EudraCT: 2019-000130-20 Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

AN OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY, TOLERABILITY, AND EFFICACY OF REGN3918 IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

Compound:	REGN3918
Clinical Phase:	3
Protocol Number:	R3918-PNH-1868
Protocol Version:	R3918-PNH-1868 Original
Date of Issue:	*See appended electronic signature page*
Medical /Study Director:	[redacted]

[redacted]

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	An open-label extension study to evaluate the long-term safety, tolerability, and efficacy of REGN3918 in patients with paroxysmal nocturnal hemoglobinuria
Site Locations	Multiple global sites
Principal Investigator	Anita Hill, MBChB (Hons), MRCP, FRCPath, Ph.D
Objectives	The primary objective of the study is to evaluate the long-term safety, tolerability, and effect on intravascular hemolysis (ie, proportion of patients achieving lactate dehydrogenase (LDH) ≤ 1.5× upper limit of normal (ULN) over 26 weeks) of REGN3918 in patients with paroxysmal nocturnal hemoglobinuria (PNH). The secondary objectives of the study are: • To evaluate the long-term effect of REGN3918 on intravascular hemolysis. • To assess the concentrations of total REGN3918 in serum. • To evaluate the occurrence of the immunogenicity of REGN3918.
Study Design	This study is an open-label, single-arm study with REGN3918. Patients who have completed 1 of the 2 parent studies (ie, either R3918-PNH-1852 [redacted]) will be eligible for screening for this 2-year open-label extension (OLE) study. This study contains 2 study periods: the 2-year open-labeltreatment period and the optional post-end-of-treatment (EOT) period (ie, after completion of the 2-year open-label treatment period). The transition of treatment with REGN3918 from the parent study to the OLE study is planned to be uninterrupted. Therefore, the day 1 visit of the 2-year open-label treatment period will occur on the same visit as the EOT study visit in the parent study and overlapping assessments do not need to be repeated in this OLE study. Patients will continue their dose of up to 800 mg once weekly (QW) from the parent study starting at day 1 in the OLE study with a potential change in dose/dosing interval (on day 1 or subsequently) only for patients in cohort A of the parent study R3918-PNH-1852, if applicable. As part of risk mitigation for this study, it is recommended for patients to receive updated meningococcal vaccination, daily oral antibiotic prophylaxis, and counselling regarding risk of Neisseria gonorrhea, as applicable. In addition, blood transfusions should proceed according to a protocol-defined algorithm. Patients who do not enter into the optional post-EOT period should be followed for 21 weeks after the end of the 2-year open-label treatment period. Patients should return for monthly visits with assessments corresponding to the week 104 (EOT) visit. The optional post-EOT period includes continued REGN3918 treatment of variable duration. Patients may continue REGN3918 treatment after they

	have completed the 2-year open-label treatment period and if they derive clinical benefit and have potential risk associated with the discontinuation of REGN3918. Eligible patients will be asked to provide separate consent for continuing onto the optional post-EOT period. The optional post-EOT period ends when 1 of the following is met: • Clinical development of REGN3918 is terminated. • Risk-to-benefit profile of REGN3918 in this patient population is deemed unfavorable. • REGN3918 is approved by the regulatory authority governing the location of the study site.
Study Duration	It is projected that the first patients enrolled and who continue into the optional post-EOT period will have a study duration of approximately 4 years and last patients enrolled will have a study duration of at least 2 years.
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 up to [redacted] patients are expected to enroll in this study.
Target Population:	The study population will consist of adult male and female patients with confirmed diagnosis of PNH who have completed 1 of the 2 parent studies (R3918-PNH-1852[redacted]).
Treatment	
Study Drug	REGN3918
Dose/Route/Schedule:	Patients will be given a dose no greater than 800 mg subcutaneous (SC) QW (±1 day) over the treatment period. 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 the home healthcare visiting professional. Clinic visits for SC administration may or may not be needed.
Endpoints	
Primary:	The primary safety endpoint is incidence and severity of treatment-emergent adverse events (TEAEs) and other safety variables during the 2-year open-label treatment period of the study in patients treated with REGN3918. Adverse events (AEs), serious AEs (SAEs), and AEs of special interest (AESIs) will be analyzed over the 2-year open-label treatment period. For other safety variables, including laboratory data, vital signs, and electrocardiograms (ECGs), analysis will be conducted in reference to the baseline of the parent study, as this is the time point prior to any exposure to REGN3918. The primary efficacy endpoint is the proportion of patients achieving LDH ≤1.5×ULN over week 26, defined as LDH ≤1.5×ULN at every scheduled time point up to week 26 (inclusive).

	The baseline for the primary analysis of the primary efficacy endpoint is the baseline of the OLE (ie, this study) as it is expected that at this time point the 2 different populations from the parent studies should converge with regard to their control of intravascular hemolysis.
Secondary:	Key secondary efficacy endpoints include: • The proportion of patients with breakthrough hemolysis over week 26 • The rate and number of units of transfusion over week 26
Procedures and Assessments	Efficacy assessments in this study include concentration of LDH in serum, number of transfusions of red blood cells (RBC) and number of units of RBC per transfusion, concentration of RBC hemoglobin, and concentration of free hemoglobin. Safety assessments include vital signs, physical examination, anthropometric measurement, ECG, and clinical laboratory testing. Pharmacokinetic assessments include concentration of total REGN3918 and total C5 in serum. Biomarker testing include measurements of the total complement hemolytic activity assay (CH50), haptoglobin, reticulocyte count, and bilirubin. Immunogenicity assessment include measurement of anti-REGN3918 antibodies. For patients who consent to optional study procedures, blood and serum samples may be collected and stored as part of optional pharmacogenomics analysis and/or future biomedical research.
Statistical Plan	*Justifcation of sample size:* As this study is a follow-on that plans to include patients from the parent studies, R3918-PNH-1852 [redacted], no calculation for sample size was performed. It is expected to enroll up to [redacted] patients with PNH based on the maximum number of patients who could complete the parent study in the selected/participating countries. *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. 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. *Efficacy analyses:* The primary efficacy endpoint is the proportion of patients achieving LDH ≤1.5×ULN over week 26, defined as LDH ≤1.5×ULN at every scheduled time point up to week 26 (inclusive). All other efficacy analyses of this study are secondary. For efficacy endpoints that are defined by dichotomy of multiple measurements of a variable through a period of time, including the proportions of patients achieving LDH ≤1.0×ULN and LDH ≤1.5×ULN over week 26, week 78, and week 104, the analysis set consists of all FAS patients. For this category of efficacy endpoints, including the primary efficacy endpoint, patients who fulfill 1 or more of the following will be considered as not meeting the endpoint:

- Discontinue prematurely from study treatment
- Have ≥50% missing values of measurements of the analyzed variable during the assessed period. Note: For the primary efficacy endpoint, it means having missing LDH value at week 13 or week 26.
- Have breakthrough hemolysis (as defined in the secondary endpoint and based on investigator judgment) while on treatment over the assessed period.

Patients who do not fulfill the above criteria will be evaluated based on their non-missing measurements of the variable.

For secondary endpoints that are defined by a change or percent change from baseline of the OLE study 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. This category of endpoints includes:

- Percent changes and changes from baseline of the OLE study in LDH levels to week 26, week 78, and week 104
- Changes from baseline of the OLE study RBC hemoglobin levels to week 26, week 78, and week 104
- Changes from baseline of the OLE study in free hemoglobin levels to week 26, week 78, and week 104

For secondary endpoints that are defined by any occurrence of a defined event during a period, the analysis set will consist of all FAS patients. This category of endpoints includes:

- The proportions of patients with breakthrough hemolysis over week 26, week 78, and week 104
- The proportions of patients who are transfusion-free (with RBCs) over week 26, week 78, and week 104

For the rates and numbers of units of transfusion with RBCs over week 26, week 78, and week 104, the analysis set consists of all FAS patients. The rate of units of transfusion for a patient will be calculated based on the duration of treatment exposure of the patient.

For binary efficacy endpoints, means and 95% confidence intervals by approximation of a one-sample t-statistic as primary analysis and by exact methods as sensitivity analysis will be calculated for this category of efficacy endpoints. Sensitivity analysis by multiple imputation of missing measurements of the analyzed variable may be performed.

For continuous efficacy endpoints, means and 95% confidence intervals will be derived from one-sample t-test, analysis of covariance (ANCOVA) modeling, or MMRM (mixed-effect model for repeated measures) analysis.

Safety analyses: Evaluation of long-term safety and tolerability of REGN3918 is part of the primary objective of the study. Safety variables including AEs, laboratory test results, and vital signs will be descriptive based on the safety population, and no formal statistical testing will be performed. Safety analysis will focus on the treatment period.

For analyses of changes from baseline in laboratory and vital signs parameters, baseline of the parent study will be considered. In addition, baseline of the current study may also be considered.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
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
EOT	End of treatment
eGFR	Estimated glomerular filtration rate
FAS	Full analysis set
GCP	Good Clinical Practice
GPI	Glycophosphatidylinositol
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
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
PFS	Pre-filled syringe
PIGA	Phosphatidylinositol glycan anchor biosynthesis class A
PK	Pharmacokinetic
PNH	Paroxysmal nocturnal hemoglobinuria
PT	Preferred term
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
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WOCP	Women of childbearing potential

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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 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). Paroxysmal nocturnal hemoglobinuria 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).

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 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 intravenous (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 [redacted] 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 [redacted], 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 weekly (QW) SC doses of 400 mg following a 15 mg/kg IV loading dose, resulted in 1 resolved serious adverse event (SAE) in the study, an episode of salpingitis of

undetermined 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.

Two studies, R3918-PNH-1852 [redacted], will be conducted in PNH patients. R3918-PNH-1852 includes patients who are treatment-naïve to complement inhibitor or have not recently received complement inhibitor therapy. [redacted] includes patients who have been treated with eculizumab for at least 26 weeks and will switch to REGN3918. Both studies will evaluate REGN3918 administered over 26 weeks in a single-arm open-label design. Both studies will be referred to as the parent studies.

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 evaluate the long-term safety, tolerability, and effect on intravascular hemolysis (ie, proportion of patients achieving LDH ≤1.5× upper limit of normal [ULN] over 26 weeks) of REGN3918 in patients with PNH.

2.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the long-term effect of REGN3918 on intravascular hemolysis
- To assess the concentrations of total REGN3918 in serum
- To evaluate the immunogenicity of REGN3918

2.3. Exploratory Objectives

The exploratory objectives of the study are:

- To explore the long-term effect on clinical thrombotic events
- To explore the long-term effect on renal function
- To explore the long-term effect of REGN3918 on complement activation and intravascular hemolysis relevant to PNH and other related diseases
- To explore the long-term effect of REGN3918 on the concentrations of total C5 protein
- To collect future biomedical research samples from consented patients in order 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

No formal statistical hypothesis will be tested.

3.2. Rationale

3.2.1. Rationale for Study Design

The current clinical trial (R3918-PNH-1868) is an open-label extension (OLE), single-arm study with a 2-year open-label treatment period followed by an optional post-end-of-treatment (EOT) period with continued treatment with REGN3918 of variable duration in patients with PNH who have completed 1 of the 2 parent studies (R3918-PNH-1852 or [redacted]). In the parent studies, the duration of the treatment period is 26 weeks because it is anticipated that there will be a rapid initiation of clinical benefit of REGN3918 on intravascular hemolysis. It is expected, if approved, that REGN3918 would be administered in clinical practice for a duration of years, which is consistent with the current practice for eculizumab and ravulizumab. The longer-term treatment duration provided through this study will enable the evaluation of whether or not the initial clinical benefit anticipated in the parent studies is maintained and will provide further insight into the safety profile.

The study population includes patients coming from the parent studies as follows:

- R3918-PNH-1852: Approximately 30 patients and up to 42 patients with PNH having active signs and symptoms who are complement inhibitor-naïve or have not recently received complement inhibitor therapy will be enrolled into this parent study.
- [redacted]

Therefore, R3918-PNH-1868 will enroll approximately up to [redacted] patients from the parent studies.

3.2.1.1. Rationale for the Primary Safety and Efficacy Endpoints

The primary objective of the study is to evaluate the long-term safety, tolerability, and effect on intravascular hemolysis of REGN3918. The long-term safety and tolerability will be assessed by the incidence and severity of treatment-emergent adverse events (TEAEs) and other safety variables during the 2-year open-label treatment period of the study. The effect on intravascular hemolysis will be assessed by the proportion of patients achieving LDH ≤1.5×ULN over 26 weeks. The treatment periods of the 2 parent studies are of 26 weeks in duration each, which is sufficient to gain information on the efficacy on intravascular hemolysis. However, these trials still leave unanswered the efficacy and longer-term-safety of REGN3918 beyond 26 weeks. The effect on intravascular hemolysis over 26 weeks in the OLE study enables an evaluation of the maintenance of effect that will have been achieved after 26 weeks in the parent studies. An LDH ≤1.5×ULN is a clinically meaningful threshold for disease activity; an LDH greater than 1.5×ULN, along with related clinical symptoms, is considered as an indication for treatment with eculizumab (Soliris PI, 2018) (Ultomiris PI, 2018) (Sahin, 2016). Reductions in LDH ≤1.5×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). The safety assessment over 2 years in the OLE study allows us to answer some key questions, such as whether the safety observed over the 26 weeks in the parent studies is maintained with prolonged treatment exposure and whether any long-term safety risks, including AEs, emerge over time. Answering such questions relies on the accrual of long-term safety data, not only to confirm initial findings from the parent studies, but also to record an acceptable risk–benefit ratio that supports the continued development of the REGN3918 program.

3.2.1.2. Rationale for Secondary Efficacy 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 (Al-Ani, 2016). In this study, breakthrough hemolysis is a key secondary efficacy endpoint, defined by the measurement of LDH ≥2×ULN concomitant with associated signs or symptoms at any time subsequent to an initial achievement of disease control (ie, LDH ≤1.5×ULN) (Brodsky, 2018). 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. An event of breakthrough hemolysis as defined here will be confirmed based on investigator judgment.

The key secondary efficacy endpoint of the number of transfusions with RBCs and the number of units of RBCs transfused and the other secondary efficacy endpoint of transfusion avoidance (as assessed by the proportion of patients who are transfusion-free) is a clinical measure of reduced disease activity. In the eculizumab pivotal studies of patients with PNH who were treatment-naïve, TRIUMPH (Hillmen, 2006) and SHEPHERD (Brodsky, 2008), 0% of patients were transfusion independent at enrollment, with 49% and 51% achieving transfusion avoidance during the studies respectively. Similarly, the more recent study evaluating ravulizumab vs. eculizumab in PNH naïve patients reported 18.4% and 17.4%, respectively, transfusion independence in the year prior to the study with 73.6% and 66.1%, respectively, transfusion avoidance over 26 weeks (Lee, 2019). In another recent study with ravulizumab vs. eculizumab in patients previously treated with eculizumab, the difference in transfusion avoidance was 5.5% (95% CI -4.27, 15.68) (Kulasekararaj, 2019). A predefined algorithm for transfusion allows for standardization in the current study and captures a clinically meaningful event related to complement mediated intravascular hemolysis.

The other secondary efficacy endpoints, proportion of patients achieving target LDH reduction and change from baseline in LDH, evaluate the accepted objective laboratory measure of control of intravascular hemolysis. 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× to 8×ULN (Roth, 2018b). Upon treatment with anti-C5 antibody, LDH levels fall rapidly in all patients with the clinical goal of achieving an LDH

of ≤1.5×ULN. In a switch paradigm, whereby patients treated with eculizumab subsequently received either ravulizumab or continued eculizumab, the percent change from baseline in LDH with ravulizumab was shown to be non-inferior as compared with eculizumab (difference of -9.21% [95% CI: –18.84, 0.42]) (Kulasekararaj, 2019). In addition to the secondary endpoint of the proportion of patients reaching an LDH ≤1.5×ULN over week 78 and over week 104, 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×ULN), LDH will be reported using change and percent change from baseline of the OLE study. 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. Reductions in 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.

3.2.2. Rationale for Dose Selection

The dose and dosing interval of REGN3918 will be a continuation of the dosage regimen from the parent studies; however, some patients in the current study may require an adjustment to the selected dosage regimen (see Section 8.2). The maximum dosage regimen will be 800 mg QW. This dosage regimen will be finalized based on the emerging data from cohort A of the parent study R3918-PNH-1852, in active PNH patients who have never received a C5 inhibitor, or have not received complement inhibitor therapy in the past 6 months and require treatment with a C5 inhibitor. A key aspect of the emerging data will focus on patients achieving LDH ≤1.5×ULN and safety at 8 weeks of treatment with REGN3918.

3.3. Benefit-Risk

The 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 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 (Soliris PI, 2018) (Hillmen, 2013). 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 8.4.1) 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 8.4.2).

Recently, serious infections with Neisseria species (other than N. meningitidis), including disseminated gonococcal infections, have been reported during eculizimab treatment (Soliris PI, 2018). Counseling about Neisseria gonorrhea prevention, testing, and treatment is to be performed in accordance with local practice/national guidelines (see Section 8.7).

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

4. ENDPOINTS

4.1. Primary and Secondary Endpoints

4.1.1. Primary Safety Endpoint

The primary safety endpoint is incidence and severity of TEAEs and other safety variables during the 2-year open-label treatment period of the study in patients treated with REGN3918.

Adverse events (AEs), SAEs, and AEs of special interest (AESIs) will be analyzed over the 2-year open-label treatment period. For other safety variables, including laboratory data, vital signs, and electrocardiograms (ECGs), analysis will be conducted in reference to the baseline of the parent study, as this is the time point prior to any exposure to REGN3918.

4.1.2. Primary Efficacy Endpoint

The proportion of patients achieving LDH ≤1.5×ULN over week 26, defined as LDH ≤1.5×ULN at every scheduled time point up to week 26 (inclusive), will be the primary efficacy endpoint.

The baseline for the primary analysis of the primary efficacy endpoint is the baseline of the OLE (ie, this study), as it is expected that at this time point the 2 different populations from the parent studies should converge with regard to their control of intravascular hemolysis.

4.1.3. Key Secondary Efficacy Endpoints

- The proportion of patients with breakthrough hemolysis over week 26
- The rate and number of units of transfusion over week 26

4.1.4. Other Secondary Endpoints

- The proportions of patients with breakthrough hemolysis over week 78 and week 104
- The rates and numbers of units of transfusion with RBCs over week 78 and week 104
- The proportions of patients who are transfusion-free (with RBCs) over week 26, week 78, and week 104
- The proportions of patients achieving adequate control of their intravascular hemolysis, defined as LDH ≤1.5×ULN at every scheduled time point up to week 78 (inclusive), and week 104 (inclusive)
- The proportions of patients achieving normalization of their intravascular hemolysis, defined as LDH ≤1.0×ULN at every scheduled time point up to week 26 (inclusive), week 78 (inclusive), and week 104 (inclusive)
- Changes and percent changes in LDH from baseline of the OLE study to week 26, week 78, and week 104
- Changes in RBC hemoglobin levels from baseline of the OLE study to week 26, week 78, and week 104
- Changes in free hemoglobin levels from baseline of the OLE study to week 26, week 78, and week 104

- Concentrations of REGN3918 in serum assessed throughout the study
- Incidence of treatment-emergent anti-drug antibodies (ADA) to REGN3918 throughout the study

4.2. Exploratory Endpoints

- Changes in renal function as measured by estimated glomerular filtration rate (eGFR) from baseline of the OLE study to week 26, week 78, and week 104
- Changes in haptoglobin from baseline of the OLE study to week 26, week 78, and week 104
- Changes in bilirubin from baseline of the OLE study to week 26, week 78, and week 104
- Changes in reticulocyte count from baseline of the OLE study to week 26, week 78, and week 104
- Changes and percent change in CH50 from baseline of the OLE study to week 26, week 78, and week 104
- Changes in total C5 from baseline of the OLE study to week 26, week 78, and week 104
- Incidences of MAVE over week 26, week 78, and week 104

5. STUDY VARIABLES

5.1. 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.

5.2. Efficacy Variables

5.2.1. Laboratory Variables for the Assessment of Efficacy

Efficacy in this study is evaluated by the following laboratory assessments:

- Serum LDH
- RBC hemoglobin
- Free hemoglobin

These laboratory variables are relevant to the characterization and disease mechanisms of PNH (Brodsky, 2014).

5.2.2. Transfusion Record

Hemolytic anemia is a clinical manifestation of PNH, and patients often require blood transfusion for symptomatic management. The frequency of blood transfusion has been used in other studies of PNH to assess efficacy (Hillmen, 2006) (Roth, 2018a).

5.3. Safety Variables

Safety variables in this study include:

- TEAEs
- ECGs
- Vital signs (temperature, sitting blood pressure, and pulse rate)
- Routine safety laboratory tests (hematology, chemistry, urinalysis, and pregnancy testing (for women of childbearing potential [WOCP] only)

5.4. Pharmacokinetic Variables

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

5.5. Immunogenicity Variables

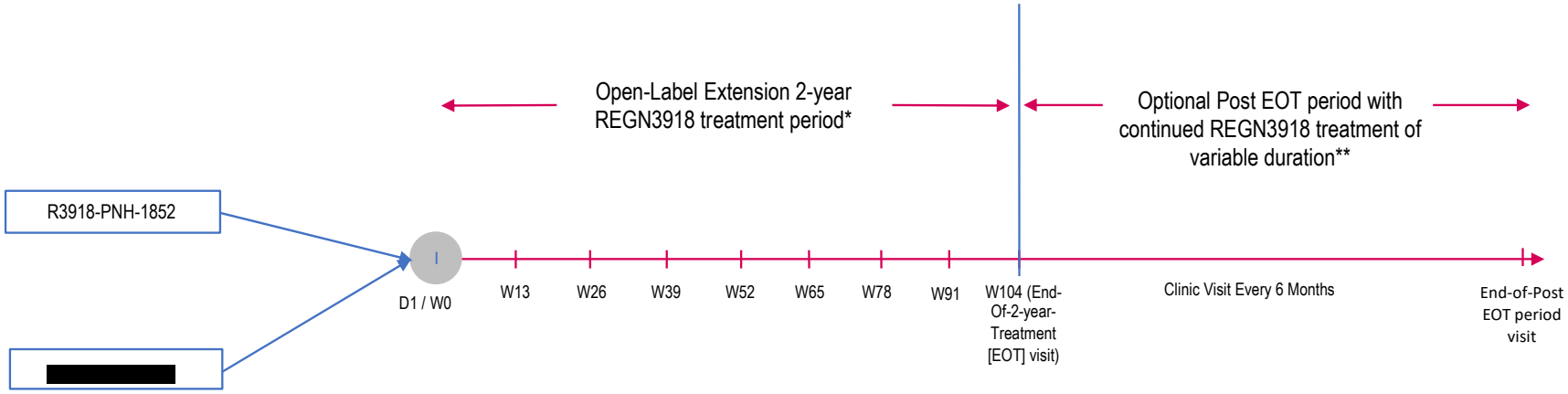
The immunogenicity variables are anti-drug antibody (ADA) status, titer, neutralizing antibody (NAb) status, and time point/visit. Samples in this study will be collected at the clinic visits specified in Table 1.

6. STUDY DESIGN

6.1. Study Description and Duration

This study is an open-label, single-arm study with REGN3918. The total number of patients included in the study is a maximum of [redacted] patients. The study schematic is presented in Figure 1.

Figure 1: Study Schema



*Patients who do not enter into the optional post-EOT period should be followed for 21 weeks after the end of the 2-year open-label treatment period. Patients should return for monthly visits with assessments corresponding to the week 104 (EOT) visit.
**The optional post-EOT period includes continued REGN3918 treatment of variable duration. Patients may continue REGN3918 treatment after they have completed the 2-year open-label treatment period if they derive clinical benefit and have potential risk upon discontinuation of REGN3918. The optional post-EOT period ends when 1 of the following is reached: clinical development of REGN3918 is terminated, risk-to-benefit profile of REGN3918 in this patient population is deemed unfavorable, or REGN3918 is approved by the regulatory authority governing the location of the study site.

6.1.1. Study Periods

This study contains 2 study periods: the 2-year open-label treatment period and the optional post-EOT period (ie, after completion of the 2-year open-label treatment period). Please see Figure 1.

6.1.1.1. Two-year Open-Label Treatment Period with REGN3918

Patients who have completed 1 of the 2 parent studies (ie, either R3918-PNH-1852 or [redacted]) will be eligible for screening for this OLE study. The 2-year open-label treatment period will have assessments as described in Table 1 occurring approximately quarterly and ending at week 104 (EOT).

The transition of treatment with REGN3918 from the parent study to the OLE study is planned to be uninterrupted. Therefore, the day 1 visit of the 2-year open-label treatment period will occur on the same visit as the EOT study visit in the parent study and overlapping assessments do not need to be repeated in this OLE study. Patients will continue their dose of up to 800 mg QW from the parent study starting at day 1 in the OLE study, with a potential change in dose/dosing interval (on day 1 or subsequently) only for patients in cohort A of the parent study R3918-PNH-1852, if applicable. As part of risk mitigation for this study, it is recommended for patients to receive updated meningococcal vaccination (Section 8.4.1), daily oral antibiotic prophylaxis (Section 8.4.2), and counselling regarding risk of Neisseria gonorrhea (Section 8.7), as applicable. In addition, blood transfusions should proceed according to the algorithm in Section 8.3. Breakthrough hemolysis is defined in Section 3.2.1.2.

Patients who do not enter into the optional post-EOT period should be followed for 21 weeks after the end of the 2-year open-label treatment period. Patients should return for monthly visits with assessments corresponding to week 104 (EOT) visit.

6.1.1.2. Optional Post-End-of-Treatment Period

The optional post-EOT period includes continued REGN3918 treatment of variable duration. Patients may continue REGN3918 treatment after they have completed the 2-year open-label treatment period and if they derive clinical benefit and have potential risk upon discontinuation of REGN3918. Eligible patients will be asked to provide separate consent for continuing onto the optional post-EOT period. The optional post-EOT period ends when 1 of the following is met:

- Clinical development of REGN3918 is terminated.
- Risk-to-benefit profile of REGN3918 in this patient population is deemed unfavorable.
- REGN3918 is approved by the regulatory authority governing the location of the study site.

The additional safety information accrued in the post-EOT period will be reported.

6.1.1.3. Duration of Study

It is projected that the first patients enrolled and who continue into the optional post-EOT period will have a study duration of approximately 4 years and the last patients enrolled will have a study

duration of at least 2 years. However, the study duration is dependent on the criteria mentioned in Section 6.1.1.2.

6.1.2. End of Study Definition

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

At a patient level, the end of study is defined as the end of treatment period (EOT) or, depending on the particular circumstances of the patient (see Section 6.1.1.2), at the end of post-EOT period, which is of variable duration.

6.2. Planned Interim Analysis

There will not be a formal interim analysis.

An interim data lock(s) for regulatory submissions of REGN3918 or publication purposes may be conducted.

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

7.1. Number of Patients Planned

Approximately up to [redacted] patients are expected to enroll in this study.

This study will be conducted at multiple global sites that enroll patients in the 2 parent studies. Enrollment for this study will be driven by enrollment in the parent studies (R3918-PNH-1852 [redacted]).

7.2. Study Population

The study population will consist of adult male and female patients with confirmed diagnosis of PNH who have completed 1 of the 2 parent studies (R3918-PNH-1852 [redacted]).

7.2.1. Inclusion Criteria

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

1. Patients with PNH who have completed, without discontinuation, study treatment in 1 of the parent studies in which they participated (either R3918-PNH-1852 [redacted])
2. Willing and able to comply with clinic visits and study-related procedures
3. Provide informed consent signed by study patient

7.2.2. Exclusion Criteria

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

1. Significant protocol deviation(s) in the parent study based on the investigator's judgment and to the extent that these would (if continued) impact the study objectives and/or safety of the patient (for example, repetitive non-compliance with dosing by the patient).
2. Any new condition or worsening of an existing condition which, in the opinion of the investigator, would make the patient unsuitable for enrollment or could interfere with the patient participating in or completing the study.
3. Pregnant or breastfeeding women
4. 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; intrauterine hormone-releasing system
    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 patient.

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

7.3. 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 9.1.2.

Rules for discontinuation of study treatment (permanent or temporary) are discussed in Section 8.5.1.

7.4. Replacement of Patients

Patients prematurely withdrawn from the study/study drug will not be replaced.

8. STUDY TREATMENTS

8.1. Investigational Treatments

REGN3918 drug product may be initially provided in lyophilized form in a sterile, single-use glass vial for SC administration that requires reconstitution with sterile water for injection to 150 mg/mL REGN3918, and then transitioned to a sterile, single-use glass vial containing a liquid 200 mg/mL REGN3918 formulation that will not require reconstitution. However, the study may begin directly with the liquid formulation. The compositions of the lyophilized and liquid formulations differ, mainly as a result of the inclusion of a viscosity reducer (arginine hydrochloride) in the high-concentration liquid formulation. The liquid drug product may then be switched to a pre-filled syringe (PFS).

Study drug will be supplied by the sponsor. The admixture solutions needed for delivery of the lyophilized drug product for SC administration will be sourced locally, or may be supplied by the sponsor, as necessary. Detailed information about the drug product and dose preparation is provided in the pharmacy manual.

8.2. Drug Administration

Patients will be given a dose no greater than 800 mg SC QW (±1 day) over the treatment period.

The dose and dosing interval of REGN3918 will be finalized based on the emerging data from cohort A of the parent study R3918-PNH-1852, in active PNH patients who have never received a C5 inhibitor, or have not received complement inhibitor therapy in the past 6 months and require treatment with a C5 inhibitor. It is anticipated that most or nearly all patients will continue their dose and dosing interval from the parent study. However, some patients may or may not require an adjustment to their dosage regimen if they enter the current study before the decision on the final dose/dosing interval is made based on the R3918-PNH-1852 study.

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 the 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 the clinical site personnel or visiting healthcare professional. Once this observation is considered satisfactory, then the study drug can be subsequently administered independently by the patient/designated person for the remainder of the study.

In addition, a patient diary will be provided prior to initiation of self-administration. 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 the study drug administration is provided in the pharmacy manual.

8.3. 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.

*Baseline is the baseline of OLE study.

8.4. Pretreatments

Enrolled patients should receive updated meningococcal vaccination, as needed, concomitant to enrollment into the OLE. Oral antibiotics are recommended during the treatment period, according to local practice.

8.4.1. Meningococcal Vaccinations

Patients will have had previous documented vaccination for meningococcus and should 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. Serologic titers for to determine adequate meningococcal immunity can be done if clinically indicated. Revaccination is not mandatory if serologic titers to serogroups of Neisseria meningitidis demonstrate adequate immunity, as per local practice.

8.4.2. Oral Antibiotics

It is recommended that daily oral antibiotic prophylaxis commence on the day of first dosing with REGN3918, 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 9.1.2). 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.

8.5. Dose Modification and Study Treatment Discontinuation Rules

8.5.1. Study Drug Discontinuation

Patients who permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete study assessments, per Section 9.1.2.

8.5.1.1. 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×ULN or

  - ALT or AST >5×ULN for more than 2 weeks, or
  - ALT or AST >3×ULN and total bilirubin >2×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

8.5.1.2. 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 upon determining, according to his/her best medical judgment, that the responsibility of the study drug in the occurrence of the concerned event was unlikely.

8.6. Management of Acute Reactions

8.6.1. Acute Injection Reactions

8.6.1.1. Systemic Injection Reactions

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 (as defined in Section 10.2) and graded using the grading scales as instructed in Section 10.2.4.

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.

8.6.1.2. Local Injection Site Reactions

Local injection site reactions must be reported as AEs and graded according to Section 10.2.4.

8.7. 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.

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

8.8. Dose Modification

Dose modification for an individual patient is not allowed by the investigator. Dose modification for the study may be conducted by the sponsor as per Section 8.2.

8.9. 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.

Treatment will be assigned by an interactive voice response system (IVRS)/interactive web response system (IWRS) and provided to the site as shown in Table 1.

8.9.1. Blinding

This is an open-label study.

8.10. Treatment Logistics and Accountability

8.10.1. 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 or PFS. The carton box and vial or PFS 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 according to labeled storage conditions at a temperature of 2ºC to 8ºC.

8.10.2. 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.

8.10.3. 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.

8.10.4. Treatment Compliance

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

8.11. Concomitant Medications

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

8.11.1. Prohibited Medications

The following medications are prohibited, with the exception of those listed in Section 8.11.2, 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

8.11.2. 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 8.4.1
- Oral antibiotic prophylaxis, as described in Section 8.4.2
- 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

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. 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:

- Vital signs and ECGs should be performed prior to blood draws and study drug administration
- PK/ADA sampling should be performed as soon as possible after an ECG
- Collect safety (including ADA), PK, efficacy, followed by biomarker samples prior to study drug administration

Patients will be provided the following:

- A patient diary will be provided to patients who self-administer the study drug to collect relevant information
- Patient safety card for Neisseria meningitidis (see Section 8.4.1)

Table 1: Schedule of Events

Study Period	2-Year Open-Label Treatment Period[1]								Optional Post-EOT Period[2]
Study Week	**Day 1/ Week 0[5]**	**Week**							**Every 6 months after EOT until End of Post-EOT period**
		13	**26**	**39**	**52**	**65**	**78**	**91**	**EOT (104)**	
Visit Window (weeks)		±1 w	±1 w	±1 w	±1 w	±1 w	±1 w	±1 w	±1 w	± 2 w
Clinic Visit	X	X	X	X	X	X	X	X	X	X
Screening/Baseline:										
Inclusion/Exclusion criteria	X									
Informed consent	X									X[2]
Demographics	X									
Medical history	X									
Height	X									
Risk assessment for Neisseria gonorrhea[3]	X									
Enrollment via IVRS/IWRS	X									
Treatment:										
REGN3918 administration[4]	←----------X[4]----------→									X
Oral antibiotics	←----------X----------→									X
Meningococcal vaccine (as needed)	←----------X----------→									X
Patient diary (if applicable, compliance check)[5]	X	X	X	X	X	X	X	X	X	X
Efficacy:										
Serum LDH[6]	X	X	X	X	X	X	X	X	X	X
Transfusion record update	X	X	X	X	X	X	X	X	X	
RBC hemoglobin[7]	X	X	X	X	X	X	X	X	X	
Free hemoglobin[7]	X	X	X	X	X	X	X	X	X	

Study Period	2-Year Open-Label Treatment Period[1]									Optional Post-EOT Period[2]
Study Week	Day 1/ Week 0[5]	Week								Every 6 months after EOT until End of Post-EOT period
		13	26	39	52	65	78	91	EOT (104)	
Visit Window (weeks)		±1 w	±1 w	±1 w	±1 w	±1 w	±1 w	±1 w	±1 w	± 2 w
Safety:										
Body weight	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X
Physical examination	X		X		X		X		X	X
Electrocardiogram	X				X				X	
Adverse events	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Patient safety card for Neisseria meningitidis	X	X	X	X	X	X	X	X	X	X
Laboratory Testing:										
Hematology[7]	X	X	X	X	X	X	X	X	X	X
Blood chemistry[6]	X	X	X	X	X	X	X	X	X	X
Pregnancy test (WOCP only)	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X
Titers to Neisseria meningitidis (only if indicated as per local practice)[8]	X	X	X	X	X	X	X	X	X	X
PK, ADA and Biomarker Samples:										
PK sample of REGN3918	X	X	X	X	X	X	X	X	X	
Total C5 (plasma)	X	X	X	X	X	X	X	X	X	
Complement hemolytic assay (serum CH50)	X	X	X	X	X	X	X	X	X	
Haptoglobin	X	X	X	X	X	X	X	X	X	
Bilirubin[6]	X	X	X	X	X	X	X	X	X	
Reticulocyte count[7]	X	X	X	X	X	X	X	X	X	
ADA sample for REGN3918	X		X		X		X		X	X[9]
Optional Research:										
Future biomedical research (optional)	X	X	X		X				X	
Whole blood for DNA isolation (optional)[10]	X									

9.1.1. Footnotes for the Schedule of Events Table

1. After completion of the 2-year open-label treatment period, patients who do not enter into the optional post-EOT period should be followed for 21 weeks. Patients should return for monthly clinic visits with assessments corresponding to week 104 (EOT) visit.
2. The optional post-EOT period includes continued REGN3918 treatment of variable duration. Patients may continue REGN3918 treatment after they have completed the 2-year open-label treatment period and if they derive clinical benefit and have potential risk to discontinue REGN3918. The optional post-EOT period ends when 1 of the following is reached: clinical development of REGN3918 is terminated, risk-to-benefit profile of REGN3918 in this patient population is deemed unfavorable, or REGN3918 is approved by the regulatory authority governing the location of the study site. Patients will be asked to provide separate consent for continuing onto the optional post-EOT period.
3. Risk assessment for Neisseria gonorrhea is described in Section 8.7.
4. Study drug administration will occur QW throughout the entire study, starting from the day 1 visit until and including the end-of-treatment visit (for the 2-year open-label treatment period) and for the optional post-EOT period (if applicable). Administration of study drug may be done at the clinical site, by a healthcare professional at the patient's home, or by self-administration/administration by the patient or designated person, respectively. These various options for administration will depend on the preference of the investigator and patient, the availability of clinical supply, and the home healthcare visiting professional, and presentation of the study drug that may change during the course of the study. If the presentation of the study drug becomes available for self-administration /administration by patient or designated person, then sufficient injection training at the scheduled administration(s) with REGN3918 will be provided prior to undertaking study drug administration. Study drug kits will be dispensed at the clinical site visit or, as applicable, transported to the patient by a healthcare professional or by a DTP service provider.

   The recommended daily oral antibiotic prophylaxis will commence on the day of dosing and will consist of penicillin V 500 mg BID, or Erythromycin 500 mg BID in the case of penicillin allergy (to be determined by the investigator). See Section 8.4.2.
5. A patient diary will be provided to collect information that may include AEs, study drug administration, concomitant medications, vital signs, etc. depending on availability of a home healthcare visiting professional and other considerations. For self-administration/administration by a designated person, a compliance check with the patient diary will be undertaken at clinic visits.
6. On visits where chemistry overlaps with serum LDH and/or bilirubin assessments, the chemistry testing will include these assessments.
7. On visits where hematology overlaps with RBC hemoglobin, free hemoglobin, and/or reticulocyte count assessments, the hematology testing will include these assessments.

8. Revaccinate patients at any time throughout the study. If the patient has had titers measured for Neisseria meningitidis and they demonstrate inadequate level of immunity, then revaccination should be done.
9. ADA samples will be collected every 12 months after EOT and until the end of post-EOT period. Samples will be used for detecting the presence of ADA only; NAb positivity will only be assessed for treatment-emergent ADA-positive samples.
10. Whole blood sample for DNA should be collected on day 1 (predose) but can be collected at a later study visit. Patients who had consented to DNA testing in the parent study and had provided a sample for analysis do not need to provide separate consent/sample for the OLE study.

9.1.2. Early Termination Visit

Patients who discontinue the study prematurely during the 2-year open-label treatment period (ie, are withdrawn from the study before the EOT visit) will be asked to return to the clinic for an early termination visit consisting of the EOT assessments described in Table 1.

Patients who discontinue treatment prematurely during the 2-year open-label treatment period should have an early EOT visit consisting of the EOT assessments described in Table 1, followed by monthly visits until 21 weeks after last dose of study drug. These monthly follow-up visits will consist of assessments listed for the EOT visit in Table 1.

Patients who discontinue the study prematurely during the optional post-EOT period (ie, are withdrawn from the study before the end of post-EOT period) will be asked to return to the clinic for an early termination visit consisting of the end of post-EOT assessments described in Table 1.

Patients who discontinue treatment prematurely during the optional post-EOT period should have an early end of post-EOT visit consisting of the end of post-EOT assessments described in Table 1, followed by monthly follow-up visits until 21 weeks after last dose of study drug consisting of assessments listed for the end of post-EOT visit.

9.1.3. 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.

9.2. Study Procedures

9.2.1. 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:

- Informed consent
- Medical history (including disease characteristics and medication history)
- Demographics
- Height
- Risk assessment for Neisseria gonorrhea (Section 8.7)
- Provide patient safety card for Neisseria meningitidis (Section 8.4.1). Replacement cards may be provided at any visit.

Patients who meet the inclusion and exclusion criteria for the study will be enrolled into the OLE study via IVRS/IWRS. The IVRS/IWRS may be contacted for drug resupply at any subsequent visit.

9.2.2. Study Drug Administration

Study drug will be administered as described in Section 8.2. Re-immunization with meningococcal vaccine(s) may be performed according to local practice (Section 8.4.1). Daily oral antibiotic prophylaxis is recommended (Section 8.4.2).

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

9.2.3. Efficacy Procedures

9.2.3.1. Serum Lactate Dehydrogenase

Blood samples for LDH testing will be collected as part of the routine safety chemistry panel (Section 9.2.4.5) according to Table 1. Serum LDH levels will be measured in a central laboratory.

9.2.3.2. Transfusion Record Update

During the study, the number of transfusions and number of units per transfusion with RBCs will be recorded in the case report form (CRF) according to Table 1.

Hemoglobin levels pre- and post-transfusion will be obtained (including local values).

9.2.3.3. Red Blood Cell Hemoglobin

Blood samples for RBC hemoglobin testing will be collected as part of the routine safety hematology panel (Section 9.2.4.5) according to Table 1 and measured in a central laboratory.

9.2.3.4. Free Hemoglobin

Blood samples for free hemoglobin testing will be collected as part of the routine safety hematology panel (Section 9.2.4.5) according to Table 1 and measured in a central laboratory.

9.2.4. Safety Procedures

9.2.4.1. Concomitant Medications

Concomitant medications will be reviewed at each visit according to Table 1.

9.2.4.2. Vital Signs

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

Vital signs will be obtained after patient has been sitting quietly for at least approximately 5 minutes. The same arm that was used in the parent study will be selected for measurement throughout the current study.

9.2.4.3. 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 the 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. If possible, the same type/model of scale should be used throughout the study.

9.2.4.4. 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 patient 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.

9.2.4.5. Laboratory Testing

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

Hematology, chemistry (except total C5), 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	Triglycerides
Carbon dioxide	Aspartate aminotransferase (AST)	Uric acid
Calcium	Alanine aminotransferase (ALT)	Creatine kinase
Glucose	Alkaline phosphatase	eGFR
Albumin	LDH	High-sensitivity C-reactive protein

*(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	Basophils
Red cell indices	Eosinophils
Platelet count	Reticulocytes

Urinalysis

pH	Protein	Leukocytes
Specific gravity	Glucose	Nitrite
Ketones	Bilirubin	

Note: If macroscopy is abnormal then reflex to microscopy.

Other Laboratory Tests

Other laboratory tests include:

- Pregnancy testing: serum human chorionic gonadotrophin pregnancy testing, urine pregnancy testing. In WOCP only. 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.
- Titers to assess risk of Neisseria meningitidis (only if indicated by local practice). Revaccination is recommended if titers do not demonstrate an adequate level of immunity (Section 8.4.1)

- PD and Exploratory Biomarker Procedures (Section 9.2.7)

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 10.1.1.

9.2.5. Drug Concentration and Total C5 Measurements

Blood samples for drug concentration (PK sample) will be collected prior to drug administration at the time points and visits listed in Table 1. The exact sampling time must be recorded, as allowed per local regulation.

Blood samples for total C5 protein (plasma) will be collected at time points according to the timepoints in Table 1

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

9.2.6. Immunogenicity Measurements and Samples

Blood samples for ADA and NAb assessments 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 biomarker research, as allowed per local regulation.

9.2.7. Pharmacodynamic and Exploratory Biomarker Procedures

Blood samples for CH50, haptoglobin, reticulocyte count, and bilirubin will be collected at time points listed in Table 1. Reticulocyte count and bilirubin are collected as part of routine safety hematology and chemistry samples, respectively (Section 9.2.4.5).

The results of analyses performed on these samples will be presented in the CSR. (Note: Data collected for these analytes in the post-EOT period are for safety monitoring only and will not be included in the PD and biomarker analysis.)

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

9.2.8. 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.

9.2.8.1. 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 (note: patients who had consented to DNA testing in the parent study and had provided a sample for analysis do not need to provide separate consent/sample for this part of the OLE study). Whole blood samples for DNA extraction should be collected on day 1 (predose), but can be collected at a later study visit (Table 1).

DNA samples will be collected for pharmacogenomics analyses. These samples will be single-coded as defined by the International Council on 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.

10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

10.1.1. General Guidelines

The investigator must promptly record all clinical events occurring during the study data collection period (see Section 10.1.2). 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 10.2. 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 10.2 for definitions).

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 10.1.4.

10.1.2. 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).

10.1.3. 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.

10.1.4. 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:
  - 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.

10.2. Definitions

10.2.1. 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).

10.2.2. 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.

10.2.3. 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 10.1.4.

10.2.4. 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.

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

10.2.5. 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.

10.3. 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.

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

During the study, the sponsor and/or the CRO will inform health authorities, IECs/IRBs, 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 Institutional Review Board (IRB)/Ethics Committee (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 IECs/IRB as appropriate.

11. 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 5.

11.1. Statistical Hypothesis

The primary objective of the study is to evaluate the long-term safety and tolerability of REGN3918 in patients with PNH, as well as the effect of REGN3918 on intravascular hemolysis as measured by LDH. No formal statistical hypothesis will be tested.

11.2. Justification of Sample Size

As this study is a follow-on that plans to include patients from the parent studies, R3918-PNH-1852 [redacted], no calculation for sample size was performed. It is expected to enroll up to [redacted] patients with PNH based on the maximum number of patients who could complete the parent study in the selected/participating countries.

11.3. Analysis Sets

11.3.1. 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 11.4.3).

11.3.2. 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.

11.3.3. Pharmacokinetic Analysis Sets

The PK analysis population 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.

11.3.4. Immunogenicity Analysis 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.

Positive treatment-emergent ADA samples will be assessed for neutralizing antibodies.

11.3.5. Exploratory Analysis Sets

11.3.5.1. Exploratory Biomarker Endpoint Analysis Set

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

11.4. 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.

11.4.1. 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 11.3)
- 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

11.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively.

11.4.3. Efficacy Analyses

The primary efficacy endpoint is the proportion of patients achieving LDH ≤1.5×ULN over week 26, defined as LDH ≤1.5×ULN at every scheduled time point up to week 26 (inclusive).

All other efficacy analyses of this study are secondary.

For efficacy endpoints that are defined by dichotomy of multiple measurements of a variable through a period of time, including the proportions of patients achieving LDH ≤1.0×ULN and LDH ≤1.5×ULN over week 26, week 78 and week 104, the analysis set consists of all FAS patients. For this category of efficacy endpoints, including the primary efficacy endpoint, patients who fulfill 1 or more of the following will be considered as not meeting the endpoint:

- Discontinue prematurely from study treatment
- Have ≥50% missing values of measurements of the analyzed variable during the assessed period. Note: For the primary efficacy endpoint, it means having missing LDH value at week 13 or week 26.
- Have breakthrough hemolysis (as defined in the secondary endpoint and based on investigator judgment) while on treatment over the assessed period.

Patients who do not fulfill the above criteria will be evaluated based on their non-missing measurements of the variable.

For secondary endpoints that are defined by a change or percent change from baseline of the OLE study 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. This category of endpoints includes:

- Percent changes and changes from baseline of the OLE study in LDH levels to week 26, week 78, and week 104
- Changes from baseline of the OLE study RBC hemoglobin levels to week 26, week 78, and week 104
- Changes from baseline of the OLE study in free hemoglobin levels to week 26, week 78, and week 104

For secondary endpoints that are defined by any occurrence of a defined event during a period, the analysis set will consist of all FAS patients. This category of endpoints includes:

- The proportions of patients with breakthrough hemolysis over week 26, week 78, and week 104
- The proportions of patients who are transfusion-free (with RBCs) over week 26, week 78, and week 104

For the rates and numbers of units of transfusion with RBCs over week 26, week 78 and week 104, the analysis set consists of all FAS patients. The rate of units of transfusion for a patient will be calculated based on the duration of treatment exposure of the patient.

For binary efficacy endpoints, means and 95% confidence intervals by approximation of a one-sample t-statistic as primary analysis and by exact methods, as sensitivity analysis will be calculated for this category of efficacy endpoints. Sensitivity analysis by multiple imputation of missing measurements of the analyzed variable may be performed, which will be detailed in the SAP.

For continuous efficacy endpoints, means and 95% confidence intervals will be derived from 1-sample t-test, analysis of covariance (ANCOVA) modeling, or MMRM (mixed-effect model for repeated measures) analysis. Handling of missing data will be specified in the SAP.

11.4.4. Safety Analysis

Evaluation of long-term safety and tolerability of REGN3918 is part of the primary objective of the study. Safety variables including AEs, laboratory test results, and vital signs will be descriptive, based on the safety population and no formal statistical testing will be performed. Safety analysis will focus on the treatment period as defined below.

For analyses of changes from baseline in laboratory and vital signs parameters, baseline of the parent study will be considered. In addition, baseline of the current study may also be considered.

11.4.4.1. Adverse Events

Definitions

For safety variables, 3 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF for the OLE study to before the first dose of study drug of the OLE study.
- The treatment period is defined as the time from the first dose of study drug of the OLE study to the end of the 2-year open-label treatment period, or, in patients who prematurely discontinue/do not enter into the optional post-EOT period, from the first dose of study drug of the OLE study to the last dose of study drug + 21 weeks (ie, 147 days).
- The posttreatment period of the OLE study is defined as the time after the treatment period of the OLE study.

Treatment-emergent adverse events are defined as those AEs that occur or worsen in severity or become serious during the treatment period or represent the exacerbation of a pre-existing condition during the 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 10.2.4), 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.

11.4.4.2. Other Safety

Vital Signs

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

Laboratory Tests

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

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

Shift tables based on baseline of the parent study 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.

Electrocardiograms

Electrocardiogram results will be summarized by parameter at each time point using descriptive statistics.

11.4.4.3. Treatment Exposure

The observation period (defined as the time between the date of first study drug administration and the date of the end of treatment visit [ie, week 104] or the date of early discontinuation for the patient) will be presented.

11.4.4.4. Treatment Compliance

Analysis of treatment compliance will be described in the SAP.

11.4.5. Pharmacokinetics

11.4.5.1. Analysis of Drug Concentration Data

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

A 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 (%), minimum, Q1, median, Q3, and maximum.

No formal statistical analysis will be performed.

11.4.6. Analysis of Immunogenicity Data

Anti-drug antibodies will be characterized by the type and titer level of the observed response.

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

- Pre-existing immunoreactivity
- Treatment-emergent response
- Treatment-boosted response
- Neutralizing antibody 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 pre-existing, treatment-boosted and treatment-emergent ADA responses, ADA titers, and NAb status presented by patient, time point, and dose cohort/group (if applicable) will be provided. Incidence of treatment-emergent ADA response and NAb status 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 ADA and NAb on individual PK profiles may be evaluated. Assessment of impact of ADA and NAb on safety and efficacy may be provided.

11.4.7. Analysis of Exploratory Pharmacodynamic and Biomarker Data

Analysis of biomarker data is defined in the SAP.

11.5. 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 in the OLE study (including last available measurement from the parent study if measurement is missing in OLE study). 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.

11.6. 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 15.1.

12. QUALITY CONTROL AND 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 described in this section.

12.1. Data Management and Electronic Systems

12.1.1. 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 the sponsor's facilities.

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) system.

12.1.2. Electronic Systems

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

- IVRS/IWRS system – randomization, study drug supply
- EDC system – data capture
- Statistical Analysis System (SAS) – statistical review and analysis
- Pharmacovigilance safety database

12.2. Study Monitoring

12.2.1. 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). 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.

12.2.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents). The site is responsible to ensure quality within their records and systems and are accountable for ensuring that all source data and CRF data are timely, accurate and complete.

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.

12.2.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic CRFs 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.

12.3. 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.

12.4. Study Documentation

12.4.1. Certification of Accuracy of Data

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

12.4.2. 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.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. 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.

13.2. 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 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 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, or if there are significant changes to the study procedures, 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.

13.3. 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.

13.4. 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.

13.5. Clinical Study Data Transparency

Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations. Treatment codes will be disseminated to each investigational site thereafter.

14. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design of the protocol or ICF without an IRB/EC-approved amendment. Where required per local legislation, regulatory authority approval will also be sought.

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

15.1. 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.

15.2. 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.

16. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

17. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

18. PUBLICATION POLICY

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

19. REFERENCES

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20. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: "An Open-label Extension Study to Evaluate the Long-term Safety, Tolerability, and Efficacy of REGN3918 in Patients with Paroxysmal Nocturnal Hemoglobinuria" 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 Extension Study to Evaluate the Long-term Safety, Tolerability, and Efficacy of REGN3918 in Patients with Paroxysmal Nocturnal Hemoglobinuria

Protocol Number: Protocol R3918-PNH-1868

Protocol Version: Protocol R3918-PNH-1868 Original

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

Signature Page for VV-RIM-00072054 v1.0

ESig Approval	[redacted]-2019 12:55:56 GMT+0000
ESig Approval	[redacted]19 13:06:12 GMT+0000
ESig Approval	[redacted]-2019 13:13:21 GMT+0000
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