Clinical Study Protocol

A Randomized, Open-Label, Two-Arm Study to Evaluate the Safety, Efficacy, and Pharmacodynamic Effects of Pozelimab and Cemdisiran Combination Treatment in Patients with Paroxysmal Nocturnal Hemoglobinuria Who Have Received Pozelimab Monotherapy

Compounds:	Pozelimab (REGN3918) Cemdisiran (ALN-CC5)
Clinical Phase:	2
Protocol Number:	R3918-PNH-2092
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[redacted]

AMENDMENT HISTORY

Overall Rationale for Amendment 1

The main purpose of this amendment is to modify the timing of the interim analysis and to align endpoints with other studies in the clinical development program.

Description of Change	Brief Rationale	Section # and Name
Modified the description of the interim analysis to allow for an analysis of the data at an earlier timepoint (week 16)	The interim analysis timing and scope is revised to allow for an earlier analysis and for the preliminary results to be shared externally (for example, upon request by regulatory authorities).	Clinical Study Protocol Synopsis: Statistical Plan Section 6.4 Planned Interim Analysis Section 11.5 Timing of Statistical Analysis
Revised and clarified the following secondary endpoints: • Maintenance of adequate control of hemolysis, defined as lactate dehydrogenase (LDH) ≤1.5 x upper limit of normal (ULN) from post-baseline (on day 1) through week 28 and from week 4 through week 28, inclusive • Normalization of LDH at each visit, defined as LDH ≤1.0 x ULN from post-baseline (on day 1) through week 28, inclusive Corresponding changes were made to secondary endpoints for the optional open-label extension period (OLEP)	The wording of the endpoint has been revised to be a patient-level metric. In addition, changes are made to clarify how these analyses will be performed and for alignment across the paroxysmal nocturnal hemoglobinuria (PNH) program: • A patient's LDH is followed longitudinally to assess the maintenance of adequate control of hemolysis over the pre-specified time period. • Normalization of LDH is analyzed by visit throughout the study.	Clinical Study Protocol Synopsis: Endpoints Section 4.1.2 Secondary Endpoints Section 4.1.2.1 Secondary Endpoints for the Optional Open-Label Extension Period Section 11.4.3.1 Secondary Efficacy Analysis
Definition of treatment exposure was revised to reflect the duration of time on study drug	This change aligns the definition of treatment exposure across the PNH program.	Section 11.4.5.3 Treatment Exposure
Added new secondary endpoint on the proportion of patients with adequate control of hemolysis at each visit	This new endpoint assesses control of hemolysis using an additional methodology and is added to align with other studies in the program.	Clinical Study Protocol Synopsis: Endpoints Section 4.1.2 Secondary Endpoints Section 4.1.2.1 Secondary Endpoints for the Optional Open-Label Extension Period Section 11.4.3.1 Secondary Efficacy Analysis
Revised "proportion of patient" endpoints to be patient-centric	This change is part of a company-wide alignment on the wording of endpoints to be patient-level metrics.	Clinical Study Protocol Synopsis: Endpoints Section 4.1.2 Secondary Endpoints Section 4.1.2.1 Secondary Endpoints for the Optional Open-Label Extension Period

Description of Change	Brief Rationale	Section # and Name
		Section 4.1.3 Exploratory Endpoints
Updated information about post-trial treatment access for patients who complete the optional open-label extension period	This change provides updated information on post-trial access to study drugs for those with a favorable benefit-risk profile for continued treatment.	Clinical Study Protocol Synopsis: Study Design, Study Duration Section 6.1 Study Description and Duration Figure 1: Study Flow Diagram Section 6.1.3 Optional Open-Label Extension Period Section 6.1.4 Post-Treatment Safety Follow-Up Period Section 8.9 Post-Trial Access to Study Treatment
The criterion for provision of an additional intravenous (IV) pozelimab dose in the event of an acute complement-activating condition was modified.	To allow for patients to receive an additional IV pozelimab dose in the event they have an elevated LDH ≥2 x ULN resulting from an acute complement-activating condition even if not meeting the protocol definition of breakthrough hemolysis.	Section 6.1.2 Open-Label Treatment Period (Day 1 to Week 28) Section 8.3.2 Intensified Treatment
Removal of the requirement for mandatory discontinuation of study drug in the event of treatment for a meningococcal infection	To allow investigators to use clinical discretion with regard to continuing complement inhibition during a serious meningococcal infection. Withdrawal of complement inhibition in the face of an ongoing complement activating condition may have serious clinical consequences.	Section 8.3.3.1 Reasons for Permanent Discontinuation of Study Drug
Removed fasting requirement for blood chemistry sample	This change reduces unnecessary study complexity as the results of the assays should not be impacted in a meaningful way by fasting status.	Section 9.2.5.2 Safety and Other Laboratory Assessments
Revised footnote on bilirubin and added magnesium for blood chemistry	This change is to include magnesium as part of safety laboratory analysis and to simplify the procedures for bilirubin.	Section 9.2.5.2 Safety and Other Laboratory Assessments
Included details regarding laboratory analyses to be performed for drug hypersensitivity events and suspected breakthrough hemolysis events	This change clarifies the sample collection for safety events of interest.	Section 9.2.5.2 Safety and Other Laboratory Assessments Section 9.1.1.1 Table 1 Schedule of Events (Treatment Period), Footnote #18
Revised schedule of events to have a separate collection for free hemoglobin	This change reflects how the actual sample collection is intended to be performed.	Table 3: Schedule of Events (Optional Open-Label Extension Period) Section 9.1.1.1 Table 1 Schedule of Events (Treatment Period), footnote #21

Description of Change	Brief Rationale	Section # and Name
		Section 9.1.1.2 Table 2 Schedule of Events (for Patients on Intensified Treatment), footnote #16 Section 9.1.1.3 Table 3 Schedule of Events (for Open-Label Extension Period), footnote #13
For patients requiring intensified treatment, clarified that samples for pozelimab concentration and total C5 will be collected on day 1r pre-dose and post-infusion	This change aligns with the timing of analysis of drug concentration in the phase 2 program.	Section 9.1.1.2 Table 2 Schedule of Events (for Patients on Intensified Treatment), footnote #18 Section 9.2.6.1 Concentrations of Total Pozelimab and Total C5
Criteria for urine culture updated	To allow urine culture to be performed per the Investigator judgment in the event of clinical suspicion of infection	Section 9.2.5.2 Safety and Other Laboratory Assessments
Changed baseline sample collection for PNH clones from day 1 to screening visit V1	This change is made to facilitate study conduct.	Table 1 Schedule of Events (Open-Label Treatment Period)
Added sample collection for immunoglobulin G	This analyte is added to better understand potential general changes in protein catabolism.	Table 1 Schedule of Events (Open-Label Treatment Period) Table 2 Schedule of Events for Patients on Intensified Treatment in the OLTP Section 9.2.5.2 Safety and Other Laboratory Assessments
Language added to allow for unused/leftover samples to be used for exploratory research.	Exploratory research (related to PNH, mechanism of action of pozelimab, target engagement and possible toxicities) can be conducted for up to 15 years post study completion (pending local regulations) in all patients using leftover/unused blood samples.	Section 9.2.8 Pharmacodynamic and Exploratory Biomarker Procedures
Removed 30-minute observation period after subcutaneous injection on the day of treatment intensification.	This is a correction; the intention was for patients to have 30-minute on-site observation only after intravenous pozelimab and the first cemdisiran and pozelimab subcutaneous injections.	Section 8.3.2 Intensified Treatment Section 9.1.1.2 Table 2 Schedule of Events (for Patients on Intensified Treatment), Footnote #7 Section 9.1.1.3 Table 3 Schedule of Events (for Open-Label Extension Period), Footnote #4
Clarified that a 30-minute monitoring period is needed only after the first (but not subsequent) cemdisiran administration	Because patients have been receiving pozelimab prior to this study, the 30-minute observation period is for reactions related to cemdisiran injection.	Section 8.1.3 Dose Administration Section 9.1.1.1 Table 1 Schedule of Events (Treatment Period), footnote #12

Description of Change	Brief Rationale	Section # and Name
Assessment of body weight added prior to any IV administration of pozelimab.	Weight is added in order to assist in the calculation of dose to be administered for IV pozelimab in patients who require treatment intensification or additional pozelimab administration in the event of a complement-activating condition.	Section 8.3.2 Intensified Treatment
Included rows for daily antibiotic prophylaxis and review of patient safety card in the safety follow-up period in the Schedule of Events	This is a correction. These procedures are intended to be performed throughout the study for risk mitigation.	Table 4 Schedule of Events (Post-Treatment Safety Follow-Up Period) Section 9.1.1.4 Table 4 Schedule of Events (Post-Treatment Safety Follow-Up Period) [new section], footnote #1 [new] and #2 [new]
Clarified visit windows versus dosing windows for the different regimen and study periods	This change is made to clarify the difference between visit windows and dosing windows in the study.	Table 2 Schedule of Events for Patients on Intensified Treatment in the OLTP Section 9.1.1.1 Table 1 Schedule of Events (Treatment Period), footnote #11 Section 9.1.1.2 Table 2 Schedule of Events (for Patients on Intensified Treatment), footnote #4, #5 [new] Section 9.1.1.3 Table 3 Schedule of Events (for Open-Label Extension Period), footnote #5
Added language to ask that patients refrain from strenuous exercise within 24 hours prior to a blood draw	This change is added to minimize the effect of vigorous exercise on blood analyses.	Section 8.8.1 Prohibited Medications and Procedures
Language on study drug administration in patients who require treatment intensification and the corresponding intensified treatment visit schedule clarified	Clarifying language has been added to ensure proper understanding of the timing of study visits and study drug administration for patients who require treatment intensification.	Section 6.1.2 Open-Label Treatment Period (Day 1 to Week 28) Section 6.1.3 Optional Open-Label Extension Period
Renumbered days in the post-treatment safety follow-up period (FUP) to days after last dose of study drug	This change is made for clarity, as patients may enter the FUP after discontinuation from any period during the study.	Table 4 Schedule of Events (Post-Treatment Safety Follow-Up Period)
Total number of screened patients revised to include all patients who signed the ICF	This change is made to consider a patient as screened upon signing the main ICF even if inclusion/ exclusion criteria are not met.	Section 11.4.1 Patient Disposition

Description of Change	Brief Rationale	Section # and Name
Revised description of Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue) to a 5-point Likert scale. A higher score indicates a higher quality of life	This is a correction.	Section 9.2.3.1 Functional Assessment of Chronic Illness Therapy–Fatigue)
Revised the on-treatment period definition to include up to 52 weeks after the last dose of study drug	This reflects an update to the safety observation period to align with other studies in the program.	Section 11.4.5.1 Adverse Events
Updated the name of the study director	This reflects an administrative change for the study.	Title Page
Updated confidentiality language	This is an administrative change to the protocol template.	Title Page
Clarifications and corrections	These are minor editorial changes for clarification and consistency, and also includes updated template language.	Throughout document

Overall Rationale for R3918-PNH-2092 Original (Admin) Amendment

The purpose of this administrative amendment is to correct visit numbering errors in the Schedule of Events.

Description of Change	Brief Rationale	Section # and Name
Visit numbers were corrected for week 24r (RV11) and week 28r (RV12).	The change was made to correct errors in visit numbering.	Table 2 Schedule of Events for Patients on Intensified Treatment in the OLTP

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
AH50	Alternative pathway hemolytic activity assay
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the curve
C	Complement component (eg, C3, C5)
CH50	Total complement hemolysis activity assay
CI	Confidence interval
COA	Clinical outcome assessment
COVID-19	Coronavirus Disease 2019
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CRP	C-reactive protein
CSR	Clinical study report
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer: Quality-of-Life Questionnaire core 30 items
EOT	End of treatment
ET	Early termination
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue score
FAS	Full analysis set
FBR	Future biomedical research
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GHS	Global health status
GPI	Glycophosphatidylinositol
IB	Investigator's brochure

ICF	Informed consent form
ICH	International Council for Harmonisation
INR	International normalized ratio
IRB	Institutional Review Board
ISR	Injection site reaction
IV	Intravenous
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
mAb	Monoclonal antibody
MAC	Membrane-attack complex
MAVE	Major adverse vascular events
MCMC	Markov Chain Monte Carlo method
MI	Multiple imputation
NAb	Neutralizing antibody
OLEP	Open-label extension period (an optional period)
OLTP	Open-label treatment period (main study period)
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PF	Physical function
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetic
PNH	Paroxysmal nocturnal hemoglobinuria
PT	Preferred term
Q2W	Every 2 weeks
Q4W	Every 4 weeks
Q8W	Every 8 weeks
QoL	Quality of life
QW	Weekly
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis System

SC	Subcutaneous
SD	Standard deviation
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Woman of childbearing potential
WOCF	Worst observation carried forward

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Randomized, Open-label, Two-arm Study to Evaluate the Safety, Efficacy, and Pharmacodynamic Effects of Pozelimab and Cemdisiran Combination Treatment in Patients with Paroxysmal Nocturnal Hemoglobinuria Who Have Received Pozelimab Monotherapy
Site Locations	Multiple centers in the European Union (EU) and Asia Pacific
Principal Investigator	A coordinating principal investigator will be identified and documented in the trial master file.
Objectives	The primary objective of the study is to evaluate the safety and tolerability of 2 dosing regimens of pozelimab and cemdisiran combination therapy during the open-label treatment period (OLTP) The secondary objectives of the study are: • To evaluate the effect of the combination treatment on the following parameters of intravascular hemolysis: lactate dehydrogenase (LDH) control, breakthrough hemolysis, and inhibition of total complement hemolysis activity (CH50) • To evaluate the effect of the combination treatment on hemoglobin levels • To evaluate the effect of the combination treatment on red blood cell (RBC) transfusion requirements • To evaluate the effect of the combination treatment on clinical outcome assessments (COA) measuring fatigue and health-related quality of life • To assess the concentrations of total pozelimab in serum and total complement component 5 (C5) and cemdisiran in plasma • To assess immunogenicity to pozelimab and cemdisiran • To evaluate the long-term safety and efficacy of the combination treatment with pozelimab and cemdisiran in an optional open-label extension period (OLEP) • To assess safety after treatment intensification with pozelimab and cemdisiran
Study Design	This is a randomized, open-label, 2-arm, 28-week study to evaluate the safety, efficacy, and pharmacodynamic (PD) effects of 2 dose regimens of pozelimab and cemdisiran combination treatment in patients with paroxysmal nocturnal hemoglobinuria (PNH) who had been receiving treatment with pozelimab monotherapy in a Regeneron-sponsored clinical study (R3918-PNH-1868). Eligible patients will be randomized 1:1 to 1 of 2 dose regimens with the pozelimab and cemdisiran combination. The study consists of 4 periods: a screening period (7 to 8 days), an OLTP (28 weeks, but will be longer for patients who are switched to treatment intensification), an optional OLEP (52 weeks), and a post-treatment safety follow-up period (52 weeks). The fourth period begins when a patient completes or

permanently discontinues study treatment (eg, at the time of premature study drug discontinuation, at the completion of study treatment in the OLTP for patients who decline the optional OLEP, or at the completion of study treatment in the optional OLEP for patients who do not continue treatment in a post-trial access setting). The treatment period begins from the first dose of the combination treatment until the end of the dosing interval of the last dose to account for the treatment effect of the final dose of study drug.

Screening (7 to 8 days)

The screening visit should occur at a scheduled or unscheduled visit of the R3918-PNH-1868 study (parent study). The dose of pozelimab should be administered at the study site on the day of the screening visit in this study, which shall occur on the day of a planned administration with pozelimab monotherapy. Subsequently, the day 1 visit for the first combination treatment dosing should occur 7 to 8 days after the last dose of pozelimab monotherapy in the parent study.

As part of risk mitigation for this study, patients should have documented vaccination against *Neisseria meningitidis* and receive updated meningococcal vaccination if needed. Daily oral antibiotic prophylaxis is recommended throughout the study. Patients should be counseled regarding risk of infection with *Neisseria gonorrhea*, as applicable based on their risk level.

In addition to screening procedures to determine eligibility, patients will be asked to complete a PNH Symptom-Specific Questionnaire daily for 7 consecutive days prior to the day 1 visit.

Patients may choose to participate in the optional OLEP, optional future biomedical research, and/or optional pharmacogenomics component of the study by signing the respective optional informed consent forms.

Treatment Period (Day 1 to Week 28)

Day 1 should be scheduled 7 to 8 days after the last dose of pozelimab monotherapy in the parent study. On day 1, after confirming eligibility, patients will be randomized in a 1:1 ratio to 1 of the 2 arms:

Arm 1: Pozelimab 400 mg SC every 4 weeks (Q4W) and cemdisiran 200 mg SC Q4W

Arm 2: Pozelimab 400 mg SC every 2 weeks (Q2W) and cemdisiran 200 mg SC Q4W

After all baseline samples are collected and all baseline assessments are performed, patients will receive the first doses of the assigned combination treatment.

Breakthrough hemolysis is assessed by the investigator throughout the study and is defined based on a pre-specified increase in LDH level along with clinical signs and symptoms of hemolysis. During the study, a patient exhibiting signs of breakthrough hemolysis plus inadequate LDH response may qualify for 28 weeks of intensified treatment. Pre-defined criteria for breakthrough hemolysis and intensified treatment is described in the protocol.

Transfusions with RBCs during the study should proceed according to the pre-defined algorithm for transfusions described in the protocol.

	Patients should be closely monitored for early signs and symptoms of meningococcal infection. Daily oral antibiotic prophylaxis is recommended. The last doses of study treatment are administered at week 24 for arm 1 and week 26 for arm 2. Patients will return for safety, efficacy, and other assessments at week 28. **Optional Open-Label Extension Period** All patients who complete the OLTP (including patients who receive intensified treatment) will be offered the opportunity to continue in an optional 52-week OLEP, whereby the transition of the combination treatment from the OLTP to the OLEP is planned to be uninterrupted (ie, day 1e visit of the OLE will correspond to the end of treatment (EOT) visit of the OLTP). Patients whose treatment was not intensified during the main study period will transition to the OLEP on a regimen of pozelimab 400 mg SC Q4W and cemdisiran 200 mg SC Q4W, regardless of their treatment assignment in the main treatment period. Patients whose treatment was intensified during the main study period will transition to the OLEP and continue on the intensified treatment regimen of pozelimab 400 mg SC Q2W and cemdisiran 200 mg SC Q4W. The OLEP will end 52 weeks after the first dose of study treatment in the OLEP, even if the patient required intensified treatment during the OLEP. For patients who complete the optional OLEP, post-trial access to treatment may be available. **Post-Treatment Safety Follow-Up** All patients who permanently stop study treatment will be asked to complete a 52-week safety follow-up period after the last dose of the study treatment. The safety follow-up period will begin when a patient completes or permanently discontinues study treatment (eg, at the time of premature study drug discontinuation, at the completion of study treatment in the OLTP for patients who decline the optional OLEP, or at the completion of study treatment in the optional OLEP for patients who do not continue treatment in a post-trial access setting).
Study Duration	The screening period is approximately 7 to 8 days. The duration of the OLTP treatment period for a patient is a minimum of approximately 28 weeks (the duration will be longer for patients who require treatment intensification, which consists of a 28-week treatment regimen starting from the day of intensification). Patients who do not continue into the optional OLEP will be followed for an additional 52 weeks after the last dose of combination treatment. Patients opting to participate in the OLEP will continue open-label treatment for a 52-week period, to be followed by a 52-week safety follow-up period after the last dose of study treatment. Patients who complete the optional OLEP may be able to continue study treatment in a post-trial access program. Patients participating in the post-trial access program will therefore not be followed in the safety follow-up period.
End of Study Definition	The end of the main study is defined as the date of the last visit of the last patient in the OLTP, including patients who discontinued treatment during

	the OLTP and are being followed in the post-treatment safety follow-up period. The end of the optional OLEP is defined as the date of the last visit of the last patient in the optional OLEP, including patients who discontinued treatment during the OLEP and are being followed in the post-treatment safety follow-up period.
Population	
Sample Size:	This study will be open to all patients who have enrolled in the Regeneron sponsored clinical study (R3918-PNH-1868) and plans to enroll approximately 24 patients with PNH.
Target Population:	This study will only enroll patients with PNH who are receiving pozelimab monotherapy in a Regeneron-sponsored clinical study (R3918-PNH-1868) and are willing to switch to the combination treatment.
Treatment	All patients will receive treatment with the pozelimab + cemdisiran combination.
Study Drug	Pozelimab
Dose/Route/Schedule:	400 mg SC Q2W or 400 mg SC Q4W 30 mg/kg IV bolus as needed may be considered for patients who experience breakthrough hemolysis (see protocol for details)
Study Drug	Cemdisiran
Dose/Route/Schedule:	200 mg SC Q4W
Intensified Treatment: (for patients who meet pre-specified criteria on LDH and breakthrough hemolysis)	Single administration of pozelimab 30 mg/kg IV loading dose on day 1 of intensification (day 1r) in addition to pozelimab 400 mg SC Q2W and cemdisiran 200 mg SC Q4W
Endpoints	
Primary:	The primary endpoint is the incidence and severity of treatment-emergent adverse events (TEAEs) through week 28 of the OLTP
Secondary:	The secondary endpoints for the OLTP are: • Percent change of LDH from pre-treatment (defined as mean of LDH values at day -7 and day 1 [prior to combination dosing]) to end-of-treatment period (defined as mean of LDH values at week 24 through week 28) • Maintenance of adequate control of hemolysis, defined as LDH ≤1.5 × upper limit of normal (ULN) from post-baseline (on day 1) through week 28 and from week 4 through week 28, inclusive

	• Adequate control of hemolysis (defined as LDH ≤1.5 × ULN) at each visit from post-baseline (on day 1) through week 28, inclusive • Normalization of LDH at each visit, defined as LDH ≤1.0 × ULN from post-baseline (on day 1) through week 28, inclusive • Area under the curve (AUC) of LDH over time from baseline through week 28 and from week 4 through week 28, inclusive • Breakthrough hemolysis (as defined in the protocol) from baseline to week 28 • Hemoglobin stabilization (defined as patients who do not receive RBC transfusion and have no decrease in hemoglobin levels of ≥2 g/dL) from baseline through week 28 • Change in hemoglobin levels from baseline to week 28 • Transfusion avoidance (defined as not requiring a RBC transfusion as per protocol algorithm) from baseline to week 28 • Rate and number of units of RBCs transfused from baseline to week 28 • Change in CH50 from baseline to week 28 • Change in fatigue as measured by Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale from baseline to week 28 • Change from baseline to week 28 in global health status/QOL scale (GHS) and physical function (PF) scores on the European Organization for Research and Treatment of Cancer: Quality-of-Life Questionnaire core 30 items (EORTC QLQ-C30) • Concentrations of total pozelimab in serum and cemdisiran in plasma, assessed throughout the study • Change from baseline in concentration of total C5 assessed throughout the study • Assessment of immunogenicity to pozelimab and cemdisiran as determined by the incidence, titer, and clinical impact of treatment-emergent anti-drug antibody responses over time • Incidence and severity of TEAEs for patients who received treatment intensification through week 28r
Procedures and Assessments	Safety procedures include measurement of body weight and routine safety assessments (vital signs, physical examination, electrocardiogram). Laboratory assessments of safety include coagulation panel, chemistry, hematology, urinalysis, and pregnancy (if applicable). Treatment-emergent adverse events and concomitant medications will be monitored throughout the study. Efficacy procedures include laboratory assessments of efficacy (LDH, hemoglobin, and CH50), transfusion record update, and clinical outcome assessments (FACIT-Fatigue, EORTC QLQ-C30, Treatment Satisfaction Questionnaire for Medication [TSQM], Patient Global Impression of

	Severity [PGIS], Patient Global Impression of Change [PGIC], daily PNH symptom-specific questionnaire). Other procedures include the collection of blood samples for biomarkers, drug concentrations, immunogenicity, and exploratory assessments.
Statistical Plan	No statistical hypothesis will be tested. **Justification of Sample Size** This study will be open to all patients who have enrolled in the Regeneron-sponsored clinical study (R3918-PNH-1868) and plans to enroll approximately 24 patients with PNH. Data from approximately 24 patients with PNH will be used to describe and explore the incidence and severity of TEAEs through week 28 of the OLTP. **Primary Analysis** The primary endpoint is the incidence and severity of TEAEs through week 28 of the OLTP. Descriptive summaries will be provided by treatment group. **Secondary Analysis** Secondary endpoints on efficacy will be analyzed using analysis of covariance (ANCOVA). Missing data will be imputed prior to analysis using multiple imputation. Means and 95% confidence intervals for the endpoint will be reported for all patients as well as for the 2 treatment arms and their difference. **Timing of Statistical Analysis** The primary analysis will be conducted as soon as all patients have been randomized and all data through week 28 have been collected and validated; this will consist of the primary safety and secondary efficacy endpoints. The OLEP analysis will be conducted when all data through week 52e of the OLEP have been collected and validated. Additional safety data from the post-treatment safety follow-up period will be included in a subsequent analysis. An interim analysis may be conducted after 6 patients have completed at least 16 weeks of the OLTP. Additional/other interim analyses may be performed to support regulatory interactions.

1. INTRODUCTION

1.1. 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), as well as on white blood cells (WBCs) and platelets, resulting in an increased risk of thrombosis. The estimated incidence of PNH is 1.3 cases per million individuals per year, and the estimated prevalence is 15.9 cases per million individuals per year (Preis, 2014).

Paroxysmal nocturnal hemoglobinuria originates from a multipotent, hematopoietic stem cell (HSC) that acquires a mutation of the phosphatidylinositol glycan anchor biosynthesis class A (PIGA) gene. The PIGA gene product is required for the biosynthesis of the glycophosphatidylinositol (GPI) anchor, a glycolipid moiety that attaches dozens of proteins to the plasma membrane of cells. Consequently, the PNH stem cell and all of its progeny have a reduction or absence of GPI-anchored proteins. The mature blood cells derived from the hematopoietic clone can have a complete deficiency (type III) or a partial deficiency (type II) of GPI-linked proteins (Hillmen, 2004). Two of the proteins that are affected by the absence of GPI anchors are complement regulatory proteins CD55 and CD59. The CD55 protein 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 increased PNH granulocyte clone size 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, active disease can be established by a history of RBC transfusion due to PNH within 3 months.

Eculizumab (Soliris®) and ravulizumab (Ultomiris®), approved for the treatment of PNH in many countries worldwide, including the United States (US) and European Union (EU) member states, are humanized monoclonal antibodies (mAbs) directed against the terminal complement protein C5. They block the formation of the MAC C5b-C9, thus protecting PNH RBCs from

complement-mediated intravascular hemolysis. Their effectiveness has been demonstrated by the reduction of lactate dehydrogenase (LDH) level and a reduced need for RBC transfusions. Eculizumab has demonstrated effectiveness over the long term by a reduced need for blood transfusion, reduced incidence of thrombosis, and an improvement in anemia, quality of life, and survival (Griffin, 2017). Eculizumab is approved for use in complement-mediated serious ultra-rare conditions (prevalence of 1 to 5 per million), including PNH, atypical hemolytic uremic syndrome (aHUS), neuromyelitis optica spectrum disorder (NMOSD), and generalized myasthenia gravis (gMG). Ravulizumab is approved in PNH and aHUS.

While eculizumab has demonstrated to be an effective therapy for these patients, not all patients receive optimal therapeutic benefit. For example, approximately 25% of patients still need recurrent, albeit less frequent, blood transfusions and half of patients achieve LDH normalization (Lee, 2019). Up to 27% of eculizumab-treated patients may experience breakthrough hemolysis, which is a recurrence of the patient's intravascular hemolysis and associated signs and symptoms. Many patients experience breakthrough hemolysis due to inadequate C5 inhibition (Brodsky, 2017). 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 (Hill, 2013)(Nakayama, 2016)(Peffault de Latour, 2015). Additionally, eculizumab is administered by intravenous (IV) infusion every 2 weeks (Q2W) and has been described as being burdensome for patients and may negatively impact quality of life (Groth, 2017). While the regulatory approval of ravulizumab has improved convenience with a dosing frequency of every 8 weeks (Q8W), it is not available in most of the world and patients still experience some hemolytic breakthrough. Moreover, 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 the 2 mAbs (Nishimura, 2014) (Sheridan, 2018). 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, there remains an unmet medical need for patients with PNH.

Regeneron has developed a combination mAb therapy, pozelimab-cemdisiran, that provides efficacy in patients with polymorphic variant C5 protein which renders eculizumab or ravulizumab ineffective, and offers the significant convenience and reduced burden of subcutaneous (SC) self-administration.

1.2. Pozelimab

Pozelimab is a human monoclonal immunoglobulin $G4^P$ ($IgG4^P$) antibody directed against C5, which inhibits terminal complement activation by preventing C5 cleavage by C5 convertase into C5a (anaphylatoxin) and C5b, thereby blocking the formation of MAC C5b-C9, a structure mediating cell lysis. Pozelimab is being developed for the treatment of PNH and other diseases in which tissue damage is mediated by terminal complement pathway activity. Pozelimab can be administered by IV or SC administration. Additionally, pozelimab binds to polymorphic variations in C5 that are not recognized by eculizumab or ravulizumab.

Pozelimab has been evaluated in a phase 1 randomized, placebo-controlled, double-blind study (R3918-HV-1659) in 56 healthy subjects in 7 dose cohorts (N=8, randomized 6:2 pozelimab:placebo for each cohort). Pozelimab was found to be generally well tolerated in ascending single-doses of 1, 3, 10, 30 mg/kg IV, and 300 mg and 600 mg SC. The seventh cohort,

a repeat-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 microbial etiology. Dose-dependent inhibition of C5 was demonstrated for the single-dose cohorts using the total complement hemolysis activity assay (CH50), an ex-vivo measure of complement lytic activity. The repeat-dose cohort demonstrated complete complement inhibition throughout the dosing period. A threshold serum concentration of approximately 100 µg/mL of pozelimab was determined sufficient to achieve complete inhibition of CH50. To account for population-based variability in C5 levels and for transient increases in complement activity secondary to intercurrent illness, a desired minimum serum concentration of pozelimab greater than the threshold was used to establish a dosing regimen for pozelimab in patients with PNH: 30 mg/kg IV loading dose followed by 800 mg SC QW.

Pozelimab is currently being evaluated in an ongoing phase 2 study in PNH patients with active signs and symptoms who are naïve to complement inhibitor therapy or have not recently received complement inhibitor therapy in the past 6 months (R3918-PNH-1852). In this open-label, single-arm treatment study, patients received pozelimab as an IV loading dose of 30 mg/kg followed by 800 mg SC QW for a period of 26 weeks. An interim analysis was performed with a total of 17 patients enrolled, among whom 10 patients completed 26 weeks (182 days) of treatment/study and 7 patients received at least 10 weeks (70 days) of pozelimab treatment. The mean baseline LDH is 6.1 × upper limit of normal (ULN), hemoglobin is 97.0 g/L and nearly 60% of patients had an RBC transfusion during the previous year. Treatment with pozelimab led to a rapid and sustained reduction in LDH through study week 26. Normalization of LDH levels was observed at day 29 in all 17 patients, including a patient with a C5 variant known to be resistant to blockade by eculizumab/ravulizumab. Reduction in LDH was sustained below 1.5 × ULN until day 183. Hemoglobin levels were also increased with mean (standard deviation [SD]) increase of 8.6 (14.1 g/L) from baseline to week 26 (N=9, data from 9 patients were available and used for the calculation). Following the pozelimab treatment, an improvement in the Functional Assessment of Chronic Illness Therapy-Fatigue score (FACIT-Fatigue, a 13-item, self-administered, clinical outcome assessment [COA] measure assessing an individual's level of fatigue over the past week) was observed with mean change (SD) of 13.1 (13.7) from baseline to week 26 (N=9). Complement inhibition as measured by a CH50 was 100% and sustained post pozelimab IV infusion on day 1 throughout day 183 (N=9). There was a total of 13 treatment-emergent adverse events (TEAEs) and no SAE; 2 TEAEs were assessed as severe and 6 were considered treatment-related; the most frequent TEAEs are headache and nausea.

It is noted that the regimen of 800 mg SC QW represents relatively high doses for a biologic agent. The currently approved anti-C5 mAbs, eculizumab and ravulizumab, are similarly dosed at high levels (maintenance dose of 900 mg IV Q2W and 3000 mg to 3500 mg IV Q8W for eculizumab and ravulizumab, respectively). For PNH, doses higher than 900 mg of eculizumab are sometimes used in practice. The requirement for such high anti-C5 mAb doses is driven by 2 factors. First, C5 levels are high and there is a need for 100% inhibition which can only be achieved with complete target engagement (Peffault de Latour, 2015); second, in order to achieve 100% inhibition on a population basis, inter- and intra-patient variability of C5 concentrations and instances of enhanced complement activation (which may occur with intercurrent illness) must be considered.

Additional background information on pozelimab and the development program can be found in the Investigator's Brochure for pozelimab.

1.3. Cemdisiran

Cemdisiran is a synthetic small interfering RNA (siRNA) targeting C5 messenger RNA (mRNA) that is covalently linked to a triantennary *N*-acetylgalactosamine (GalNAc) ligand. Cemdisiran is designed to suppress liver production of C5 protein, when administered via SC injection. C5 is encoded by a single gene and is expressed and secreted predominantly by hepatocytes. Through the RNA interference pathway, the cemdisiran siRNA leads to the degradation of C5 mRNA by RNases, thereby reducing C5 protein production, leading to reduced levels of circulating C5 protein.

Cemdisiran has been evaluated in a phase 1/2 study in healthy subjects and patients with PNH who are naïve to anti-C5 treatment or on a background therapy of eculizumab (ALN-CC5-001): 32 healthy subjects were treated with single SC doses of cemdisiran ranging from 50 mg to 900 mg, 24 healthy subjects were treated with multiple doses of cemdisiran ranging from 100 mg to 600 mg (dosing weekly, every other week or monthly), and 6 patients with PNH were treated with cemdisiran at 200 mg or 400 mg dosed weekly in an open-label manner with varying durations (as monotherapy in 3 eculizumab-naïve patients or in combination with eculizumab in 3 patients who were on stable eculizumab treatment before the start of the study). Dose-dependent and durable reduction in C5 protein and complement activity were observed and the maximum reduction in C5 was between 90% and 99%. However, the maximum reduction in C5 levels achieved by cemdisiran monotherapy did not completely inhibit complement activity and was not sufficient in achieving adequate LDH reduction. Importantly, although cemdisiran monotherapy was insufficient in achieving adequate reduction in LDH, patients with PNH who were treated with cemdisiran co-administered with eculizumab were able to reduce their eculizumab dose and/or increase the interval between eculizumab doses while maintaining clinically meaningful inhibition of complement activity.

Additional background information on cemdisiran and the development program can be found in the Investigator's Brochure for cemdisiran.

1.4. Pozelimab + Cemdisiran: A Combination Approach

The benefit of blocking C5 complement activity in PNH has been clearly established by eculizumab (Soliris®) and ravulizumab (Ultomiris®). The pozelimab and cemdisiran combination offer potential additional benefits over existing standard-of-care by providing better control of breakthrough hemolysis and improving the dosing regimen. It is expected that cemdisiran will reduce C5 production, thereby reducing the level of circulating free C5. With reduced levels of free C5 in circulation, combination treatment may provide adequate control of hemolysis with either lower doses of pozelimab or a longer dosing interval.

This study is designed to evaluate the safety, efficacy, and pharmacodynamic (PD) effects of the pozelimab and cemdisiran combination in patients with PNH who were previously receiving investigational pozelimab monotherapy. Pharmacokinetic (PK)/PD modeling of observed data from both pozelimab and cemdisiran first-in-human studies in healthy subjects and patients with PNH (naïve to anti-C5 treatment or on a background therapy of eculizumab) suggests that, by

combining cemdisiran and pozelimab, the desired C5 suppression may be maintained with significantly lower doses of both agents and a longer dosing interval for pozelimab, from once weekly to potentially once every 4 weeks.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to evaluate the safety and tolerability of 2 dosing regimens of pozelimab and cemdisiran combination therapy during the open-label treatment period (OLTP).

2.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the effect of the combination treatment on the following parameters of intravascular hemolysis: LDH control, breakthrough hemolysis, and inhibition of total complement hemolysis activity (CH50)
- To evaluate the effect of the combination treatment on hemoglobin levels
- To evaluate the effect of the combination treatment on RBC transfusion requirements
- To evaluate the effect of the combination treatment on COAs measuring fatigue and health related quality of life
- To assess the concentrations of total pozelimab in serum and total C5 and cemdisiran in plasma
- To assess immunogenicity to pozelimab and cemdisiran
- To evaluate the long-term safety and efficacy of pozelimab and cemdisiran in an optional open-label extension period (OLEP)
- To assess safety after treatment intensification with pozelimab and cemdisiran

2.3. Exploratory Objectives

The exploratory objectives of the study are:

- To explore the effect of the combination treatment on clinical thrombosis events
- To explore the effect of the combination treatment on renal function and renal injury biomarkers
- To explore the effect of the combination treatment on complement activation and intravascular hemolysis relevant to PNH and other related diseases
- To explore the effect of the combination treatment on PNH clone size
- To evaluate the effect of the combination treatment on treatment satisfaction
- To explore the effect of the combination treatment on a novel COA measuring PNH-specific symptoms
- To study the combination treatment mechanism of action (including relationship to safety and efficacy), complement pathway biology, PNH and related complement-mediated diseases

- To explore the effect of the combination treatment on PNH symptoms
- To explore potential differences in genotype and gene expression that may influence efficacy and safety of the combination treatment for further understanding of C5, PNH, or other conditions associated with complement-mediated injury (for patients who consent to participate in a genomics sub-study)
- To explore safety and efficacy after dose intensification with pozelimab and cemdisiran
- To explore the long-term effects of the combination treatment on clinical and PD assessments in an optional OLEP

3. HYPOTHESIS AND RATIONALE

3.1. Hypotheses

The clinical hypothesis is that pozelimab + cemdisiran combination treatment has an acceptable safety and tolerability profile in patients with PNH.

3.2. Rationale

3.2.1. Rationale for Study Design

This trial is designed as a randomized, open-label, 28-week treatment study to assess the safety, efficacy, and PD effects of 2 dose regimens of pozelimab and cemdisiran combination in patients with PNH who have been treated with pozelimab monotherapy for at least 26 weeks. The primary objective of this study is to evaluate the safety and tolerability of pozelimab and cemdisiran combination therapy in patients with PNH. Background for the clinical development for pozelimab and cemdisiran is provided in Section 1 and the respective Investigator's Brochures.

The study does not include a placebo control, as it is considered unacceptable when there is a proven intervention (ie, eculizumab or ravulizumab) and patients with PNH who are not on C5 inhibition face risks of serious or irreversible harm from sequelae of the disease.

Patients will be randomized in 1:1 ratio to receive pozelimab 400 mg SC Q4W and cemdisiran 200 mg SC Q4W (arm 1) or pozelimab 400 mg SC Q2W and cemdisiran 200 mg SC Q4W (arm 2). The former regimen is the intended treatment for use in planned phase 3 studies, and the latter regimen represents a dose intensification regimen, which may be considered in the planned phase 3 studies for patients whose hemolysis is not well controlled with the Q4W dosing regimen (Section 8.3.2). The data obtained from this study will be used to support the dose selections of treatment for the pozelimab and cemdisiran combination development program.

In addition to safety, the study includes secondary efficacy endpoints to assess the effect of the combination treatment on control of intravascular hemolysis, as measured by LDH, which is central to the clinical monitoring of PNH (Rother, 2005), including during eculizumab therapy. An LDH of at least 1.5 × ULN along with related clinical symptoms is considered an indication of active PNH, and for treatment with eculizumab (Sahin, 2016)(Soliris®, 2019). Furthermore, reductions in LDH below the 1.5 × ULN threshold with eculizumab therapy have been shown to correlate with improvement in patient's symptoms, quality of life measures, and transfusion requirements (Brodsky, 2008).

The use of LDH as a measure of intravascular hemolysis allows for an objective and precise means to gauge whether the control of intravascular hemolysis with pozelimab monotherapy is sustained when the patients are switched to pozelimab and cemdisiran combination treatment. The assessment of intravascular hemolysis is central to the clinical monitoring of PNH, as demonstrated in eculizumab and ravulizumab studies and accepted by US Food and Drug Administration (FDA) and European Medicines Agency (EMA) (Rother, 2005). Pivotal eculizumab studies, pivotal ravulizumab studies using eculizumab as a comparator, and the PNH registry have shown that the active PNH population has LDH elevated in the range of 6 to 8 × ULN (Röth, 2018). Upon treatment with an anti-C5 antibody, LDH levels fell rapidly and markedly in the patients with active PNH. An LDH of 1.5 × ULN is a clinically meaningful threshold for

disease activity: an LDH >1.5 × ULN, along with related clinical symptoms, is considered a marker for treatment with eculizumab (Sahin, 2016).

The study has a treatment duration of 28 weeks in the OLTP, which is considered sufficient to provide an adequate understanding of the safety, efficacy, and PD effects of the combination treatment for continued development. Based on modeling and simulation using available PK/PD data from pozelimab or cemdisiran treatment in healthy subjects and patients with PNH, it is expected that, by week 28, pozelimab 400 mg SC Q4W and cemdisiran 200 mg SC Q4W should have reached steady state and the effect on LDH will be the sole contribution of the assigned treatment combination regimen without impact from pozelimab 800 mg SC QW.

The long-term safety and efficacy of the combination treatment will be assessed by providing the patients who complete the main OLTP on combination treatment an opportunity to participate in an optional long-term OLEP, in which patients shall continue to receive study treatment for an additional 52 weeks. Patients who opt not to participate in the OLEP (or those who stop treatment for any reason) will be followed for 52 weeks after the last dose of study treatment, to monitor for safety as the study drugs are gradually eliminated from the body. Patients who complete the OLEP and stop study treatment will also be followed for 52 weeks after their last dose of study treatment. Additional considerations on post-study treatment access are described in Section 8.9.

3.2.2. Rationale for Dose Selection

Two combination dose regimens will be evaluated in this study:

- Pozelimab 400 mg SC Q4W and cemdisiran 200 mg SC Q4W
- Pozelimab 400 mg SC Q2W and cemdisiran 200 mg SC Q4W

Pozelimab: In the completed phase 1 study in healthy subjects (R3918-HV-1659), pozelimab was found to be generally well-tolerated at single doses up to 30 mg/kg IV and 600 mg SC, or 4 doses of 400 mg SC QW preceded by a 15 mg/kg IV loading dose. Maximum C5 inhibition with complete suppression of complement activity, as measured by a CH50 assay, was observed at higher doses (≥3 mg/kg IV dosing). The PK of total pozelimab appears non-linear at lower concentrations, becoming linear as concentrations increase. This is thought to be due to a concentration-dependent and saturable, target-mediated elimination. In the ongoing phase 2 study in patients with PNH who are naïve to anti-C5 treatment (R3918-PNH-1852), no safety signal has emerged after receiving a loading dose of 30 mg/kg IV of pozelimab (day 1) followed by 800 mg SC QW (starting on day 8). Interim analysis showed efficacy, with normalization of LDH levels observed at day 29 in all 17 patients and LDH reduction sustained below 1.5 × ULN until day 183. More information regarding the results of the phase 1 and phase 2 studies is provided in the Investigator's Brochure for pozelimab.

Cemdisiran: Cemdisiran has been evaluated in a phase 1/2 study in healthy subjects and patients with PNH who are naïve to anti-C5 treatment or on a background therapy of eculizumab (ALN-CC5-001). Cemdisiran had an acceptable safety profile in healthy subjects following a single injection at doses up to 900 mg SC or following repeated injections at doses up to 400 mg QW or 600 mg Q2W. In the 6 patients with PNH included in the study, the safety of cemdisiran was acceptable at 200 mg QW and 400 mg QW, either administered as a single agent or on a background of eculizumab at standard doses. A single dose of 600 mg cemdisiran achieved a C5

concentration of 12.3±1.47 µg/mL by day 14 and 2.3±0.76 µg/mL by day 56. Inhibition of C5 was dose-dependent and durable, with >90% knockdown of C5 beginning on day 21 and persisting through day 238. However, the relationship between C5 concentrations and complement activity is asymptotic, such that, even with 90% to 99% reduction in C5 levels, there is still incomplete inhibition of complement activity. A maximum of 99% C5 suppression was achieved following 200 mg weekly cemdisiran monotherapy, and little to no more suppression was achieved with higher dose levels (up to 600 mg bi-weekly); therefore, cemdisiran monotherapy was not sufficient in achieving adequate LDH reduction. More information regarding the results of the phase 1/2 study is provided in the Investigator's Brochure for cemdisiran.

Combination: The goal of combining pozelimab and cemdisiran is to rapidly and continuously suppress concentrations of C5 to pharmacologically inactive levels. To inform the choice of the dosing regimen for the combination therapy in patients with PNH, a target-mediated drug disposition (TMDD) population PK model for pozelimab and a population PK/PD model for cemdisiran were developed based on respective data on healthy subjects. The models for pozelimab and cemdisiran were combined by introducing C5 production suppression effect of cemdisiran to the synthesis rate of C5 in the TMDD model for pozelimab. The unified model was used to perform simulations to inform dose selection of pozelimab in combination with cemdisiran.

Based on simulations, it is expected that pozelimab 400 mg SC Q4W and cemdisiran 200 mg SC Q4W (ie, the intended combination regimen in the planned phase 3 studies) is sufficient to maintain the suppression of C5 to biologically inactive levels. In addition, at steady-state, the simulated total and free pozelimab concentration-time profiles are superimposable. This is consistent with the extremely low concentration of free C5 predicted by the unified population PK/PD model.

Intensified Treatment: The intensified regimen of pozelimab 30 mg/kg IV loading dose + pozelimab 400 mg SC Q2W and cemdisiran 200 mg SC Q4W in this study is included to provide extra C5 suppression that some patients may need to achieve adequate control of intravascular hemolysis and is intended to be used for patients whose hemolysis is not adequately controlled with the Q4W dosing regimen in the planned phase 3 studies. Both regimens will be evaluated in this study to support dose regimen selection in the planned phase 3 studies for the pozelimab and cemdisiran combination development program.

3.3. Risk-Benefit

A risk-benefit statement with respect to the overall development program is provided in the Investigator's Brochure for pozelimab and the Investigator's Brochure for cemdisiran. The combination treatment of pozelimab and cemdisiran is being developed in patients with PNH for the reasons outlined in Section 1.4. The following sections describe potential risks and strategies for mitigation.

3.3.1. Potential Risk of Neisseria Infection

An established risk of blocking C5 complement activity is increased susceptibility to infections, specifically to encapsulated organisms, the most potentially severe of which is infection with *Neisseria meningitidis* (Figueroa, 1991). The risk for meningococcal infection is largely driven by the degree of inhibition of C5. Two different agents acting on C5 through independent pathways are not expected to increase the risk for meningococcal infection above that of each of the

individual agents. This expectation is based on the goal of complement inhibition therapy and human genetic data. The objective of pozelimab and cemdisiran combination therapy is complete inhibition of C5 activity. Once this is achieved, then further inhibition is not possible and the anticipated risk is not expected to increase further. Human genetic data reveals that the increased risk of infections with *Neisseria* species (spp) occurs when there is homozygous loss of complement factor 5 (C5). Importantly, individuals who are C5 heterozygous loss of function do not have increased risk of infection with *Neisseria* spp (Platonov, 1997).

Experience with eculizumab suggests that pretreatment with appropriate vaccinations covering multiple serotypes and concurrent therapy with oral antibiotics is effective at substantially mitigating this risk (Hillmen, 2013)(McNamara, 2017)(NHS England, 2013)(Soliris®, 2019). Current treatment guidelines for PNH and the eculizumab package insert recommend such vaccinations prior to dosing. 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. 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).

In this study, vaccination prior to study treatment initiation (or at the time of administration, based on local practice, see Section 8.2.1) will be required to mitigate the risk of infection by encapsulated organisms to a level that has been considered acceptable in other anti-C5 clinical development programs. In addition to vaccination, monitoring for early signs and symptoms of infection (Section 8.2.2), providing a patient safety card that describes the signs and symptoms of infection and steps to follow in case of suspected infection, as well as concurrent therapy with recommended oral antibiotics (Section 8.2.3) will further mitigate this risk. These risk mitigation strategies have been acceptable and well tolerated in the precedent healthy volunteer and PNH patient studies for pozelimab and cemdisiran individually as well as in other anti-C5 clinical development programs.

Recently, serious infections with *Neisseria* species (other than *N. meningitidis*), including disseminated gonococcal infections, have been reported during eculizumab treatment (Soliris®, 2019). Therefore, patients will undergo a risk assessment and counseling regarding the potential risk of *Neisseria gonorrhea* as per the investigator's local guidelines. Patients will be counseled about *N. gonorrhea* prevention and regular testing will be advised for at-risk patients. A risk-factor assessment will be based on local practice or national guidelines to determine if the patient is at risk, which would lead to further management of prevention, testing, and treatment of *N. gonorrhea* (Section 8.2.4).

3.3.2. Liver Function Test Abnormalities

Liver function test abnormalities are noted as a potential risk due to the targeted delivery of cemdisiran to hepatocytes and were carefully followed in the cemdisiran program. No signal has emerged from the phase 1 and 2 clinical studies to date. In the healthy volunteer study with cemdisiran, about 30% to 40% of healthy subjects had asymptomatic, transient, mild elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) that were less than 3 × ULN in the cemdisiran dosing arms. In patients with PNH (n=6), one patient had a related

adverse event (AE) of increased transaminases with ALT and AST greater than 3 × ULN. The patient had several underlying contributing factors and the AE resolved within 120 days of onset in the setting of ongoing cemdisiran pharmacology. The patient was rechallenged in a compassionate use setting and no increase ALT or AST ≥3 × ULN has been reported. Additional details may be found in the Investigator's Brochure for cemdisiran.

In this study, patients will be closely monitored for ALT and AST abnormalities. Those with significant ALT or AST abnormalities, or known liver function impairment, will be excluded from participating in the study (Section 7.2.2). Levels of ALT and AST will be closely followed throughout the trial. Individual patient stopping rules will include a mandatory discontinuation of study treatment if specific thresholds for ALT or AST are met as per protocol (Section 8.3.3). These mitigation steps are considered sufficient to address this potential risk.

3.3.3. Study Conduct in Response to Coronavirus Disease 2019

Recognizing that the "Coronavirus Disease 2019" (COVID-19, caused by severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) pandemic will have an impact on the conduct of clinical trials, the Sponsor does not intend to screen any patients in this study until the impact of the COVID-19 pandemic is deemed manageable and no longer interfering with the conduct of trials at individual sites, and patients can safely participate in this study. Until then, the Sponsor plans to obtain approvals from Health Authorities/Ethics Committees to enable initiation of study sites for this study, as allowed by local laws and regulations.

4. ENDPOINTS

4.1. Primary and Secondary Endpoints

4.1.1. Primary Endpoint

The primary endpoint is the incidence and severity of TEAEs through week 28 of the OLTP.

4.1.2. Secondary Endpoints

The secondary endpoints for the OLTP are:

- Percent change of LDH from pre-treatment (defined as mean of LDH values at day -7 and day 1 [prior to combination dosing]) to end-of-treatment period (defined as mean of LDH values at week 24 through week 28)
- Maintenance of adequate control of hemolysis, defined as LDH ≤1.5 × ULN from post-baseline (on day 1) through week 28 and from week 4 through week 28, inclusive
- Adequate control of hemolysis (defined as LDH ≤1.5 × ULN) at each visit from post-baseline (on day 1) through week 28, inclusive
- Normalization of LDH at each visit, defined as LDH ≤1.0 × ULN from post-baseline (on day 1) through week 28, inclusive
- Area under the curve (AUC) of LDH over time from baseline though week 28 and from week 4 through week 28, inclusive
- Breakthrough hemolysis (as defined in Section 6.2) from baseline through week 28
- Hemoglobin stabilization (defined as patients who do not receive RBC transfusion and have no decrease in hemoglobin levels of ≥2 g/dL) from baseline through week 28
- Change in hemoglobin levels from baseline to week 28
- Transfusion avoidance (defined as not requiring a RBC transfusion as per protocol algorithm) from baseline to week 28
- Rate and number of units of RBCs transfused from baseline to week 28
- Change in CH50 from baseline to week 28
- Change in fatigue as measured by Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale from baseline to week 28
- Change from baseline to week 28 in global health status/quality of life scale (GHS/QoL) and physical function (PF) scores on the European Organization for Research and Treatment of Cancer: Quality-of-Life Questionnaire core 30 items (EORTC QLQ-C30)
- Concentrations of total pozelimab in serum and cemdisiran in plasma, assessed throughout the study
- Change from baseline in concentration of total C5 assessed throughout the study

- Assessment of immunogenicity to pozelimab and cemdisiran as determined by the incidence, titer, and clinical impact of treatment-emergent anti-drug antibody (ADA) responses over time
- Incidence and severity of TEAEs for patients who received treatment intensification through week 28r

4.1.2.1. Secondary Endpoints for the Optional Open-Label Extension Period

The secondary endpoints for the optional OLEP are:

- Change and percent change of LDH from day 1e to week 24e and week 52e of the OLEP
- Maintenance of adequate control of hemolysis, defined as LDH ≤1.5 × ULN from day 1e of the OLEP through week 24e and week 52e
- Adequate control of hemolysis (defined as LDH ≤1.5 × ULN) at each visit from day 1e of the OLEP through week 52e
- Normalization of LDH at each visit, defined as LDH ≤1.0 × ULN from day 1e of the OLEP through week 52e
- Area under the curve (AUC) of LDH over time between day 1e of the OLEP though week 52e
- Breakthrough hemolysis from day 1e of the OLEP through week 24e and week 52e
- Hemoglobin stabilization (defined as patients who do not receive RBC transfusion and have no decrease in hemoglobin levels of ≥2 g/dL) from day 1e to week 24e and week 52e of the OLEP
- Change in hemoglobin levels from day 1e to week 24e and week 52e of the OLEP
- Transfusion avoidance (defined as not requiring a RBC transfusion as per protocol algorithm) from day 1e to week 24e and week 52e of the OLEP
- Rate and number of units of RBCs transfused from day 1e to week 24e and week 52e of the OLEP
- Change and percent change in CH50 from day 1e to week 16e, week 24e and week 52e of the OLEP
- Change in fatigue as measured by FACIT-Fatigue scale from day 1e to week 52e of the OLEP
- Change in global health status/quality of life scale (GHS/QoL) and physical function (PF) scores on the European Organization for Research and Treatment of Cancer: Quality-of-Life Questionnaire core 30 items (EORTC QLQ-C30) from day 1e to week 52e of the OLEP
- Incidence and severity of TEAEs during the 52-week OLEP in patients treated with pozelimab and cemdisiran combination therapy

- Concentrations of total pozelimab in serum and total C5 and cemdisiran in plasma, assessed over time during the OLEP
- Assessment of immunogenicity to pozelimab and cemdisiran as determined by the incidence, titer, and clinical impact of treatment-emergent anti-drug antibody (ADA) responses over time during the OLEP

4.1.3. Exploratory Endpoints

The exploratory endpoints for the OLTP are:

- Treatment intensification throughout the study
- Incidence of MAVE (defined in Section 10.1.4) from baseline to week 28
- Change in renal function as measured by estimated glomerular filtration rate (eGFR) from baseline to week 28
- Percent change in free hemoglobin from baseline to week 28
- Change in bilirubin from baseline to week 28
- Change in reticulocyte count from baseline to week 28
- Change and percent change in the alternative pathway hemolytic activity assay (AH50) from baseline to week 28
- Proportion of PNH erythrocytes and granulocytes from baseline to week 28
- Change from baseline to week 28 in functional scale scores (Role functioning, Emotional Functioning, Cognitive Functioning and Social Functioning) and symptom scale scores (Fatigue, Nausea and vomiting, Pain, Dyspnoea, Insomnia, Appetite loss, Constipation, Diarrhoea) of the EORTC QLQ-C30
- Stability in global health status, functioning and symptoms as measured by the EORTC QLQ-C30 from baseline to week 28
- Comparison of treatment satisfaction (as assessed by the Treatment Satisfaction Questionnaire for Medication [TSQM]) at baseline vs. treatment at week 28
- Change in Patient Global Impression of Severity (PGIS) from baseline to week 28, including questions on PNH symptoms, impacts and fatigue
- Patient Global Impression of Change (PGIC) at week 28, including questions on PNH symptoms, impacts and fatigue
- Change in PNH symptoms as measured by the PNH symptom-specific questionnaire from baseline to week 28

Exploratory endpoints related to the analyses for those patients receiving dose intensification and patients participating in the OLEP will be provided in the statistical analysis plan (SAP).

5. STUDY VARIABLES

5.1. Demographic and Baseline Characteristics

In accordance with local regulations, baseline characteristics will be collected and may include standard demographic information (eg, age, race, weight, height, etc), disease characteristics, medical history, and medication history for each patient.

Note: The data will be used to describe the patient population under study and may inform whether there are differences in the safety or efficacy profile based on the defined patient characteristics. In addition, collection of data on race and ethnicity may be required by certain regulatory agencies, such as the FDA.

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:

- LDH (serum): LDH as a measure of intravascular hemolysis allows for an objective and precise means to gauge whether the control of intravascular hemolysis is sustained when the patients are switched to pozelimab and cemdisiran combination treatment.
- Hemoglobin: Hemolytic anemia is a hallmark of PNH.
- CH50: The CH50 assay will be used to confirm complete inhibition of complement activity has been achieved throughout the dosing interval in patients with PNH.

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) (Röth, 2018).

5.2.3. Clinical Outcome Assessments

Brief descriptions of COAs are provided in Section 9.2.3 and include the following:

- FACIT-Fatigue
- EORTC-QLQ-C30
- TSQM
- PNH Symptom-Specific Questionnaire
- PGIS
- PGIC

5.3. Safety and Anthropometric Variables

Safety and anthropometric variables in this study include:

- Body weight
- TEAEs, including breakthrough hemolysis events (defined in Section 6.2) and adverse events of special interest (AESIs; defined in Section 10.1.3 and Section 10.1.4)
- Vital signs
- Electrocardiogram (ECG)
- Physical examination
- Routine safety laboratory tests (hematology, chemistry, urinalysis, and pregnancy testing [for women of childbearing potential or WOCBP])
- Concomitant medications and treatments

5.4. Pharmacokinetic Variables

The PK variables are the concentrations of total pozelimab, total C5 (target), cemdisiran, cemdisiran metabolites, and time.

5.5. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, neutralizing antibody (NAb) and nominal sampling time point/visit.

5.6. Pharmacodynamic and Other Biomarker Variables

Pharmacodynamic and other biomarker variables include, but are not limited to, the following:

- CH50 (an assay assessing the activity of the classical pathway of complement) will be used to measure C5 activity. This is the principle PD marker for the study and is also an efficacy variable in this study (Section 5.2.1)
- Parameters of intravascular hemolysis: ie, haptoglobin, reticulocyte count, and bilirubin
- Free hemoglobin
- Alternative pathway hemolytic activity, as measured by AH50
- Complement activation markers: ie, sC5b-C9
- PNH clone size: ie, PNH erythrocytes and granulocytes

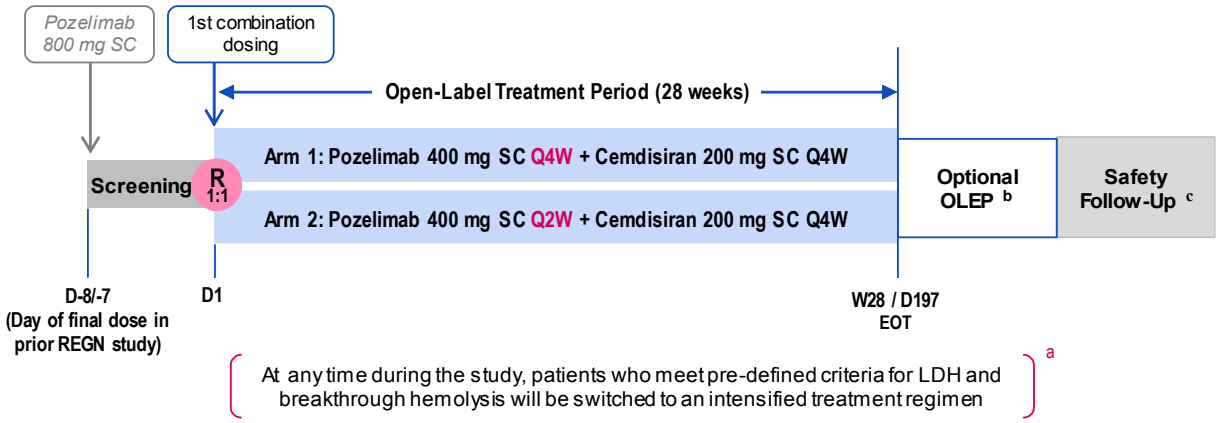
The list may be altered or expanded, as it is recognized that more relevant or novel biomarkers may be discovered during the course of this study. The biomarkers studied will be ones believed to be relevant to the understanding of efficacy, pathophysiology of indication target engagement, mechanism of action, and possible toxicities of pozelimab and cemdisiran.

6. STUDY DESIGN

6.1. Study Description and Duration

This is a randomized, open-label, 2-arm, 28-week study to evaluate the safety, efficacy, and PD effects of 2 dose regimens of pozelimab and cemdisiran combination treatment in patients with PNH who had been receiving treatment with pozelimab monotherapy in a Regeneron-sponsored clinical study (R3918-PNH-1868). A schematic of the study design is shown in Figure 1. Eligible patients will be randomized 1:1 to 1 of 2 dose regimens with the pozelimab and cemdisiran combination. The study consists of 4 main periods: a 7- to 8-day screening period, a 28-week OLTP (this main study period will be longer for patients who require intensified treatment), an optional 52-week OLEP, and a 52-week post-treatment safety follow-up period. The fourth period begins when a patient completes or permanently discontinues study treatment (eg, at the time of premature study drug discontinuation, at the completion of study treatment in the OLTP for patients who decline the optional OLEP, or at the completion of study treatment in the optional OLEP for patients who do not continue study treatment in a post-trial access program immediately following the study). The treatment period begins from the first dose of the combination treatment until the end of the dosing interval of the last dose to account for the treatment effect of the final dose of study drug.

Figure 1: Study Flow Diagram



D, day; EOT, end of treatment period; OLEP, open-label extension period; Q2W, every 2 weeks; Q4W, every 4 weeks; R, randomize; REGN, Regeneron; SC, subcutaneous; W, week

a Patients will receive a one-time intensified treatment if they meet criteria of breakthrough hemolysis and LDH response as described in Section 8.3.2.

b OLEP (52 weeks): Patients whose treatment was not intensified during the OLTP will transition to the OLEP on a regimen of pozelimab 400 mg SC Q4W and cemdisiran 200 mg SC Q4W, regardless of their treatment assignment in the OLTP. Patients whose treatment was intensified during the OLTP will transition to the OLEP and continue with the intensified treatment regimen of pozelimab 400 mg SC Q2W and cemdisiran 200 mg SC Q4W.

c Safety follow-up period (52 weeks post-dose): Patients who complete or permanently discontinue study treatment (eg, at the time of premature study drug discontinuation, at the completion of study treatment in the OLTP for patients who decline the optional OLEP, or at the completion of study treatment in the optional OLEP) will be monitored for safety until 52 weeks after the last dose of study treatment. Patients who complete the optional OLEP may be able to continue study treatment in a post-trial access program. Patients participating in the post-trial access program will therefore not be followed in the safety follow-up period.

6.1.1. Screening (Day -8/-7 to Day -1)

The screening period is 7 to 8 days. The screening visit should occur at a scheduled or unscheduled visit of the R3918-PNH-1868 study (parent study).The dose of pozelimab should be administered at the study site on the day of the screening visit in this study, which shall occur on the day of a planned administration with pozelimab monotherapy.

Assessments that are common to both study protocols (R3918-PNH-1868 and R3918-PNH-2092) should not be duplicated during the screening visit for this study.

During the screening visit in this study, patients will be administered their dose of 800 mg pozelimab SC as required in the parent study, and this should occur after all study procedures have been completed for both the parent study and this study. Subsequently, the day 1 visit with the combination treatment dosing in this study should occur 7 to 8 days after the last dose of pozelimab monotherapy in the parent study.

Patients who screen fail in this study should continue with their current 800 mg pozelimab dosing regimen in the parent study. Patients may be rescreened up to 2 times in this study with agreement by the Sponsor if:

- The day 1 visit cannot be scheduled 7 to 8 days after the screening visit

or

- The patient was deemed ineligible for another reason and the Investigator believes that the patient may be eligible upon rescreening

Rescreening for this study should take place at a scheduled or unscheduled visit on the day of a planned administration with pozelimab in the parent study.

Patients who are randomized in this study will permanently discontinue treatment in the parent study with the last visit assessments in the parent study being considered as end of treatment/end of study visit assessments.

Patients who are randomized in this study will receive their first dose of the combination treatment with cemdisiran and pozelimab on day 1, as required per protocol (Section 6.1.2).

As part of risk mitigation for this study, patients should have documented vaccination against *Neisseria meningitidis* and receive updated meningococcal vaccination if needed (Section 8.2.1). Daily oral antibiotic prophylaxis is recommended throughout the study (Section 8.2.3). Patients should be counseled regarding risk of infection with *Neisseria gonorrhea*, as applicable based on their risk level (Section 8.2.4).

In addition to screening procedures to determine eligibility, patients will be asked to complete a PNH Symptom-Specific Questionnaire daily for 7 consecutive days prior to the day 1 visit.

Patients may choose to participate in the optional OLEP, optional future biomedical research, and/or optional pharmacogenomics component of the study by signing the respective optional informed consent forms (ICFs).

6.1.2. Open-Label Treatment Period (Day 1 to Week 28)

Day 1 should be scheduled 7 to 8 days after the last dose of pozelimab monotherapy in the parent study. On day 1, after confirming eligibility, patients will be randomized in 1:1 ratio to 1 of 2 arms:

- Arm 1: Pozelimab 400 mg SC Q4W and cemdisiran 200 mg SC Q4W
- Arm 2: Pozelimab 400 mg SC Q2W and cemdisiran 200 mg SC Q4W

Patients randomized into this study must be discontinued from the parent study.

After all baseline samples are collected and all baseline assessments are performed, patients will receive the first doses of the assigned combination treatment. During the study, injection training may be provided for patients or caregivers who are interested in home-dosing, if this option is available. Upon successful completion of injection training, study treatment administration may be continued by the study staff, by another healthcare professional, by the patient (self-administration), or by a designated person at the patient's preferred location, as applicable (Section 8.1). In addition, study procedures, including sample collection for laboratory analysis, may be performed at the study clinic or at another location that is more convenient for the patient (including home visits), if this option is available and with agreement from the sponsor.

Safety Considerations

Breakthrough hemolysis is assessed by the investigator throughout the study and is defined in Section 6.2. During the study, a patient exhibiting an event of breakthrough hemolysis and inadequate LDH response may qualify for intensified treatment; patients who have an LDH increase ≥2 x ULN due to an acute complement-activating condition may qualify for an additional IV pozelimab dose. Details and requirements are described in Section 8.3.2. Study assessments for patients who require intensified treatment will restart from day 1r for the 28-week treatment period following Table 2.

The decision to transfuse with RBCs during the study should proceed according to the predefined criteria in Section 6.3.

Patients should be closely monitored for the entire study for early signs and symptoms of meningococcal infection (and other infections related to encapsulated organisms) and evaluated immediately if an infection is suspected (Section 8.2.2). Patients will be provided a patient safety card describing signs and symptoms of suspected meningococcal infection along with instructions to follow in case of a potential meningococcal infection as well as information for non-investigator health care provider for awareness. Daily oral antibiotic prophylaxis is recommended (Section 8.2.3).

Study Procedures

Study procedures include laboratory assessments of efficacy (LDH, hemoglobin, and CH50), transfusion record update, COAs, body weight, and routine safety assessments (vital signs, physical examination, ECG, safety laboratory testing). Treatment-emergent adverse events and concomitant medications will be monitored throughout the study. Patients will provide blood samples for biomarkers, drug concentration for potential PK/PD assessment, immunogenicity, and exploratory assessments. Study procedures are described in Table 1 (schedule of events for OLTP).

The last doses of study treatment are administered at week 24 for arm 1 and week 26 for arm 2. Patients will return for safety, efficacy, and other assessments at the end of treatment (EOT) visit at week 28. For patients who restarted on intensified treatment during the study, the last doses of study treatment are administered at week 26r. Patients will return for safety, efficacy, and other assessments at the EOT visit at week 28r.

6.1.3. Optional Open-Label Extension Period

All patients who complete the OLTP treatment period (including patients who receive intensified treatment) will be offered the opportunity to continue in an optional 52-week OLEP, whereby the transition of the combination treatment from the OLTP to the OLEP is planned to be uninterrupted (ie, day 1e visit of the OLEP will correspond to the EOT visit of the OLTP, and any common assessments will be performed once for both visits). Study assessments and conduct for the OLEP are as described previously for the OLTP and are detailed in Table 3 (schedule of events for the optional OLEP).

- Patients who are randomized to arm 1 (pozelimab 400 mg SC Q4W and cemdisiran 200 mg SC Q4W) who have not received treatment intensification will continue the Q4W regimen for both pozelimab and cemdisiran starting on day 1e
- Patients who are randomized to arm 2 (pozelimab 400 mg SC Q2W and cemdisiran 200 mg SC Q4W) who have not received treatment intensification will switch to the Q4W regimen for both pozelimab and cemdisiran starting on day 1e
- Patients who received treatment intensification during the main treatment period will continue with the intensified treatment regimen (pozelimab 400 mg SC Q2W and cemdisiran 200 mg SC Q4W) throughout the OLEP

During the OLEP, patients who are not on intensified treatment who meet the pre-defined criteria for treatment intensification will follow the dosing scheme as described in Section 8.3.2 with the new regimen starting on the day of intensification, and will continue their visit schedule at the next OLEP visit. This means that starting on the day of intensification (ie, day pre-defined criteria have been met), the patient will receive a single administration of pozelimab 30 mg/kg IV followed by SC administration of pozelimab and cemdisiran the same day. Thereafter, the patients will receive pozelimab 400 mg Q2W and cemdisiran 200 mg Q4W starting from the day of intensification (±3 days). The visit schedule for the OLEP will remain unchanged.

The OLEP will end 52 weeks after the first dose of study treatment in the OLEP, even if the patient required intensified treatment during the OLEP. For patients who complete the optional OLEP, post-trial access to treatment may be available (Section 8.9).

6.1.4. Post-Treatment Safety Follow-Up Period

Patients who permanently discontinue study treatment for any reason will be monitored in a post-treatment safety follow up period until 52 weeks after their last dose of study treatment. The safety follow-up period will begin when a patient completes or permanently discontinues study treatment (eg, at the time of premature study drug discontinuation, at the completion of study treatment in the OLTP for patients who decline the optional OLEP, or at the completion of study treatment in the optional OLEP for patients who do not continue treatment in a post-trial access setting).

Follow-up visits may be conducted at the study clinic, at home, or remotely (eg, by phone, if applicable). Study procedures include assessment of vital signs, physical examination, blood collection (hematology and chemistry), and monitoring for AEs, pregnancy reporting, and concomitant medications. Study visits and procedures are described in Table 4 (schedule of events for the safety follow-up period).

Patients who permanently discontinue study treatment should be treated in accordance with local standards of care.

6.1.5. End of Study Definition

The end of main study is defined as the date of the last visit of the last patient in the OLTP, including patients who discontinued treatment during the OLTP and are being followed in the post-treatment safety follow-up period of the OLTP.

The end of the optional OLEP is defined as the date of the last visit of the last patient in the optional OLEP, including patients who discontinued treatment during the OLEP and are being followed in the post-treatment safety follow-up period of the OLEP.

6.2. Breakthrough Hemolysis

Patients who experience breakthrough hemolysis may receive intensified treatment as described in Section 8.3.2.

Breakthrough hemolysis is defined below as an increase in LDH with concomitant signs or symptoms associated with hemolysis:

- An increase in LDH occurs when:
  - LDH ≥2 × ULN if pre-treatment LDH is ≤1.5 × ULN or
  - LDH ≥2 × ULN after initial achievement of LDH ≤1.5 × ULN if pre-treatment LDH is >1.5 × ULN
- The signs or symptoms should correspond to those known to be associated with intravascular hemolysis due to PNH, limited to the following: new onset or worsening fatigue, headache, dyspnea, hemoglobinuria, abdominal pain, scleral icterus, erectile dysfunction, chest pain, confusion, dysphagia, new thrombotic event, anemia including hemoglobin value significantly lower (ie, ≥2 g/dL decrease) as compared to patient's known baseline hemoglobin values.

6.3. Transfusion Algorithm

Transfusions with RBCs during the screening period and while the patient is receiving study treatment may proceed according to the following predefined criteria that will trigger a transfusion, as clinically indicated. The actual number of units to be transfused should be consistent with the practice when patients were in their parent studies, as best as possible, and at the discretion of the investigator:

- Transfuse with RBCs if hemoglobin level is ≤9 g/dL with new onset or worsening signs or symptoms resulting from anemia that are of sufficient severity to warrant transfusion, or

- Transfuse with RBCs if hemoglobin level is ≤7 g/dL with or without signs or symptoms from anemia

6.4. Planned Interim Analysis

An interim analysis may be conducted after 6 patients have completed at least 16 weeks of the OLTP. Additional/other interim analyses may be performed to support regulatory interactions.

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

7.1. Number of Patients Planned

This study will be open to all patients who have enrolled in the Regeneron-sponsored clinical study R3918-PNH-1868 and plans to enroll approximately 24 patients with PNH. The study enrollment will be considered complete once all patients in R3918-PNH-1868 who consent to participate in this study are enrolled into this study.

7.2. Study Population

This study will only enroll patients with PNH who are receiving pozelimab monotherapy in a Regeneron-sponsored clinical study (R3918-PNH-1868) and are willing to switch to the combination treatment.

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 are receiving treatment with pozelimab monotherapy in the R3918-PNH-1868 study
2. Provide informed consent signed by study patient
3. Willing and able to comply with clinic/remote visits and study-related procedures

7.2.2. Exclusion Criteria

A patient who meets any of the criteria listed below will be excluded from the study. Patients may be rescreened up to 2 times after discussion between the investigator and the sponsor.

1. Documented*, positive polymerase chain reaction (PCR) or equivalent test based on regional recommendations for COVID-19 or suspected SARS-CoV-2 infection and:
    a. Have not recovered from COVID-19 (ie, all COVID-19-related symptoms and major clinical findings which can potentially affect the safety of the patient have not been resolved), and
    b. Did not have 2 negative results from a nucleic acid amplification (PCR) test or equivalent test based on regional recommendations for COVID-19 to confirm that the patient is negative for SARS-CoV-2 or, if COVID-19 PCR (or equivalent) testing is not feasible, at least 3 months have transpired since the initial diagnosis

    * **Note**: Screening for COVID-19 will not be performed as part of eligibility assessments for this study
2. Patients with documented history of liver cirrhosis or patients with liver disease with evidence of currently impaired liver function; or patients with ALT or AST (unrelated to PNH) >3× ULN at the screening visit (1 repeat lab is allowed during screening)

3. 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)
4. Any new condition or worsening of an existing condition which, in the opinion of the investigator, would make the patient unsuitable for enrollment or would jeopardize the safety of the patient
5. Known hypersensitivity to cemdisiran or any component of cemdisiran formulation
6. Pregnant or breastfeeding women
7. Women of childbearing potential (WOCBP)* 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 52 weeks after the last dose. Highly effective contraceptive measures include:
   a. stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening;
   b. intrauterine device (IUD); intrauterine hormone-releasing system (IUS);
   c. bilateral tubal ligation;
   d. vasectomized partner (provided that the male vasectomized partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has obtained medical assessment of surgical success for the procedure); and/or
   e. sexual abstinence†, ‡.

   *WOCBP are defined as women who are fertile following menarche until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

   A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to determine the occurrence of a postmenopausal state. The above definitions are according to the Clinical Trial Facilitation Group (CTFG) guidance (CTFG, 2020). 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 drugs. 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 (LAM) are not acceptable methods of contraception.

Note: The use of a female or male condom is not sufficient as a contraceptive measure but may be considered for the safety or prevention of sexually transmitted diseases. 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.

Patient who are withdrawn prematurely from the study will be asked to complete the early termination (ET) visit, as described in Section 9.1.2.

Rules for discontinuation of study treatment (permanent or temporary) are discussed in Section 8.3.3.

7.4. Replacement of Patients

Patients prematurely discontinued from study treatment will not be replaced.

8. STUDY TREATMENTS

8.1. Investigational Treatment

8.1.1. Pozelimab

Pozelimab drug product will be provided in a sterile, single-use glass vial for SC administration and/or IV administration (for intensified treatment) and will be supplied by the sponsor.

Detailed information about the drug product and instructions on dose preparation are provided in the pharmacy manual.

8.1.2. Cemdisiran

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

Detailed information about the drug product and instructions on dose preparation are provided in the pharmacy manual.

8.1.3. Dose Administration

On day 1, patients should be monitored for at least 30 minutes after receiving the first cemdisiran injection. A 30 minute monitoring period is not needed after the pozelimab injection.

During the study, administrations of the combination treatment can be performed by the patient himself/herself or a designated person or a healthcare professional at patient's preferred location (if possible) or by site personnel during the study visits, based on the preference of investigator and patient, local regulations as well as availability of healthcare professional. Sufficient injection training with the combination dose administration will be provided. After training, observation of administration by patient/designated person will be conducted by clinical site personnel and may be conducted in person at the patient's home or via telemedicine. Once this observation is considered satisfactory, the combination dose administration can be subsequently performed by a patient or a designated person for the remainder of the study.

In addition, a patient diary will be provided prior to initiation of self-administration to collect data on study treatment administration. The diary should be completed upon each 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.

The dosing windows for the 2 dosing regimens are as follows:

- Pozelimab 400 mg SC Q4W and cemdisiran 200 mg SC Q4W (±7 days)
- Pozelimab 400 mg SC Q2W and cemdisiran 200 mg SC Q4W (±3 days)

Note: Study procedures may have instructions pertaining to the timing relative to dosing. Therefore, dosing should be coordinated with the study visit windows, which are described in the Schedule of Events tables in Section 9.

8.2. Risk Mitigation and Background Treatments

8.2.1. Meningococcal Vaccinations

Patients will have had previous documented vaccination for meningococcus (serotypes A, C, Y, W and serotype B if available) from a prior Regeneron sponsored study, but may be revaccinated if prior vaccination is more than 5 years prior to screening. Patients should be revaccinated less than 5 years prior to screening if required according to current national vaccination guidelines for vaccination use with complement inhibitors or local practice. If vaccination precedes the initiation of study treatment by less than 2 weeks, then the patient must receive antibiotic prophylaxis for a minimum of 2 weeks from the date of vaccine administration.

During the course of the study, the investigator should ensure the patient continues to meet the requirement for vaccination as stated above. Patients who require re-vaccination during the study should continue study treatment. Vaccinations will be sourced locally by the investigator or designee and reimbursed by the sponsor.

8.2.2. Monitoring for Meningococcal Infection

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 to follow in case of a potential meningococcal infection, as well as information for the non-investigator healthcare provider for awareness.

8.2.3. Oral Antibiotics

It is recommended that daily oral antibiotic prophylaxis with either a penicillin or macrolide class antibiotic commence on the day of first dosing of study drug (or per timing of meningococcal vaccination, Section 8.2.1) and continue for the duration of the study, unless the risks outweigh the benefits or it is inconsistent with local practice. It is recommended that prophylaxis be continued for at least 52 weeks after last dose of pozelimab and cemdisiran combination treatment, including for patients who prematurely discontinue study drug. If the investigator prescribes antibiotic prophylaxis, then the investigator should follow the local prescribing information, particularly as it relates to warnings, precautions, monitoring, etc, which may necessitate additional monitoring, attention to drug-drug interactions, and other considerations.

Ultimately, the decision to administer prophylaxis with oral antibiotics, the start day of administration, the duration of prophylaxis, and the choice and dosing regimen of antibiotics will be at the discretion of the investigator and should be consistent with local guidelines for use with complement inhibitors. Oral antibiotics will be sourced locally by the investigator or designee and reimbursed by the sponsor.

8.2.4. Risk Management of *Neisseria Gonorrhea*

Patients should be counseled about *N. 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 of prevention, testing, and treatment of *N. gonorrhea*.

Testing and treatment should be in accordance with local practice or 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.

8.3. Dose Modification and Study Treatment Discontinuation Rules

8.3.1. Dose Modification

Dose modification for an individual patient is not allowed, unless the patient meets the criteria for intensified treatment as described in Section 8.3.2.

8.3.2. Intensified Treatment

Patients will be given intensified treatment if they meet both of the following criteria:

- Breakthrough hemolysis that is not due to a complement activating condition (ie, intercurrent infection) *

  * For LDH increase ≥2 x ULN due to a complement activating condition, see footnote at the end of section

- Inadequate LDH response (ie, LDH >1.5 × ULN) that is sustained (ie, on 2 consecutive measurements spanning at least 2 weeks)

Patients' treatment will be intensified depending on their assigned treatment group as outlined below. An assessment of the patient's weight should be performed on the day of the IV pozelimab load in order to calculate the appropriate dose.

- Patients randomized to pozelimab 400 mg SC Q4W and cemdisiran 200 mg SC Q4W will receive a single administration of pozelimab 30 mg/kg IV on the day of intensification + an intensified pozelimab regimen of 400 mg Q2W along with cemdisiran 200 mg Q4W starting on the day of intensification. The patients will be treated with the intensified SC dose regimen for additional 28 weeks to complete the study, with the last doses of the intensified treatment at week 24r (for cemdisiran) and week 26r (for pozelimab).
- Patients randomized to pozelimab 400 mg SC Q2W and cemdisiran 200 mg SC Q4W will receive a single administration of pozelimab 30 mg/kg IV on the day of intensification + a re-initiation of the assigned combination regimen of pozelimab 400 mg SC Q2W and cemdisiran 200 mg SC Q4W starting on the day of intensification. The patients will continue the same SC dose regimen for additional 28

weeks to complete the study, with the last doses of the intensified treatment at week 24r (for cemdisiran) and week 26r (for pozelimab).

Patients who undergo treatment intensification may require unscheduled visit(s) prior to intensification. During the OLTP, patients whose treatment is intensified should follow Table 2 (schedule of events for patients on intensified treatment), with the day of intensification anchored to day 1r (RV1). Patients who restarted on an intensified treatment will be considered to have completed the OLTP once they receive 28 weeks of the intensified treatment and complete Week 28r assessments.

During the OLEP, patients who are not on intensified treatment who meet criteria for treatment intensification will receive a single administration of pozelimab 30 mg/kg IV based on their current weight on the day of intensification + an intensified regimen of pozelimab 400 mg Q2W along with cemdisiran 200 mg Q4W starting on the day of intensification and for the remainder of the OLEP. Patients will continue their visit schedule at the next OLEP visit.

Patients who experience breakthrough hemolysis that is not due to a complement activating condition and meet criteria for treatment intensification are eligible to receive intensification of pozelimab only once (whether during the main treatment period or the OLEP), beyond which no further intensification will be permitted.

Note: In the event of an LDH increase ≥2 x ULN due to an acute complement activating condition during the OLTP or OLEP, an IV bolus of pozelimab 30 mg/kg IV may be given at the discretion of the investigator and in consultation with the sponsor. An assessment of the patient's weight should be performed on the day of the IV pozelimab load in order to calculate the appropriate dose. This is not considered treatment intensification. No other changes will be made to the study treatment regimen (ie, the regular dose and frequency of pozelimab and cemdisiran will proceed unchanged). Patients will continue onto the next visit of their current visit schedule.

Note: The IV dose should be administered first. The SC doses should be given at least 30 minutes after completion of the IV administration. Information related to acute reactions are provided in Section 8.4.

8.3.3. Study Drug Discontinuation

Patients who permanently discontinue from study treatment regardless of treatment period should be encouraged to remain in the study. Those who agree and do not withdraw from the study will be asked to return to the clinic for all remaining study visits per the visit schedule, including the safety follow-up period, until 52 weeks after their last dose of study treatment.

Patients who permanently discontinue from study treatment and who opt to withdraw from the study will be asked to return for an ET visit consisting of applicable assessments for the corresponding study period per Section 9.1.2.

Patients who permanently discontinue study treatment should be treated in accordance with local standards of care.

8.3.3.1. 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 treatment
- Liver impairment as evidenced by 1 or more of the following criteria and no other reason can be found to explain the following lab abnormalities, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; PNH-related complication; or another drug capable of causing the observed injury:
  - ALT or AST >8× ULN, or
  - ALT or AST >5× ULN for >2 weeks, or
  - ALT or AST >3× ULN and total bilirubin >2× ULN (or international normalized ratio [INR] >1.5)
- Patient withdrawal of consent
- Patient noncompliance as determined by the investigator (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

Note: A documented, positive PCR or equivalent test per local recommendations for COVID-19 is not considered an automatic reason for permanent discontinuation and should be discussed with the medical monitor. It may be a reason for permanent discontinuation if the benefit-risk assessment of continuing treatment with pozelimab and cemdisiran is deemed unfavorable.

8.3.3.2. Reasons for Temporary Discontinuation of Study Drug

Temporary discontinuation may be considered by the investigator because of suspected AEs. Study treatment may resume after resolution of the condition that led to temporary discontinuation of study treatment. Alternatively, the investigator can reinitiate study treatment under close and appropriate clinical and/or laboratory monitoring once the investigator has considered, according to his/her best medical judgment, that there is an unlikely relationship between the occurrence of the AE and the study treatment.

After re-initiation of study treatment, the patient should receive any missed dose as soon as possible. The patient should then return to the original dosing schedule.

Note regarding infection with SARS-CoV-2: if in the investigator's medical judgement, it is in the patient's best interest to interrupt treatment with cemdisiran/pozelimab until the patient recovers from SARS-CoV-2, then it is advisable that two repeat COVID-19 PCR tests, or equivalent tests depending on regional recommendations, be conducted to confirm the patient is negative for SARS-CoV-2. If COVID-19 PCR testing is not feasible, it is advised that at least three months have transpired since the initial diagnosis. The investigator may resume treatment with cemdisiran/pozelimab under close clinical monitoring if the Investigator feels that the benefit of resuming therapy outweighs the risk and the patient has no new contraindications to

treatment. Input from the Sponsor regarding the permissible duration of interruption to allow resumption of treatment may be sought.

8.4. Management of Acute Reactions

8.4.1. Acute Injection Reactions

8.4.1.1. Systemic Injection Reactions

Emergency equipment and medication for the treatment of systemic reactions must be available at the clinical site for immediate use. All systemic injection reactions must be reported as AEs and graded using the grading scales as instructed in Section 10.2.5.

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

8.4.1.2. Local Injection Site Reactions

Local injection site reactions (ISRs) must be reported as AEs and graded according to Section 10.2.5.

In this study, ISRs related to study treatment are reported as AESIs as defined in Section 10.1.3 and Section 10.1.4. Additional details about the event may be collected.

8.4.2. Acute Intravenous Infusion Reactions

In this study, pozelimab IV may be given in the event of a breakthrough hemolysis (Section 8.3.2).

Patients should be observed for 30 minutes after the infusion.

Emergency equipment and medication for the treatment of infusion reactions must be available at the clinical site for immediate use. All infusion reactions must be reported as AEs (as defined in Section 10.2.4) and graded using the grading scales as instructed in Section 10.2.5.

In this study, infusion reactions related to study treatment are reported as AESIs as defined in Section 10.1.3 and Section 10.1.4. Additional details about the event may be collected.

8.4.2.1. Interruption of the Intravenous Infusion

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

- Sustained/severe cough
- Rigors/chills
- Rash, pruritus (itching)
- Urticaria (hives, welts, wheals)
- Diaphoresis (sweating)
- Hypotension
- Dyspnea (shortness of breath)

- Vomiting
- Flushing

The reaction(s) should be treated symptomatically, and the infusion may be restarted at 50% of the original rate provided that the symptoms are adequately managed.

If the investigator feels there is a medical need for treatment or discontinuation of the infusion other than described above, he/she should use clinical judgment to provide the appropriate response according to typical clinical practice.

8.4.2.2. Termination of the Intravenous Infusion

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

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

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

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

8.5. Method of Treatment Assignment

On day 1, eligible patients will be randomized in a 1:1 ratio to receive:

- Arm 1: Pozelimab 400 mg SC Q4W and cemdisiran 200 mg SC Q4W
- Arm 2: Pozelimab 400 mg SC Q2W and cemdisiran 200 mg SC Q4W

Randomization will be performed according to a central randomization scheme provided by an interactive web response system (IWRS) to the designated study pharmacist (or qualified designee).

8.6. Blinding

This is an open-label study.

8.7. Treatment Logistics and Accountability

8.7.1. Packaging, Labeling, and Storage

Open-label study drug will be packaged in cartons and will display the product lot number on the carton and vial label.

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

8.7.2. 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 / returned to the sponsor or designee.

8.7.3. 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.

8.7.4. Treatment Compliance

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

8.8. Concomitant Medications and Procedures

Any treatment administered from the time of informed consent to the end of the post-treatment safety follow-up period will be considered concomitant medication. This includes medications that were started before the study and are ongoing during the study.

8.8.1. Prohibited Medications and Procedures

The following medications are prohibited, with the exception of those listed in Section 8.8.2, as described below:

- Beginning on day 1 and continuing throughout the study, while the patient is receiving the study treatment, the patient should not take any other complement inhibitor therapy
- Other investigational treatments during the course of the study
- In addition, within 24 hours prior to each clinic visit when blood is drawn, the patient should not consume any alcohol and refrain from strenuous exercise if possible

8.8.2. Permitted Medications and Procedures

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 8.2.1
- Oral antibiotic prophylaxis as recommended, as described in Section 8.2.3
- Oral contraceptives and hormone-replacement therapy may continue
- Acetaminophen/paracetamol, aspirin, or ibuprofen at the recommended dose per the local prescribing information
- 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 in the prior 26 weeks from enrollment. Any other medications may undergo dose adjustment or discontinuation at the discretion of the investigator.
- Any other medication required for the treatment of patient's background medical conditions

8.9. Post-Trial Access to Study Treatment

Post-trial access to pozelimab and cemdisiran will be provided until regulatory approval has been granted in the region the patient resides and consistent with sponsor guidelines. Such access to pozelimab and cemdisiran will be based on the request of the patient and investigator in line with local regulations, provided that the patient meets all post-trial access sponsor requirements.

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. Schedule of Events

In light of the public health emergency related to COVID-19, the continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms. Examples of such mechanisms may include, but are not limited to, any of the following: phone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. Additionally, no waivers to deviate from protocol enrollment criteria due to COVID-19 will be granted. All temporary mechanisms utilized and deviations from planned study procedures due to COVID-19 are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.

Study assessments and procedures are presented by study period and visit. Study procedures, including sample collection for laboratory analysis, may be performed at the study clinic or at another location that is more convenient for the patient (including home visits), if this option is available and with sponsor approval.

Table 1: Schedule of Events (Open-Label Treatment Period)

	Screening Period	Open-Label Treatment Period [3]											
Study Procedure (Visit) [1,2]	**Screening V1**	**V2**[4]	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**EOT**[5] **V13**
Week	**Up to -1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**28**
Day	**Up to -8**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**113**	**141**	**169**	**197**
Window (day)	**--**	**--**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-7/+3**	**-7/+3**	**-7/+3**	**-7/+3**
Screening/Baseline:													
Inclusion/Exclusion	x	x											
Informed consent	x												
Informed consents for OLEP, FBR, and genomics research (optional)	x												
Medical history [6]	x												
Prior medications [7]	x												
Demographics	x												
Height	x												
Documentation of vaccination for *Neisseria meningitidis* (or revaccination) [8]	x												
Risk assessment for *Neisseria gonorrhea* [9]	x												
Patient safety card for *Neisseria meningitidis* [10]	x	x	x	x	x	x	x	x	x	x	x	x	x
Randomization		x											
Study Treatment:													
Arm 1 only: Pozelimab 400 mg SC Q4W [11]		x[12]			x		x		x	x	x	x	
Arm 2 only: Pozelimab 400 mg SC Q2W [11]		x[12]		x	x	x	x	x	x	x	x	x[11]	
Cemdisiran 200 mg SC Q4W [11]		x[12]			x		x		x	x	x	x	
Injection training/patient instructions (as needed) [13]			<----------x---------->										
Patient diary [14]	x [15]	x	x	x	x	x	x	x	x	x	x	x	x
Antibiotics prophylaxis (recommended) [16]	<----------x---------->												
Revaccination against meningococcal infection *(if needed)*	<----------x---------->												
Clinical Outcome Assessments:													
FACIT-Fatigue		x		x	x		x		x	x	x	x	x
EORTC-QLQ-C30		x		x	x		x		x	x	x	x	x
TSQM		x		x	x		x		x	x	x	x	x
PNH symptom-specific questionnaire (daily) [17]	<----------x---------->												

	Screening Period	Open-Label Treatment Period [3]											
Study Procedure (Visit) [1,2]	**Screening V1**	**V2**[4]	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**EOT**[5] **V13**
Week	**Up to -1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**28**
Day	**Up to -8**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**113**	**141**	**169**	**197**
Window (day)	**--**	**--**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-7/+3**	**-7/+3**	**-7/+3**	**-7/+3**
PGIS		x			x				x		x		x
PGIC					x				x		x		x
Safety and Anthropometric:													
Body weight	x				x		x		x	x	x	x	x
Vital signs	x			x	x		x		x	x	x	x	x
Physical examination	x				x				x				x
Electrocardiogram	x												x
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x
Breakthrough hemolysis assessment [18]	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant meds/treatments	x	x	x	x	x	x	x	x	x	x	x	x	x
Transfusion record update	x	x	x	x	x	x	x	x	x	x	x	x	x
Laboratory Testing [19] **:**													
Titers to measure *N. meningitidis* (only if required per parent study)	x												
Coagulation panel	x	x	x	x	x	x	x	x	x	x	x	x	x
Chemistry (long panel) including LDH [20]	x	x	x	x	x	x	x	x	x	x	x	x	x
Hematology [21]	x	x	x	x	x		x		x	x	x	x	x
Immunoglobulin G		x			x				x				
Pregnancy test (WOCBP only): serum (S) or urine (U)	s	u			u		u		u	u	u	u	u
Urinalysis	x	x	x	x	x		x		x	x	x	x	x
Pharmacokinetics and Immunogenicity Sampling:													
Pozelimab conc. sample [22]	x	x	x	x	x		x		x	x	x	x	x
Cemdisiran and its metabolite conc. sample [23]		x			x				x			x	
Pozelimab immunogenicity sample [24]	x								x				x
Cemdisiran immunogenicity sample [24]		x							x				x
Total C5 (plasma) [22]	x	x	x	x	x		x		x	x	x	x	x
Biomarkers:													
Free hemoglobin	x	x			x		x		x	x	x	x	x
Haptoglobin	x	x			x				x				x
Complement hemolytic assay (serum CH50) [25]	x	x	x	x	x		x		x	x	x	x	x

	Screening Period	Open-Label Treatment Period [3]											
Study Procedure (Visit) [1,2]	**Screening V1**	**V2**[4]	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**EOT**[5] **V13**
Week	**Up to -1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**28**
Day	**Up to -8**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**113**	**141**	**169**	**197**
Window (day)	**--**	**--**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-7/+3**	**-7/+3**	**-7/+3**	**-7/+3**
Complement hemolytic assay (serum AH50) [25]	x	x	x	x	x		x		x	x	x	x	x
sC5b-9 (plasma)	x	x	x	x	x		x		x	x	x	x	x
PNH erythrocyte cells	x						x				x		x
PNH granulocyte cells	x						x				x		x
Optional research:													
Serum and plasma for FBR (optional)	x				x				x				x
Whole blood sample for DNA isolation for genomics research (optional) [26]		x											
Whole blood RNA sample for genomics research (optional)		x	x										x

Footnotes for Table 1 (treatment period) are provided in Section 9.1.1.1.

Table 2: Schedule of Events for Patients on Intensified Treatment in the OLTP

Study Procedure (Visit) [1,2]	Intensified Treatment Period in the OLTP [3]											
	RV1	RV2	RV3	RV4	RV5	RV6	RV7	RV8	RV9	RV10	RV11	EOT RV12
Week	**0r**	**1r**	**2r**	**4r**	**6r**	**8r**	**10r**	**12r**	**16r [5]**	**20r [5]**	**24r [5]**	**28r [6]**
Day	**1r**	**8r**	**15r**	**29r**	**43r**	**57r**	**71r**	**85r**	**113r**	**141r**	**169r**	**197r**
Window (day)	**--**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-7/+3**	**-7/+3**	**-7/+3**	**-7/+3**
Intensified Treatment:												
Pozelimab 30 mg/kg IV (loading dose) [4]	x[7]											
Pozelimab 400 mg SC Q2W [4]	x[7]		x	x	x	x	x	x	x	x	x[4]	
Cemdisiran 200 mg SC Q4W [4]	x[7]			x		x		x	x	x	x	
Injection training/patient instructions (as needed) [8]		<----------x---------->										
Patient diary [9]	x	x	x	x	x	x	x	x	x	x	x	x
Antibiotics prophylaxis (recommended) [10]	<----------x---------->											
Revaccination against meningococcal infection *(if needed)*	<----------x---------->											
Clinical Outcome Assessments:												
FACIT-Fatigue	x		x	x		x		x	x	x	x	x
EORTC-QLQ-C30	x		x	x		x		x	x	x	x	x
TSQM	x		x	x		x		x	x	x	x	x
PNH symptom-specific questionnaire (daily) [11]	<----------x---------->											
PGIS	x			x				x		x		x
PGIC				x				x		x		x
Safety and Anthropometric:												
Patient safety card for *Neisseria meningitidis* [12]	x	x	x	x	x	x	x	x	x	x	x	x
Body weight	x			x		x		x	x	x	x	x
Vital signs	x		x	x		x		x	x	x	x	x
Physical examination	x			x				x				x
Electrocardiogram												x
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x
Breakthrough hemolysis assessment [13]	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant meds/treatments	x	x	x	x	x	x	x	x	x	x	x	x
Transfusion record update	x	x	x	x	x	x	x	x	x	x	x	x
Laboratory Testing [14]:												
Coagulation panel	x	x	x	x	x	x	x	x	x	x	x	x
Chemistry (long panel) including LDH [15]	x	x	x	x	x	x	x	x	x	x	x	x

Study Procedure (Visit) [1,2]	Intensified Treatment Period in the OLTP [3]											
	RV1	RV2	RV3	RV4	RV5	RV6	RV7	RV8	RV9	RV10	RV11	EOT RV12
Week	**0r**	**1r**	**2r**	**4r**	**6r**	**8r**	**10r**	**12r**	**16r [5]**	**20r [5]**	**24r [5]**	**28r [6]**
Day	**1r**	**8r**	**15r**	**29r**	**43r**	**57r**	**71r**	**85r**	**113r**	**141r**	**169r**	**197r**
Window (day)	**--**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-7/+3**	**-7/+3**	**-7/+3**	**-7/+3**
Hematology [16]	x	x	x	x		x		x	x	x	x	x
Immunoglobulin G	x			x				x				
Pregnancy test (WOCBP only) [17]	u			u		u		u	u	u	u	u
Urinalysis	x	x	x	x		x		x	x	x	x	x
Pharmacokinetics and Immunogenicity Sampling:												
Pozelimab drug conc. sample [18]	x	x	x	x		x		x	x	x	x	x
Cemdisiran and its metabolite conc. sample [19]	x			x				x			x	
Pozelimab immunogenicity sample [20]	x							x				x
Cemdisiran immunogenicity sample [20]	x							x				x
Total C5 (plasma) [18]	x	x	x	x		x		x	x	x	x	x
Biomarkers:												
Free hemoglobin	x			x		x		x	x	x	x	x
Haptoglobin	x			x				x				x
Complement hemolytic assay (serum CH50) [21]	x	x	x	x		x		x	x	x	x	x
Complement hemolytic assay (serum AH50) [21]	x	x	x	x		x		x	x	x	x	x
sC5b-9 (plasma)	x	x	x	x		x		x	x	x	x	x
PNH erythrocyte cells	x					x				x		x
PNH granulocyte cells	x					x				x		x

Footnotes for this table (patients on intensified treatment) can be found in Section 9.1.1.2

Table 3: Schedule of Events (Optional Open-Label Extension Period)

Study Procedure (Visit) [1,2]	**Optional Open-Label Extension Period**						
	OLEP-1 [3]	**OLEP-2** [5]	**OLEP-3** [5]	**OLEP-4** [5]	**OLEP-5** [5]	**OLEP-6** [5]	**OLEP-7**
Week	**0e**	**8e**	**16e**	**24e**	**32e**	**40e**	**52e**
Day	**1e**	**57e**	**113e**	**169e**	**225e**	**281e**	**365e**
Window (day)	**--**	**-7/+3**	**-7/+3**	**-7/+3**	**-7/+3**	**-7/+3**	**-7/+3**
Treatment [4] **:**							
Pozelimab 400 mg SC Q2W or Q4W [5]	x	x	x	x	x	x	x
Cemdisiran 200 mg SC Q4W [5]	x	x	x	x	x	x	x
Injection training/patient instructions (as needed) [6]	<----------x---------->						
Patient diary [7]	x	x	x	x	x	x	x
Antibiotics prophylaxis (recommended) [8]	<----------x---------->						
Revaccination against meningococcal infection (if needed)	<----------x---------->						
Clinical Outcome Assessments:							
FACIT-Fatigue	x			x			x
EORTC-QLQ-C30	x			x			x
PGIS	x			x			x
PGIC	x			x			x
Safety and Anthropometric:							
Patient safety card for *Neisseria meningitidis* [9]	x	x	x	x	x	x	x
Body weight	x	x	x	x	x	x	x
Vital signs	x	x	x	x	x	x	x
Physical examination	x		x		x		x
Electrocardiogram	x						x
Adverse events	x	x	x	x	x	x	x
Breakthrough hemolysis assessment [10]	x	x	x	x	x	x	x
Concomitant meds/treatments	x	x	x	x	x	x	x
Transfusion record update	x	x	x	x	x	x	x
Laboratory Testing [11] **:**							
Coagulation panel	x	x	x	x	x	x	x
Chemistry (long panel) including LDH [12]	x	x	x	x	x	x	x
Hematology [13]	x	x	x	x	x	x	x
Pregnancy test (WOCBP only) [14]	u	u	u	u	u	u	u
Urinalysis	x	x	x	x	x	x	x

Study Procedure (Visit) [1,2]	**Optional Open-Label Extension Period**						
	OLEP-1 [3]	**OLEP-2** [5]	**OLEP-3** [5]	**OLEP-4** [5]	**OLEP-5** [5]	**OLEP-6** [5]	**OLEP-7**
Week	**0e**	**8e**	**16e**	**24e**	**32e**	**40e**	**52e**
Day	**1e**	**57e**	**113e**	**169e**	**225e**	**281e**	**365e**
Window (day)	**--**	**-7/+3**	**-7/+3**	**-7/+3**	**-7/+3**	**-7/+3**	**-7/+3**
Pharmacokinetics and Immunogenicity:							
Pozelimab conc. sample [15]	x			x			x
Cemdisiran and its metabolite conc. samples [16] (pre-dose and 2 to 6 hours post-dose)	x			x			x
Pozelimab immunogenicity sample [17]	x			x			x
Cemdisiran immunogenicity sample [17]	x			x			x
Total C5 (plasma) [15]	x			x			x
Biomarkers:							
Free hemoglobin	x						x
Haptoglobin	x						x
Complement hemolytic assay (serum CH50) [18]	x		x		x		x
Complement hemolytic assay (serum AH50) [18]	x		x		x		x
sC5b-9 (plasma)	x		x		x		x
PNH erythrocyte cells	x			x			x
PNH granulocyte cells	x			x			x
Optional research:							
Serum and plasma for FBR (optional)	x						x
Whole blood RNA sample for genomics research (optional)	x						x

Table 4: Schedule of Events (Post-Treatment Safety Follow-Up Period)

	Post-Treatment Safety Follow-Up Period					
Patients in the OLTP who discontinue study treatment will be asked to remain in the study until week 28 EOT (or week 28r for patients who restarted on intensified treatment) and follow the original schedule of events as applicable. After the week 28 EOT visit, their entry point into the safety follow-up schedule will depend on the number of weeks that have elapsed since their last dose (ie, a patient who is 20 weeks after their final dose of study treatment at EOT will enter into the safety follow-up period at visit FU-4 [26 weeks after last dose])	Patients who completed week 28 (with last doses administered at week 24 or week 26, or week 26r) who choose not to continue treatment in the OLEP, patients who complete the OLEP, and patients who permanently discontinue treatment during the OLEP will start here:					
Study Procedure	**FU-1**	**FU-2**	**FU-3**	**FU-4**	**Phone visit FU-5**	**Phone visit FU-6**
Week (after last dose of study drug)	8	12	16	26	38	52
Day (after last dose of study drug)	57	85	113	183	267	365
Window (day)	±10	±10	±10	±10	±10	±10
Safety Assessments						
Patient safety card for *Neisseria meningitidis*[1]	<----------X---------->					
Antibiotics prophylaxis (recommended)[2]	<----------X---------->					
Vital signs	x	x	x	x		
Physical examination		x		x		
Concomitant meds and procedures	x	x	x	x	x	x
Adverse event reporting	x	x	x	x	x	x
Pregnancy reporting	x	x	x	x	x	x
Laboratory Testing						
Hematology	x	x	x	x		
Blood chemistry	x	x	x	x		

9.1.1. Footnotes for the Schedule of Events Tables

9.1.1.1. Table 1 Schedule of Events (Treatment Period)

1. Visits between week 6 and up to week 24 may be at the clinical site, or another preferred location, such as patient's home. The location will be dependent on availability of home healthcare visiting professional as well as the preferences of the investigator and patient. In the event of travel restrictions due to a global pandemic, alternative mechanisms such as but not limited to telemedicine visits may be implemented to maintain continuity of study conduct.
2. When multiple procedures are performed on the same day, the sequence of procedures is as follows: COAs → ECG → vital signs, physical examination, safety monitoring, lab collection → study treatment administration → any pre-specified post-dose sample collection.
3. Patients who are restarted on an intensified treatment will undergo an adjustment to their scheduled visits. Patients may require unscheduled visit(s) as needed and should be subsequently followed per Table 2
4. The day 1 visit should take place 7 to 8 days after the screening visit. Patients may be rescreened if they cannot schedule the screening visit and the day 1 visit over a period of 7 to 8 days.
5. If the patient agrees to continue into the optional OLEP, the EOT visit of the OLTP will correspond to the day 1e visit of the OLEP (see Table 3). Any common assessments will be performed once for both visits.
6. Transfusions, breakthrough hemolysis history, and laboratory parameters for measurement of hemolysis (such as LDH, bilirubin, haptoglobin, reticulocyte count, and hemoglobin) should be obtained for the past 52 weeks, if possible. Prior history of thrombosis and *Neisseria* infections will be collected. Ongoing PNH symptoms and signs will also be collected. Information collected from parent studies may be used whenever possible.
7. Including pozelimab administration.
8. Patients will have had previous documented vaccination for meningococcus (serotypes A, C, Y, W and serotype B if available) in the Regeneron-sponsored parent study, but may be revaccinated if prior vaccination is more than 5 years from screening. Alternatively, patients may be revaccinated in accordance with current national vaccination guidelines for vaccination use with complement inhibitors or local practice. Patients who require revaccination may be rescreened.
9. A risk factor assessment for *Neisseria gonorrhea* infection is recommended, and counseling is advised for at-risk patients.
10. A patient safety card will be distributed to patients at screening and risk information will be reviewed. Replacement cards may be given to the patient as needed.

11. During OLTP, the dose of cemdisiran and pozelimab SC should be given on the day of the corresponding study visit whenever possible. Study treatment administration should always be the last procedure after all blood sample collection and study assessments have been completed unless otherwise specified.

    - If pozelimab or cemdisiran cannot be administered on the day of the corresponding study visit, the combination may be administered up to 3 days before or up to 3 days after the planned dosing date for Q2W dosing, provided that the combination dosing takes place after the corresponding study visit has been completed. For patients receiving pozelimab 400 mg SC Q2W + cemdisiran 200 mg SC Q4W, the dosing window (±3 days) is the same or narrower than the visit window (±3 days before week 16 or -7/+3 days on and after week 16).
    - If pozelimab or cemdisiran cannot be administered on the day of the corresponding study visit, the combination may be administered up to 7 days before or 7 days after the planned dosing date for Q4W dosing, provided that the combination dosing takes place after the corresponding study visit has been completed. For patients receiving pozelimab 400 mg SC Q4W + cemdisiran 200 mg SC Q4W, the visit window (±3 days before week 16 or -7/+3 days starting from week 16) is narrower than the dosing window (±7 days).

    Care must be taken to coordinate dosing for visits where a post-dose sample is collected to measure the concentration of cemdisiran and its metabolites. The final SC dosing of the combination (pozelimab and cemdisiran) during the OLTP is at week 24 for arm 1 and the final SC dosing of cemdisiran is at week 24 with pozelimab at week 26 for arm 2.
12. Patients should be monitored for at least 30 minutes after completing the first cemdisiran injection. A 30 minute monitoring period is not needed after the pozelimab injection.
13. Injection training will be provided to patients who desire self-injection or injection by a designated person. Site should observe patient self-injection or injection by a designated person and confirm adequacy. Patient instruction materials will be provided. SC injections may either be performed by the site personnel or another healthcare professional at the patient's home or preferred location, or be administered by the patient or a designated person who has successfully completed the injection training.
14. If study treatment is given by the patient or by a designated person, the patient will complete a diary for recording compliance with study treatment administration. If patient diary is provided to the patient, then it should be reviewed at each clinic visit and data collected into the case report forms (CRFs). On the final visit, the diary should be collected by the site.
15. At the screening visit, patient diary should be reviewed for the R3918-PNH-1868 (parent) study.
16. Daily oral antibiotic prophylaxis against *Neisseria meningitidis* is recommended starting on the first day of dosing with study treatment and continuing until 52 weeks after discontinuation of study treatment.

17. Patient will complete daily PNH Symptom-Specific Questionnaire for 7 consecutive days prior to day 1 visit. Patients should try to complete the PNH Symptom-Specific Questionnaire at the same time each day whenever possible.
18. Breakthrough hemolysis assessment: If a patient is suspected of having a breakthrough hemolysis event, then in addition to the required laboratory collection, additional samples will be collected as described for suspected breakthrough hemolysis assessment in Section 9.2.5.2 unless already noted in the schedule of events for that visit. If the suspected event does not occur at a scheduled visit then an unscheduled visit should occur with an evaluation of the patient and collection of samples for suspected breakthrough hemolysis assessment as described in Section 9.2.5.2.
19. Clinical lab samples will be collected prior to any study drug administration (pre-dose) unless otherwise specified. The same methodology will be applied across study visits for lab sample collection, handling and processing, as best as possible, to preserve the quality of samples and minimize hemolysis. The coagulation blood sample (tube) must always be collected first, followed by the blood chemistry sample (tube).
20. Serum LDH, C-reactive protein (CRP), and bilirubin (total and direct) will be assessed as part of the blood chemistry analysis. Blood chemistry sample should be collected before study treatment administration (pre-dose). During lab collection, handling and processing, the same methodology will be applied across study visits, as best as possible, to preserve the quality of sample and avoid hemolysis during sample processing. If the investigator or sponsor suspects that the lab result is not an accurate reflection of the patient's condition, the lab sample should be repeated.
21. Hematology sample should be collected before study treatment administration (pre-dose).
22. Blood samples for pozelimab concentration analysis and total C5 analysis will be obtained on the specified days prior to any study treatment administration (pre-dose).
23. Blood samples for cemdisiran concentration analysis and concentrations of its metabolites will be collected on the specified days prior to any study treatment administration (pre-dose) and 2 to 6 hours post cemdisiran administration. The post-dose sample should be carefully coordinated with the dosing of cemdisiran and may be collected at the clinic or by a visiting health care professional.
24. Blood samples for immunogenicity will be collected on the specified days prior to any study treatment administration (pre-dose). At the visits where immunogenicity samples are to be taken, the sample should be collected with the sample for drug concentration. In the event of suspected treatment-related SAEs, such as anaphylaxis or hypersensitivity, additional samples for drug concentration and immunogenicity may be collected at or near the onset and the resolution of the event.
25. Blood samples for CH50 (efficacy endpoint) and AH50 will be obtained prior to any study treatment administration (pre-dose).
26. Whole blood samples for DNA extraction (optional) should be collected on day 1 (pre-dose) but can be collected at a later study visit. Patients who had consented to DNA testing

in a prior Regeneron study with pozelimab and had provided a sample for analysis do not need to provide separate consent/sample for this study

9.1.1.2. Table 2 Schedule of Events (for Patients on Intensified Treatment)

1. Visits between week 6r and week 24r may be at the clinical site, or another preferred location, such as patient's home. The location will be dependent on availability of home healthcare visiting professional as well as the preferences of the investigator and patient. In the event of travel restrictions due to a global pandemic, alternative mechanisms such as but not limited to telemedicine visits may be implemented to maintain continuity of study conduct.
2. When multiple procedures are performed on the same day, the sequence of procedures is as follows: COAs → ECG → vital signs, physical examination, safety monitoring, lab collection → study drug administration → any pre-specified post-dose sample collection.
3. The intensified treatment schedule will be anchored to the day of intensification (ie, a reset occurs with the day of intensification becoming the day 1r visit and subsequent visits following the schedule of events for intensified treatment). Patients who receive intensified treatment will be considered to have complete the study once they finish the 28-week treatment period with the intensified treatment (ie, after completing week 28r EOT assessments).
4. During the intensified treatment period in the OLTP, the dose of cemdisiran and pozelimab SC should be given on the day of the corresponding study visit whenever possible. Study treatment administration should always be the last procedure after all blood sample collection and study assessments have been completed unless otherwise specified. If pozelimab or cemdisiran cannot be administered on the day of the corresponding study visit, the combination may be administered up to 3 days before or up to 3 days after the planned dosing date provided that the dosing takes place after the corresponding study visit has been completed. For example, the day 29r (week 4r) visit can take place from day 26r to day 32r given the visit window of ±3 days for the week 4r visit. The dose of pozelimab and cemdisiran therefore can be given from day 26r to day 32r, but only on or after the week 4r visit assessments have been performed. Similarly, the day 113r (week 16r) visit can take place from day 106r to day 116r given the visit window of -7/+3 days for the week 16r visit. The dose of pozelimab and cemdisiran can be given from day 110r to day 116r, but only on or after the week 16r visit assessments have been performed. Care must be taken to coordinate dosing for visits where a post-dose sample is collected to measure concentration of cemdisiran and its metabolites. For patients on intensified treatment in the OLTP, the final SC dose of cemdisiran is at week 24r and the final SC dose of pozelimab is at week 26r.
5. For these visits, the dosing window (±3 days) is narrower than the study visit window (-7/+3 days).
6. If the patient agrees to continue into the optional OLEP, the EOT visit of the OLTP will correspond to the day 1e visit of the OLEP (see Table 3). Any common assessments will be performed once for both visits.
7. On day 1r, pozelimab IV will be given first, with a 30-minute observation period before administration of SC doses. Subsequent pozelimab SC dose will be administered Q2W and cemdisiran SC dose will be administered Q4W. The SC injections may either be performed

by the site personnel or another healthcare professional at patient's home or preferred location, or be administered by the patient or by a designated person who has successfully completed the injection training.

8. Injection training will be provided to patients who desire self-injection or injection by a designated person. Site should observe patient self-injection or injection by a designated person and confirm adequacy. Patient instruction materials will be provided.
9. If study treatment is given by the patient or by a designated person, the patient will complete a diary for recording compliance with study treatment administration. If patient diary is provided to the patient, then it should be reviewed at each clinic visit and data collected into the CRFs. On the final visit, the diary should be collected by the site.
10. Daily oral antibiotic prophylaxis against *Neisseria meningitidis* is recommended until 52 weeks after discontinuation of study treatment.
11. Patients should try to complete the PNH Symptom-Specific Questionnaire at the same time each day whenever possible.
12. Patient safety card: Site should review the instructions on the safety card with the patient at each visit. Replacement cards may be given to the patient as needed.
13. Breakthrough hemolysis assessment: If a patient is suspected of having a breakthrough hemolysis event, then in addition to the required laboratory collection, additional samples for drug concentrations of pozelimab will be collected unless already noted in the schedule of events for that visit. If the suspected event does not occur at a scheduled visit then an unscheduled visit should occur with an evaluation of the patient and collection of coagulation, chemistry, and drug concentrations of pozelimab.
14. Clinical lab samples will be collected prior to any study drug administration (pre-dose) unless otherwise specified. During lab collection, handling and processing, the same methodology will be applied across study visits, as best as possible, to preserve the quality of sample and avoid hemolysis. The coagulation blood sample (tube) must always be collected first, followed by the blood chemistry sample (tube).
15. Serum LDH, CRP, and bilirubin (total and direct) will be assessed as part of the blood chemistry analysis. Blood chemistry sample should be collected before study treatment administration (pre-dose). During lab collection, handling and processing, the same methodology will be applied across study visits, as best as possible, to preserve the quality of sample and avoid hemolysis during sample processing. If the investigator or sponsor suspects that the lab result is not an accurate reflection of the patient's condition, the lab sample should be repeated.
16. Hematology sample should be collected before study treatment administration (pre-dose).
17. Pregnancy test for WOCBP: A urine test will be done at all visits indicated. Any positive urine pregnancy test should be confirmed with a serum pregnancy test.
18. On day 1r, obtain blood sample for pozelimab concentration and total C5 prior to IV administration of pozelimab and also within 15 minutes after the end of the IV infusion. At subsequent timepoints, blood samples for pozelimab drug concentration analysis and total C5 analysis will be obtained prior to any study treatment administration (pre-dose).

19. Blood samples for cemdisiran drug concentration analysis and concentrations of its metabolites will be collected on the specified days prior to any study treatment administration (pre-dose) and 2 to 6 hours post cemdisiran administration. The post-dose sample should be carefully coordinated with the dosing of cemdisiran and may be collected at the clinic or by a visiting health care professional.
20. Blood samples for immunogenicity will be collected on the specified days prior to any study treatment administration (pre-dose). At the visits where immunogenicity samples are to be taken, the sample should be collected with the sample for drug concentration. In the event of suspected treatment-related SAEs, such as anaphylaxis or hypersensitivity, additional samples for drug concentration and immunogenicity may be collected at or near the onset and the resolution of the event.
21. Blood samples for CH50 (efficacy endpoint) and AH50 will be obtained prior to any study treatment administration (pre-dose).

9.1.1.3. Table 3 Schedule of Events (for Open-Label Extension Period)

1. Visits may be at the clinical site or another preferred location, such as the patient's home. The location will depend on availability of home healthcare visiting professional as well as the preferences of the investigator and patient. In the event of travel restrictions due to a global pandemic, alternative mechanisms such as but not limited to telemedicine visits may be implemented to maintain continuity of study conduct.
2. When multiple procedures are performed on the same day, the sequence of procedures is as follows: COAs → ECG → vital signs, physical examination, safety monitoring, lab collection → study drug administration → any pre-specified post-dose sample collection.
3. Day 1e of OLEP should be scheduled on the same day as week 28 (or week 28r for patients on intensified treatment) of the OLTP, and any common assessments will be performed once for both the OLTP and OLEP visits.
4. *For patients who did not receive intensified treatment during OLTP:* At any time during the OLEP, patients who meet pre-specified criteria will receive intensified treatment consisting of a pozelimab 30 mg/kg IV loading dose followed 30 minutes later by the initiation of pozelimab 400 mg SC Q2W and cemdisiran 200 mg SC Q4W. Patients should be observed for 30 minutes in the interim between the IV and SC doses. Patients will continue their visit schedule at the next OLEP visit.
5. During the OLEP, the dose of cemdisiran and pozelimab SC should be given on the day of the corresponding study visit whenever possible. Study treatment administration should always be the last procedure after all blood sample collection and study assessments have been completed unless otherwise specified:

    - If pozelimab or cemdisiran cannot be administered on the day of the corresponding study visit, the combination may be administered up to 3 days before or up to 3 days after the planned dosing date, provided that the combination dosing takes place after the corresponding study visit has been completed. For patients receiving pozelimab 400 mg SC Q2W + cemdisiran 200 mg SC Q4W, the dosing window (±3 days) is narrower than the visit window (-7/+3 days).
    - If pozelimab or cemdisiran cannot be administered on the day of the corresponding study visit, the combination may be administered up to 7 days before or 7 days after the planned dosing date, provided that the combination dosing takes place after the corresponding study visit has been completed. For patients receiving pozelimab 400 mg SC Q4W + cemdisiran 200 mg SC Q4W, the visit window (-7/+3 days) is narrower than the dosing window (±7 days).

    Care must be taken to coordinate dosing for visits where a post-dose sample is collected to measure concentration of cemdisiran and its metabolites. For patients whose treatment is not intensified during the OLEP, the last doses of cemdisiran and pozelimab are administered at week 52e. For patients whose treatment was intensified during the OLEP, the last doses of study treatment will be determined based on the time of treatment intensification.

6. Injection training will be provided to patients who desire self-injection or injection by a designated person. Site should observe patient self-injection or injection by a designated person and confirm adequacy. Patient instruction materials will be provided.
7. If study treatment is given by the patient or by a designated person, the patient will complete a diary for recording compliance with study treatment administration. If patient diary is provided to the patient, then it should be reviewed at each clinic visit and data collected into the CRFs. On the final visit, the diary should be collected by the site.
8. Daily oral antibiotic prophylaxis against *Neisseria meningitidis* is recommended until 52 weeks after discontinuation of study treatment.
9. Patient safety card: Site should review the instructions on the safety card with the patient at each visit. Replacement cards may be given to the patient as needed.
10. Breakthrough hemolysis assessment: If a patient is suspected of having a breakthrough hemolysis event, then in addition to the required laboratory collection, additional samples for drug concentrations of pozelimab will be collected unless already noted in the schedule of events for that visit. If the suspected event does not occur at a scheduled visit then an unscheduled visit should occur with an evaluation of the patient and collection of coagulation, chemistry, and drug concentration of pozelimab.
11. Clinical lab samples will be collected prior to any study drug administration (pre-dose) unless otherwise specified. During lab collection, handling and processing, the same methodology will be applied across study visits, as best as possible, to preserve the quality of sample and avoid hemolysis. The coagulation blood sample (tube) must always be collected first, followed by the blood chemistry sample (tube).
12. Serum LDH, CRP, and bilirubin (total and direct) will be assessed as part of the blood chemistry analysis. Blood chemistry sample should be collected before study treatment administration (pre-dose). During lab collection, handling and processing, the same methodology will be applied across study visits, as best as possible, to preserve the quality of sample and avoid hemolysis during sample processing. If the investigator or sponsor suspects that the lab result is not an accurate reflection of the patient's condition, the lab sample should be repeated.
13. Hematology sample should be collected before study treatment administration (pre-dose).
14. Pregnancy test for WOCBP: A urine test will be done at all visits indicated. Any positive urine pregnancy test should be confirmed with a serum pregnancy test.
15. Blood samples for pozelimab concentration analysis and total C5 analysis will be obtained on the specified days prior to any study treatment administration (pre-dose).
16. Blood samples for cemdisiran concentration analysis and concentrations of its metabolites will be collected on the specified days prior to any study treatment administration (pre-dose) and 2 to 6 hours post cemdisiran administration. The post-dose sample should be carefully coordinated with the dosing of cemdisiran and may be collected at the clinic or by a visiting health care professional.
17. Blood samples for immunogenicity will be collected on the specified days prior to any study treatment administration (pre-dose). At the visits where immunogenicity samples

are to be taken, the sample should be collected with the drug concentration sample. In the event of suspected treatment-related SAEs, such as anaphylaxis or hypersensitivity, additional drug concentration and immunogenicity samples may be collected at or near the onset and the resolution of the event.

18. Blood samples for CH50 (efficacy endpoint) and AH50 will be obtained prior to any study treatment administration (pre-dose).

9.1.1.4. Table 4 Schedule of Events (Post-Treatment Safety Follow-Up Period)

1. Patient safety card: Site should review the instructions on the safety card with the patient at each visit. Replacement cards may be given to the patient as needed.
2. Daily oral antibiotic prophylaxis against *N. meningitidis* is recommended until 52 weeks after discontinuation of study treatment.

9.1.2. Early Termination Visit

During the OLTP (or intensified OLTP), patients who prematurely discontinue from study treatment who are withdrawn from the study will be asked to return to the clinic: once for an ET visit consisting of week 28 EOT assessments described in Table 1.

During the optional OLEP, patients who prematurely discontinue from study treatment who also withdraw from the study will be asked to return to the clinic once for an ET visit consisting of week 52e assessments described in Table 3.

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/uninterpretable laboratory results, for follow-up of AEs, to evaluate events of breakthrough hemolysis (Section 6.2), to provide intensified treatment (Section 8.3.2), or for any other reason, as warranted. In the event of suspected treatment-related SAEs, such as anaphylaxis or hypersensitivity, additional drug concentration and immunogenicity samples may be collected at or near the onset and the resolution of the event.

9.2. Study Procedures

9.2.1. Procedures Performed Only at the Screening Visit

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

- Informed consent (including optional sub-studies)
- Medical history, including disease characteristics
- Prior medications
- Demographics
- Height
- Documentation of meningococcal vaccination or revaccination (Section 8.2.1)

- Patient safety card for meningococcal infection (Section 8.2.2): This card will be provided to the patient at baseline. At subsequent visits, risk information will be reviewed and replacement cards may be given to the patient as needed.
- Sample to assess FSH (to determine postmenopausal status, if applicable; Section 7.2.2)
- Risk assessment for *N. gonorrhea* (Section 8.2.4)

Additionally, the following procedures may be performed for the parent study (R3918-PNH-1868):

- Titers to measure *N. meningitidis* (if required per parent study)
- Review patient diary for the parent study
- Other study procedures required per the parent study. Assessments that are common to both study protocols (R3918-PNH-1868 and R3918-PNH-2092) should not be duplicated during the screening visit for this study. Dosing for the parent study should be performed last, after all other screening and parent study visit procedures have been completed for both study protocols

Additional details about the timing and conduct of the screening visit is provided in Section 6.1.1. At the discretion of the investigator, additional visits during the screening period may be scheduled as needed to complete screening procedures. Patients may be rescreened up to 2 times after discussion between the investigator and the sponsor.

The day 1 dosing visit should occur 7 to 8 days after the last dose in the parent study.

9.2.2. Study Treatment

Study treatment administration is the last procedure at any visit and should be performed after all other study procedures for the visit have been completed, with the exception of any prespecified post-dose assessments or blood sample collection. Study drug supply will be managed through the IWRS as needed.

Study drugs will be administered starting from day 1 based on the patient's assigned dosing regimen. Details are described in Section 8.1.

It is recommended that patients begin daily oral antibiotic prophylaxis starting from day 1 (Section 8.2.3).

Starting from day 1, injection training may be provided to patients or caregivers if this option is available (Section 8.1). A patient diary will be provided to record study drug administration for patients who opt to self-administer. The diary will be reviewed at each visit for treatment compliance.

For patients who opt to continue study treatment in the OLEP, patients whose treatment was not intensified during the main study period will transition to the OLEP on a regimen of pozelimab 400 mg SC Q4W and cemdisiran 200 mg SC Q4W, regardless of their treatment assignment in the main treatment period. Patients whose treatment was intensified during the main study period will transition to the OLEP and continue on the intensified treatment regimen of pozelimab 400 mg SC Q2W and cemdisiran 200 mg SC Q4W.

Procedures related to study treatment are described in Table 1 (OLTP), Table 2 (patients on intensified treatment in OLTP), and Table 3 (optional OLEP).

9.2.3. Clinical Outcome Assessments

The following COAs are self-reported and will be completed by the patient at time points according to in Table 1 (OLTP) and Table 2 (patients on intensified treatment in OLTP), and Table 3 (optional OLEP).

9.2.3.1. Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)

The FACIT-Fatigue is a 13-item, self-administered COA assessing an individual's level of fatigue during their usual daily activities over the past week. This questionnaire is part of the FACIT measurement system, a compilation of questions measuring health-related QoL in patients with cancer and other chronic illnesses. The FACIT-Fatigue assesses the level of fatigue using a 5-point Likert scale ranging from 0 (not at all) to 4 (very much). Scores range from 0 to 52, with higher scores indicating a higher quality of life. Although the FACIT-Fatigue was originally developed to assess fatigue in patients with cancer, it has been used in trials evaluating the efficacy of eculizumab (Brodsky, 2008) (Hillmen, 2006). The FACIT-Fatigue has demonstrated content validity among patients with PNH (Weitz, 2013).

9.2.3.2. European Organization for the Research and Treatment of Cancer: Quality of Life of Cancer Patients Questionnaire-30 (EORTC-QLQ-C30)

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

9.2.3.3. Treatment Satisfaction Questionnaire for Medication (TSQM)

The TSQM is a generic measure that assesses patients' satisfaction with their medication (Atkinson, 2004) (Atkinson, 2005). The TSQM is an 9-question, self-administered COA measure which assesses 3 domains of satisfaction: effectiveness (3 items), convenience (3 items), and global satisfaction (3 items). For each question, the patient rates his/her satisfaction either on a 7-point Likert scale (ranging from extremely dissatisfied to extremely satisfied) or a 5-point Likert scale (ranging from extremely dissatisfied to not dissatisfied at all), with higher scores representing greater satisfaction. The instrument was developed using patient input and has evidence of psychometric validity.

9.2.3.4. PNH Symptom-Specific Questionnaire

The PNH symptom-specific questionnaire is self-administered and will collect daily information on PNH symptoms including: fatigue, shortness of breath, muscle weakness, headache, abdominal pain, pain in back/legs, chest discomfort, difficulty sleeping, difficulty thinking clearly, and difficulty swallowing. The instrument was developed by conducting a literature review, consulting with clinical expert input, and through patient interviews assessing comprehensiveness of symptoms collected and the patient's ability to read, understand, and respond to the questionnaire. The questionnaire was developed in accordance with regulatory guidelines (FDA, 2009) and scientific best practices (Patrick, 2011).

Patients should try to complete the PNH symptom specific questionnaire at the same time each day whenever possible.

9.2.3.5. Patient Global Impression of Severity (PGIS)/Patient Global Impression of Change (PGIC)

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

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

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

9.2.4. Safety and Anthropometric Procedures

9.2.4.1. Body Weight

Body weight will be assessed at time points specified in Table 1 (OLTP) and Table 2 (patients on intensified treatment in OLTP), Table 3 (optional OLEP). Patients should void (empty bladder) prior to weight assessment. Patients should be wearing undergarments or very light clothing and no shoes during weight assessments. If possible, the same type/model of scale should be used throughout the study.

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 (OLTP), Table 2 (patients on intensified treatment in OLTP), Table 3 (optional OLEP), and Table 4 (safety follow-up period).

Vital signs will be obtained after patient has been in the sitting position quietly for at least approximately 5 minutes.

9.2.4.3. Physical Examination

A physical examination will be performed at time points according to Table 1 (OLTP), Table 2 (patients on intensified treatment in OLTP),Table 3 (optional OLEP), and Table 4 (safety follow-up period). 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.

9.2.4.4. Electrocardiogram

Electrocardiograms should be performed before blood is drawn during visits requiring blood draws. A standard 12-lead ECG will be performed at time points according to Table 1 (OLTP), Table 2 (patients on intensified treatment in OLTP), and Table 3 (optional OLEP).

Twelve-lead ECGs will be systematically recorded after the patient has been in the semi-recumbent position for at least 10 minutes.

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.

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

9.2.4.5. Blood Transfusion

Transfusions with RBCs during the study should proceed according to the predefined criteria in Section 6.3. Any blood transfusion will be captured in the transfusion record CRF at every visit according to Table 1 (OLTP), Table 2 (patients on intensified treatment in OLTP),Table 3 (optional OLEP), and Table 4 (safety follow-up period). Hemoglobin levels pre- and post-transfusion will be obtained (including local values).

9.2.4.6. Safety Monitoring

At every visit, AEs will be collected and assessed as described in Section 10. Unscheduled visits may be scheduled to collect blood samples as part of safety monitoring (Section 9.1.3).

In addition, at each visit during the OLTP (Table 1) or intensified treatment period in the OLTP (Table 3) or OLEP (Table 2), changes to concomitant medications or procedures will be recorded (Section 8.8).

During the safety follow-up period, AEs and events of pregnancy will be monitored. Other safety assessments for the follow-up period (eg, vital signs, physical examination, concomitant medications, and laboratory evaluation) are described in Table 4.

9.2.5. Laboratory Testing

9.2.5.1. Laboratory Assessments of Efficacy

9.2.5.1.1. Lactate Dehydrogenase

Samples for LDH testing are collected as part of the blood chemistry panel (Section 9.2.5.2) and will be collected prior to dosing of the combination at visits according to Table 1 (OLTP), Table 2 (patients on intensified treatment in OLTP), and Table 3 (optional OLEP).

Care must be taken with the collection of LDH as it is the primary endpoint in the study. During blood collection, the same methodology should be applied across all visits, as best as possible. **Every precaution should be taken to avoid hemolysis. The coagulation blood must always be collected before the chemistry panel blood sample.** Detailed instructions are provided in the study-related documents provided to the study site and should be reviewed prior to each collection.

9.2.5.1.2. Hemoglobin

Samples for hemoglobin testing are collected as part of the hematology panel (Section 9.2.5.2) and will be collected prior to dosing of the combination at visits according to Table 1 (OLTP), Table 2 (patients on intensified treatment in OLTP), Table 3 (optional OLEP).

9.2.5.1.3. CH50

Samples for CH50 testing will be collected prior to dosing of the combination at visits according to Table 1 (OLTP), Table 2 (patients on intensified treatment in OLTP), and Table 3 (optional OLEP).

9.2.5.2. Safety and Other Laboratory Assessments

Samples for laboratory testing will be collected at visits according to Table 1 (OLTP), Table 2 (patients on intensified treatment in OLTP), Table 3 (optional OLEP), and Table 4 (safety follow-up period). The coagulation blood sample (tube) must always be collected first, followed by the blood chemistry sample (tube).

Hematology, chemistry (except total C5, CH50 and sC5b-9), and urinalysis are planned to be analyzed by a central laboratory. Local laboratory may be acceptable in special circumstances (eg, for eligibility) after discussion and agreement from the sponsor. Pregnancy testing may be performed at a central or a local laboratory. Other testing will be done by a central or specialized laboratory as outlined in the laboratory manual. Tests will include:

Coagulation Panel

Prothrombin time

Activated partial thromboplastin time (APTT)

Blood Chemistry

Sodium	Total protein, serum	Bilirubin*
Potassium	Creatinine**	Uric acid
Chloride	Blood urea nitrogen/blood urea	C-reactive protein (CRP)
Carbon dioxide/bicarbonate	Aspartate aminotransferase (AST)	Magnesium
Calcium	Alanine aminotransferase (ALT)	
Glucose	Alkaline phosphatase	
Albumin	Lactate dehydrogenase (LDH)	

* Obtain total, direct and indirect bilirubin

** In addition, the estimated glomerular filtration rate will be calculated with the CKD-EPI equation (Levey, 2009)

Hematology

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

Urinalysis

pH	Protein	Leukocyte esterase	Urobilinogen
Specific gravity	Glucose	Nitrite	
Ketones	Bilirubin	Blood	

Note: If macroscopy (urine dipstick) is abnormal, urine microscopy will be performed. A urine culture should be performed if there is a clinical suspicion of infection, per investigator judgment.

Other Laboratory Tests

Other laboratory tests include:

- Screening samples collected for the determination of eligibility (Section 9.2.1)
- Immunoglobulin G (IgG) will be assessed at the timepoints specified in the schedule of events (Section 9.1)
- Pregnancy testing (WOCBP only): serum human chorionic gonadotrophin pregnancy testing, urine pregnancy testing. Any positive urine pregnancy test will be confirmed with a serum test.
  Note: 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.
- Unscheduled blood collection for drug hypersensitivity events including suspicion of an AE potentially due to large drug-target-drug (DTD) immune complexes. At minimum to include: complete blood count (CBC), erythrocyte sedimentation rate

(ESR), chemistry, complement component 3 (C3), complement component 4 (C4), drug concentration, ADA (against pozelimab), and urinalysis (including microscopic evaluation).

- Unscheduled blood collection for suspected breakthrough hemolysis events should include, at a minimum, CBC, reticulocyte count, chemistry, coagulation parameters, D-dimer, total C5, CH50, ADA (against pozelimab), and drug concentrations of pozelimab, as applicable.
- Measurements of drug concentration (Section 9.2.6)
- Immunogenicity measurements (Section 9.2.7)
- Pharmacodynamic and exploratory biomarkers (Section 9.2.8)
- Optional: Future research and pharmacogenomics (Section 9.2.9 and Section 9.2.10)

Abnormal Laboratory Values and Laboratory Adverse Events

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

Significantly abnormal test results or uninterpretable samples that occur after start of treatment should 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.

9.2.6. Blood Collection for Drug Concentrations

9.2.6.1. Concentrations of Total Pozelimab and Total C5

Samples to measure the concentration of total pozelimab and total C5 will be collected prior to any study drug administration at time points specified in Table 1 (OLTP) and Table 2 (patients on intensified treatment in OLTP), and Table 3 (optional OLEP). For patients who require intensified treatment, samples for total pozelimab and total C5 will also be collected within 15 minutes post-infusion on day 1r.

Detailed instructions for blood sample collection are in the laboratory manual.

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

9.2.6.2. Concentrations of Cemdisiran and Cemdisiran Metabolites

Samples to measure the concentration of cemdisiran and cemdisiran metabolites will be collected at time points specified in Table 1 (OLTP), Table 2 (patients on intensified treatment in OLTP), and Table 3 (optional OLEP). At each time point, blood samples will be collected prior to any SC study drug administration and 2 to 6 hours after study drug administration. Detailed instructions for blood sample collection are in the laboratory manual.

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

9.2.7. Immunogenicity Measurements and Samples

Samples for ADA assessment will be collected separately for pozelimab and for cemdisiran at time points listed in Table 1 (OLTP), Table 2 (patients on intensified treatment in OLTP), and Table 3 (optional OLEP).

Samples that are positive in the pozelimab ADA assay may be banked for the analysis of NAb, until the pozelimab NAb assay is available. Samples will not be analyzed for anti-cemdisiran neutralizing activity. Detailed instructions for blood sample collection are in the laboratory manual.

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

9.2.8. Pharmacodynamic and Exploratory Biomarker Procedures

Samples for biomarkers will be collected at time points specified in Table 1 (OLTP), Table 2 (patients on intensified treatment in OLTP), and Table 3 (optional OLEP). Detailed instructions for blood sample collection are in the laboratory manual. Biomarker variables are described in Section 5.6 and include:

- CH50 (serum)
- Parameters of intravascular hemolysis: ie, haptoglobin, reticulocyte count, and bilirubin
- Free hemoglobin
- AH50 (serum)
- Complement activation markers: ie, sC5b-C9
- PNH clone size: ie, PNH erythrocytes and granulocytes

Biomarker measurements will be performed in specified matrix to determine effects of pozelimab and cemdisiran on relevant physiological and pathogenic processes. The list may be altered or expanded, as it is recognized that more relevant or novel biomarkers may be discovered during the process of this study. The biomarkers studied will be ones believed to be relevant to the pathophysiology of PNH, target engagement, mechanism of action, and possible toxicities.

Any unused or leftover samples, collected for any purpose from this study, may be kept for up to 15 years after study completion (or for a shorter period of time if required per local regulations) for use in exploratory research related to pathophysiology of PNH and related diseases, target engagement, mechanism of action for pozelimab or cemdisiran, and possible toxicities.

Biomarker results will be reported separately from the CSR, unless biomarker measurements are included in primary or secondary objectives.

9.2.9. Future Biomedical Research (Optional)

Patients who agree to participate in the future biomedical research (FBR) sub-study will be required to consent to this optional sub-study before samples are banked for FBR. Additional

samples will be collected for FBR at time points according to Table 1 (treatment period) and Table 3 (optional OLEP). Residual biomarker samples for study-related research, as well as unused drug concentration and immunogenicity samples, will be stored for up to 15 years after the final date of the database lock (or for a shorter time period if required per regional laws and regulations). The samples may be utilized for FBR that may or may not be directly related to the study, including being used as reference samples and assay development or validation. The results of these future biomedical research analyses will not be presented in the CSR.

9.2.10. Pharmacogenomic Analysis (Optional)

Patients who agree to participate in the genomics sub-study will be required to consent to this optional sub-study before collection of the samples. Whole blood samples for DNA extraction should be collected on day 1/baseline (predose), but can be collected at a later study visit (note: patients who had consented to DNA testing in R3918-PNH-1852 or R3918-PNH-1868 and had provided a DNA sample for analysis do not need to provide separate consent/sample for this study, but consent/sample collection will be needed for the RNA analysis). Whole blood samples for RNA extraction will be collected at time points according to Table 1 (treatment period) and Table 3 (optional OLEP). DNA and RNA samples will be collected for pharmacogenomics analyses to understand the genetic determinants of safety and efficacy associated with the treatments in this study and the molecular basis of PNH and related diseases. 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 (or for a shorter time period if required per regional laws and regulations). If there are specific site or country requirements involving the pharmacogenomic analyses which the sponsor is unable to comply with, samples will not be collected at those sites.

The purpose of the pharmacogenomic analyses is to identify genomic associations with clinical or biomarker response to pozelimab and/or cemdisiran, other PNH clinical outcome measures and possible AEs. In addition, associations between genomic variants and prognosis or progression of PNH as well as 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, and transcriptome sequencing (or other methods for quantitating RNA expression) 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 adverse events occurring during the study data collection, from the time of signing the ICF to the end of study. Medical conditions that existed or were diagnosed prior to the signing of the ICF will be recorded as part of medical history. Abnormal laboratory values and vital signs observed at the time of ICF 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 drugs 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, 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 (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 study) 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 10.1.3.

10.1.2. 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.

10.1.3. 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**.
- **Selected AESIs** (serious and nonserious)**:** Adverse events of special interest for this study include the following:
  - Moderate or severe hypersensitivity reactions potentially related to study treatment
  - Moderate or severe infusion reactions due to study treatment administration
  - Suspected *Neisseria* infection
  - MAVE: Includes thrombophlebitis/deep vein thrombosis, pulmonary embolus, myocardial infarction, unstable angina, renal vein or artery thrombosis, acute peripheral vascular occlusion, hepatic vein thrombosis, portal vein thrombosis mesenteric/visceral vein thrombosis or infarction, mesenteric/visceral arterial thrombosis or infarction, transient ischemic attack, cerebral arterial occlusion/cerebrovascular accident, cerebral venous occlusion, gangrene (nontraumatic; non-diabetic), amputation (nontraumatic; non-diabetic)
  - Liver transaminase elevations as evidenced by 1 or more of the following criteria:
    - ALT or AST > 8× ULN, or
    - ALT or AST >5× ULN for >2 weeks, or
    - ALT or AST >3× ULN and total bilirubin >2× ULN (or INR >1.5)

  Note: This AESI must be reported to Sponsor within 24 hours once the investigator confirms the abnormal laboratory value.

- **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 patient during the study or within 52 weeks of the last dose of study drug. Any complication of pregnancy affecting a female 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.
- **Symptomatic overdose**: Accidental or intentional overdose of at least 2 times the intended dose of study drug within the intended therapeutic window, if associated with an AE.

10.1.4. Other Adverse Events of Special Interest that do not Require Expedited Reporting to Sponsor

Although these AESIs do not require expedited reporting to sponsor, the following events are of interest and will involve the collection of additional details in separate CRFs:

- ISR due to study treatment administration
- Mild infusion reactions due to study treatment administration
- Mild hypersensitivity reactions due to study treatment administration

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 E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 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 a hospital admission (any duration) or an emergency room visit 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 are defined in Section 10.1.3 (AESIs requiring expedited reporting) and Section 10.1.4 (other AESIs).

10.2.4. Infusion Reactions

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

10.2.5. Severity

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

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

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

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

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

Infusion Reactions

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

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

Moderate: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, non-steroidal anti-inflammatory drugs [NSAIDs], narcotics, IV fluids); prophylactic medications indicated for ≤24 hours.

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

Injection Site Reactions

The severity of ISRs 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

10.2.6. Causality

The investigator must provide causality assessment as whether or not there is a reasonable possibility that the drug caused the adverse event, 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 state (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 state (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, Global Patient Safety; 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 contract research organization (CRO) will inform health authorities, Institutional Review Board (IRB)/Ethics Committee (EC), and the participating investigators of any Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring in other study centers or other studies of the active study drug (pozelimab and cemdisiran), as appropriate per local reporting requirements. In addition, the sponsor and/or CRO will comply with any additional local safety reporting requirements.

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

Event expectedness for study drug (pozelimab and cemdisiran) is assessed against the Reference Safety Information section of the IB that is effective for expedited safety reporting.

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

11. STATISTICAL PLAN

This section provides a high-level description of the planned analyses and will serve as the basis for the SAP for the study.

Endpoints are listed in Section 4. Analysis variables are listed in Section 5.

11.1. Statistical Hypothesis

No statistical hypothesis will be tested.

11.2. Justification of Sample Size

This study will be open to all patients who have enrolled in the Regeneron sponsored clinical study (R3918-PNH-1868) and plans to enroll approximately 24 patients with PNH.

Data from approximately 24 patients with PNH will be used to describe and explore the incidence and severity of TEAEs through week 28 of the OLTP.

11.3. Analysis Sets

11.3.1. Safety Analysis Sets

The safety analysis set (SAF) includes all randomized patients who received any amount of study drug; it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

The OLEP SAF includes all patients who participated in the OLEP who received any amount of study drug in the OLEP.

11.3.2. Efficacy Analysis Sets

The full analysis set (FAS) includes all randomized patients who received any amount of study drugs and have at least 1 post-baseline assessment; it is based on the treatment allocated (as randomized). Efficacy endpoints will be analyzed using the FAS.

The OLEP FAS includes all patients who participated in the OLEP who received any amount of study drug in the OLEP and have at least 1 post-baseline assessment in the OLEP.

11.3.3. Pharmacokinetic Analysis Sets

The PK analysis set includes all treated patients who received any amount of study drug (SAF) and who had a at least 1 non-missing analyte measurement following the first dose of study drug. The PK analysis set is based on the actual treatment received.

The OLEP PK analysis set includes all patients who participated in the OLEP who received any amount of study drug in the OLEP and who had at least 1 non-missing analyte measurement following the first dose of study drug in the OLEP.

11.3.4. Immunogenicity Analysis Sets

The ADA analysis set includes all treated patients who received any amount of study drug (SAF) and had at least 1 non-missing ADA result following the first study dose of study drug. The ADA

analysis set is based on the actual treatment received. Patients' baseline immunogenicity status for pozelimab will be determined from the initial treatment study.

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

The OLEP ADA analysis set includes all treated patients who participated in the OLEP who received any amount of study drug in the OLEP and had at least 1 non-missing ADA result following the first OLEP dose.

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

11.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, standard deviation, Q1, median, Q3, minimum, and maximum.

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

11.4.1. Patient Disposition

The following will be provided:

- The total number of screened patients: signed the main ICF
- The total number of randomized patients: received a randomization number
- The total number of patients who discontinued the study, and the reasons for discontinuation
- The total number of patients who discontinued from study treatment, and the reasons for discontinuation
- A listing of patients treated but not randomized, patients randomized but not treated, and patients randomized but not treated as randomized
- A listing of patients prematurely discontinued from treatment, along with reasons for discontinuation
- Total number of patients who received treatment intensification
- Total number of patients who continued into the OLEP

11.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group, and by all patients combined.

Baseline is defined as the last available value prior to study drug administration unless otherwise specified.

11.4.3. Efficacy Analyses

11.4.3.1. Secondary Efficacy Analysis

There are no primary efficacy endpoints in this study.

For secondary endpoints for the OLTP that are defined by the change or percent change from baseline to a time point in a variable, the analysis set will consist of all treated patients who have a non-missing baseline measurement of the variable. Means and 95% confidence intervals (CI) for the endpoints will be reported for both treatment arms and their difference.

These endpoints include:

- Percent change in LDH from pre-treatment (as defined by the mean LDH value at day -7 and day 1 [prior to combination dosing]) to EOT period (as defined by the mean value at week 24 and week 28 in the OLTP)
- Change in CH50 levels from baseline to week 28
- Change from baseline in concentration of total C5 assessed throughout the study
- Change in hemoglobin levels from baseline to week 28
- Change in FACIT-Fatigue from baseline to week 28
- Change from baseline to Week 28 in GHS and PF scores on the EORTC QLQ-C30

For the above secondary endpoints, the SAP will describe the multiple imputation approach.

For binary secondary endpoints, all treated patients will be analyzed. Proportions of patients meeting the criteria and 95% CIs by an exact method for the endpoints will be reported for both treatments and their difference:

- Proportion of patients who maintain adequate control of their hemolysis, defined as LDH $\leq 1.5 \times$ ULN from post-baseline (on day 1) through week 28 and from week 4 through week 28, inclusive (A patient will be treated as not maintaining adequate control of hemolysis if he/she is missing >25% of scheduled LDH measurements, missing any 2 consecutive LDH measurements, received intensified treatment, or permanently discontinued treatment. Patients with breakthrough hemolysis will be treated as non-responders. For other patients, control of hemolysis will be assessed by non-missing LDH measurements.)
- Proportion of patients with adequate control of hemolysis at each visit from post-baseline (on day 1) through week 28, inclusive
- Proportion of patients with normalization of LDH at each visit, defined as LDH $\leq 1.0 \times$ ULN from post-baseline (on day 1) through week 28, inclusive
- Proportion of patients with breakthrough hemolysis from baseline through week 28 (Non-responder imputation will be applied for patients who receive intensified treatment)

- Proportion of patients who achieve hemoglobin stabilization (defined as patients who do not receive a RBC transfusion and have no decrease in hemoglobin levels of ≥2 g/dL) from baseline through week 28
- Proportion of patients who are transfusion-free (defined as not requiring a RBC transfusion as per protocol algorithm) from baseline through week 28

For the rate and number of units of transfusion with RBCs from baseline through week 28, the analysis set will consist of all treated patients who never received intensified treatment. The rate of units of transfusion for a patient will be calculated based on the duration of treatment exposure of the patient. Means and 95% CIs by a one-sample t-statistic will be reported for both treatments and their difference.

For the AUC of LDH over time from baseline though week 28 and from week 4 through week 28, the analysis set will include all treated patients. First, missing values will be imputed using the multiple imputation approach described in the SAP. Then, the AUC will be computed using the complete set of LDH values. Mean AUC, 95% CIs, and other summary statistics will be provided for both treatment arms and their difference.

Secondary efficacy analysis for the optional OLEP will be performed using the same approach as described for corresponding analyses in the OLTP.

11.4.4. Control of Multiplicity

Not applicable

11.4.5. Safety Analysis

The primary endpoint in this study is the incidence and severity of TEAEs through week 28 of the OLTP.

11.4.5.1. Adverse Events

Definitions

For safety variables, 3 observation periods are defined:

- The pre-treatment period is defined as the time from signing the ICF to before the first dose of study drug for this study
- The on-treatment period is defined as the day from first dose of study drug to either:
  - the last dose of study drug in the OLTP (or intensified OLTP) for those not continuing in the OLEP plus 52 weeks, or
  - the last dose in the OLEP for those continuing in the OLEP plus 52 weeks
- The post-treatment period is defined as the time after the end of the on-treatment period

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

Analysis

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). Coding will be to lowest level terms. The 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 10.2.5), presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT
- Treatment-emergent AESIs (defined with a PT or a prespecified grouping)

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

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

11.4.5.2. Other Safety

Vital Signs

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

Laboratory Tests

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

Number and percentage of patients with a potentially clinically significant value (PCSV) at any post-randomization time point will be summarized for each clinical laboratory test for all patients and separately for patients in whom the PCSV criterion was normal or missing at baseline.

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

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

ECG

Electrocardiogram parameters (PR interval, QT interval, QTcF interval, QRS interval, and heart rate [from ventricular rate]) will be summarized by visit and change from baseline to each scheduled and collected assessment time.

Listings will be provided with flags indicating PCSVs.

11.4.5.3. Treatment Exposure

Treatment exposure (ie, defined as time on study drug) will be presented separately for pozelimab and cemdisiran.

The duration of study drug for a study period is calculated as:

> (Date of last administration of study drug - date of the first administration of study drug administration for the study period) + 1 day

Summaries (including the number of patients exposed, the duration of exposure, and the dose regimen to which patients were exposed) will be provided for pozelimab and for cemdisiran.

11.4.5.4. Treatment Compliance

Compliance with protocol-defined study drug dosing will be calculated as follows:

> Treatment compliance = (Number of study drug doses taken during treatment period) / (Number of study drug doses planned for the treatment period) × 100%

Separate summaries will be provided for pozelimab and cemdisiran.

11.4.6. Pharmacokinetics

11.4.6.1. Analysis of Drug Concentration Data

The concentrations of total pozelimab, total C5, cemdisiran, and cemdisiran metabolites over time and selected pharmacokinetic parameters will be summarized by descriptive statistics for each of the treatment groups.

No formal statistical hypothesis testing will be performed.

11.4.7. Analysis of Immunogenicity Data

Immunogenicity will be characterized by the ADA response, titer and NAb response observed:

- Pre-existing immunoreactivity, defined as a positive ADA assay response at baseline, with all post-dose ADA results negative, or a positive assay response at baseline, with all post-dose ADA assay responses less than 4-fold for anti-cemdisiran antibody assay or 9-fold for anti-pozelimab antibody assay over baseline titer levels
- Treatment-emergent ADA response, defined as any post-first dose positive ADA assay response when the baseline results are negative or missing
- Treatment-boosted ADA response, defined as any post-first dose positive ADA assay response that is 4-fold for anti-cemdisiran antibody assay or 9-fold for anti-pozelimab antibody assay over baseline titer levels when baseline is positive in the ADA assay
- Maximum ADA titer categories
  - Low (titer <1,000)
  - Moderate (1,000≤ titer ≤10,000)
  - High (titer >10,000)
- NAb status in the anti-pozelimab NAb assay, for samples that are positive in the pozelimab ADA assay

Listings of pre-existing, treatment-boosted, and treatment-emergent ADA responses, ADA titers, and NAb positivity presented by patient, time point, and cohort will be provided. Incidence of treatment-emergent ADA and NAb will be assessed as absolute occurrence (N) and percent of patients (%), grouped by cohort and ADA titer level.

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

11.4.8. Analysis of Pharmacodynamic and Exploratory Biomarker Data

Analysis of CH50 is described in Section 11.4.3.1. Analysis of other biomarker data is defined in the SAP. Unless specified as a secondary endpoint, the results of other biomarkers may not be presented in the CSR.

11.5. Timing of Statistical Analysis

A planned interim analysis may be conducted as described in Section 6.4.

The primary analysis will be conducted as soon as all patients have been randomized and all data through week 28 have been collected and validated; this will consist of the primary safety and secondary efficacy endpoints.

The OLEP analysis will be conducted when all data through week 52e of the OLEP have been collected and validated.

Additional safety data from the post-treatment safety follow-up period will be included in a subsequent analysis.

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 Regeneron (sponsor).

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

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

12.1.2. Electronic Systems

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

- IWRS system – randomization, study drug supply
- EDC system – Medidata Rave
- SAS – statistical review and analysis
- Pharmacovigilance safety database
- Clinical outcomes assessments

12.2. Study Monitoring

12.2.1. Monitoring of Study Sites

Regeneron uses a study-specific risk-based approach to study monitoring and oversight, aligned with risk based quality principles, outlined in ICH E6 (R2) Guideline for Good Clinical Practice. Risk-Based Quality Monitoring (RBQM) methodology focuses on employing a fit-for-purpose monitoring strategy, supported either directly by Regeneron as sponsor, or via our CRO partners. RBQM strategies include: reduced source data verification (SDV), targeted source data review (SDR), the use of off-site/remote and triggered on-site monitoring visits, and Centralized Monitoring to identify site level risks and study level trends. The investigator must allow study-related monitoring activities to occur.

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. 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 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 investigation 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.

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20. INVESTIGATOR'S AGREEMENT

I have read the attached protocol, "A Randomized, Open-label, Two-arm Study to Evaluate the Safety, Efficacy, and Pharmacodynamic Effects of Pozelimab and Cemdisiran Combination Treatment in Patients with Paroxysmal Nocturnal Hemoglobinuria Who Have Received Pozelimab Monotherapy", 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 Lead, and Biostatistician)

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

Study Title: A Randomized, Open-label, Two-arm Study to Evaluate the Safety, Efficacy, and Pharmacodynamic Effects of Pozelimab and Cemdisiran Combination Treatment in Patients with Paroxysmal Nocturnal Hemoglobinuria Who Have Received Pozelimab Monotherapy

Protocol Number: R3918-PNH-2092

Protocol Version: R3918-PNH-2092 Amendment 1

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 Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

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