STUDY TO EVALUATE THE EFFICACY AND SAFETY OF REGN3918 IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) WHO ARE COMPLEMENT INHIBITOR-NAIVE OR HAVE NOT RECENTLY RECEIVED COMPLEMENT INHIBITOR THERAPY

Protocol Number: Protocol R3918-PNH-1852

Protocol Version: Protocol R3918-PNH-1852 Amendment 2

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison

See appended electronic signature page

Sponsor's Responsible Clinical Study Team Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

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