NCT05131204
EudraCT 2020-002761-33
IND Number: 151173

Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A RANDOMIZED, OPEN-LABEL ECULIZUMAB AND RAVULIZUMAB CONTROLLED, NON-INFERIORITY STUDY TO EVALUATE THE EFFICACY AND SAFETY OF POZELIMAB AND CEMDISIRAN COMBINATION THERAPY IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA WHO ARE CURRENTLY TREATED WITH ECULIZUMAB OR RAVULIZUMAB

Compound:	Pozelimab (REGN3918) Cemdisiran (ALN-CC5)
Clinical Phase:	3
Protocol Number:	R3918-PNH-2022
Study Name:	ACCESS-2
Protocol Version:	R3918-PNH-2022 Amendment 1
Amendment 1 Date of Issue:	*See appended electronic signature page*
Original Date of Issue:	11 Aug 2021
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AMENDMENT HISTORY

Primary Rationale for Amendment 1

The main purpose for this amendment is to include new secondary endpoints and provide details on the planned analyses for the phase 3 development program.

Description of Change	Brief Rationale	Section # and Name
Added new endpoints on "maintenance of adequate control". Language is added to clarify the difference between the following endpoints relating to adequate control of LDH: • Maintenance of adequate control of hemolysis assesses the proportion of patients who consistently had an LDH ≤1.5xULN at each study visit during the analysis period • Adequate control of hemolysis presents the model-adjusted odds ratio of the proportion of patients meeting LDH criteria of ≤1.5 x ULN at each study visit specified in the analysis period	Additional clarification is provided to explain the differences in analysis methodology for these two endpoints pertaining to control of LDH.	Section 11.2 Justifications of Sample Size and Non-Inferiority Margins
Revised language to clarify how the analyses for the following key secondary endpoints will be performed: • Maintenance of adequate control of hemolysis, defined as LDH ≤1.5 × ULN from week 8 through week 36, inclusive • Transfusion avoidance after day 1 through week 36, inclusive (defined as not requiring a red blood cell [RBC] transfusion as per protocol algorithm based on hemoglobin values after day 1)	Changes are made to clarify how these analyses will be performed: • A patient's LDH is followed longitudinally to assess the maintenance of adequate control of hemolysis over time; this revised wording will also help distinguish this endpoint from a newly added secondary endpoint assessing adequacy of hemolysis control by visit. • For transfusion avoidance, patients who meet the protocol-defined transfusion criteria will be included in the analysis, regardless of whether a transfusion was administered.	Clinical Study Protocol Synopsis: Endpoints Section 4.1.2 Key Secondary Endpoints

Description of Change	Brief Rationale	Section # and Name
For endpoints on maintenance of adequate control of hemolysis, adequate control of hemolysis, and normalization of LDH: • Timeframe for key secondary analysis for these endpoints is revised to the period from week 8 to week 36 • Timeframe for the period from after day 1 to week 36 are retained as other secondary endpoints	The changes were made to prioritize the evaluation of efficacy to the period after the combination of pozelimab and cemdisiran has been introduced. The efficacy endpoints including the time period after the first introduction of cemdisiran, but prior to the introduction of the combination, have been reprioritized as other secondary endpoints.	Clinical Study Protocol Synopsis: Endpoints, Statistical Analysis Section 4.1.2 Key Secondary Endpoints Section 4.1.3 Other Secondary Endpoints Section 11.2 Justification of Sample Size and Non-Inferiority Margins
For the endpoint on breakthrough hemolysis: • Removed definition of breakthrough hemolysis from endpoint • Specified this endpoint will only be evaluated in patients with baseline LDH ≤1.5 x ULN	The first change reduces redundancy, as the definition of breakthrough hemolysis is provided in Section 6.3. Since an event of breakthrough hemolysis requires an increase in LDH after achievement of LDH ≤1.5 x ULN, patients entering the study without adequate control of LDH on eculizumab or ravulizumab (LDH >1.5 x ULN at baseline) may not achieve the required level of LDH control and therefore will not be susceptible to meet the criteria for breakthrough hemolysis. Limiting the endpoint analysis to those patients meeting an LDH threshold of ≤1.5 x ULN at baseline will ensure that there is a balance in the number of patients in each treatment group that may be susceptible to a breakthrough hemolysis event	Clinical Study Protocol Synopsis: Endpoints Section 4.1.2 Key Secondary Endpoints Section 4.1.3 Other Secondary Endpoints
Wording added describing how the non-inferiority margins for the endpoints of maintenance of adequate control of hemolysis and adequate control of hemolysis were derived	This change is needed to accommodate the addition of the endpoint of adequate control of hemolysis. Justification for the non-inferiority margin for the endpoint of maintenance of adequate control of hemolysis is also added	Section 11.1 Statistical Hypothesis Section 11.2 Justifications of Sample Size and Non-Inferiority Margins
Non-inferiority margins were recalculated for the endpoint of hemoglobin stabilization to improve the preservation of treatment effect to 50%	Per FDA Guidance on Non-Inferiority Trials (2016), 50% is the minimum recommended amount of benefit to be preserved in order to claim non-inferiority	Table 5: Summary of Data for Non-Inferiority Margin Calculations
Table 4 was updated to capture revisions to non-inferiority margin calculations for key secondary endpoints	Changes are made to correct errors in the prior version and to include calculations for all key secondary endpoints	Table 5 Summary of Data for Non-Inferiority Margin Calculations

Description of Change	Brief Rationale	Section # and Name
Wording added to describe the analysis method for the endpoint of normalization of LDH	As normalization of LDH is a secondary endpoint, a description of this analysis is added	Clinical Study Protocol Synopsis: Statistical Plan Section 11.4.3.2 Secondary Efficacy Analysis
Clarified the definition of baseline for LDH for patients taking eculizumab or ravulizumab at entry. In Sections 9.1.1.1 (footnote #2), 9.2.1, and 11.4.3, information regarding baseline is removed to reduce redundancy. For safety and other efficacy analyses, baseline is the last value of the assessment preceding the first study drug administration (note: the value must be on or before day 1).	Language was added to clarify that the baseline LDH is the pre-dose parameter. Given the different dose administration frequency of eculizumab and ravulizumab, the timing of these baseline assessments differs (ie, a pre-study drug administration value for patients taking eculizumab at entry and a screening value for patients taking ravulizumab at entry).	Section 6.1.1 Screening Period Section 6.3 Breakthrough Hemolysis Section 9.1.1.1 Table 1 Schedule of Events for the Open-Label Treatment Period, Footnote #2 Section 9.2.1 Procedures Performed Only at the Screening Period Section 11.4.3 Efficacy Analyses Section 11.4.5 Safety Analysis
Removed from the primary endpoint details regarding the definition of baseline	This change reduces redundancy in the protocol providing a common location for the definition of baseline.	Section 4.1 Primary and Secondary Endpoints Section 4.1.1 Primary Endpoint Section 6.3 Breakthrough Hemolysis
For the safety endpoint referenced below, specified that the time period of the analysis corresponds to 36 weeks, which is the duration of the open-label treatment period, instead of indicating more generically 'throughout the study' • Incidence and severity of treatment-emergent SAEs, TEAEs of special interest and TEAEs leading to treatment discontinuation over 36 weeks	This change clarifies the endpoint duration to be 36 weeks, which is the duration of the open label treatment period of the study	Section 4.1.3 Other Secondary Endpoints
Added new exploratory endpoint [redacted]	This new endpoint [redacted]	Section 4.1.4 Exploratory Endpoints

Description of Change	Brief Rationale	Section # and Name
Revised wording of endpoints to remove "proportion of patients" from the endpoint in order to present the endpoints in terms of patient-level metrics	This is a template change to revise endpoints to be patient-level metrics. The statistical metric to be presented as the outcome of the analysis will be described in the description of the analysis.	Clinical Study Protocol Synopsis: Endpoints Section 4.1.2 Key Secondary Endpoints Section 4.1.4 Exploratory Endpoints
Clarified that patients who are currently being treated with eculizumab or ravulizumab may be considered for this study Removed from eligibility criteria #3 language regarding the timing of the last administration of ravulizumab in the parent study (R3918-PNH-2021) prior to the entry into this study (R3918-PNH-2022).	This is a minor correction for clarification to ensure that patients are included only if treatment with eculizumab or ravulizumab is ongoing. Additional changes made to align with revisions to the last ravulizumab dose administration in the R3918-PNH-2021 study.	Section 7.2.1 Inclusion Criteria, #3
Revised exclusion criterion to clarify that patients will be excluded if they are receiving acute treatment such as platelet transfusions and granulocyte colony stimulating factors	Patients receiving these acute treatments are excluded because the effect of these treatments may confound the screening value upon which patient eligibility is based resulting in a screening value that might not be a true reflection of the patient's clinical status/bone marrow function	Section 7.2.2 Exclusion Criteria, #6
Modified exclusion criteria to provide alternative units for reticulocyte count	This change clarifies the reticulocyte count in units consistent with those reported by the central laboratory to facilitate appropriate assessment of patient eligibility by the study site	Section 7.2.2 Exclusion Criteria, #6.c
Modified exclusion to allow a subset of patients with human immunodeficiency virus (HIV) to participate in the study.	This change was requested by a health authority to allow patients with HIV to participate in the study if their condition would not put them at a greater risk of developing adverse events	Section 7.2.2 Exclusion Criteria, #13
Clarified the exclusion criterion on liver transaminase abnormalities to exclude patients with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) abnormalities that are elevated due to conditions unrelated to PNH or its complications	The exclusion criterion is revised to clarify that patients with abnormalities in liver transaminases related to Paroxysmal nocturnal hemoglobinuria (PNH) or its complications are not excluded	Section 7.2.2 Exclusion Criteria, #17
Added a sub-criterion to exclude patients who are ineligible for clinical trial participation due to local regulations.	This exclusion criterion accounts for protected populations that are ineligible for clinical trials per local regulations. This change is requested by an ethics committee for clarity.	Section 7.2.2 Exclusion Criteria, #26.e

Description of Change	Brief Rationale	Section # and Name
In the list of highly effective contraceptive measures, added "tubal ligation or tubal occlusion". Clarified that regnancy testing and contraception are required for women of childbearing potential but not required for women who are post-menopausal or permanently sterile.	This is a template update. Tubal ligation is a permanent and irreversible contraceptive method; however, neither are considered sterilization. Therefore, women with bilateral tubal ligation or tubal occlusion will require pregnancy testing.	Section 7.2.2 Exclusion Criteria, #29.c Section 9.2.4.7 Laboratory Testing
Added exclusion criterion to exclude patients who are non-responsive to eculizumab or ravulizumab.	Patients who are non-responsive to eculizumab or ravulizumab would not be appropriate for this study, as they may be randomized to continue a treatment that has been shown to be ineffective for their condition. Patients with C5 polymorphisms non-responsive to eculizumab or ravulizumab will be evaluated in a separate study.	Section 7.2.2 Exclusion Criteria, #30 Section 9.1.1.1 Footnotes for Table 1, Schedule of Events for the Open-Label Treatment Period, #4
Added exclusion criterion for patients with hemoglobin ≤7 g/dL. The exclusion criterion clarifies that patients are allowed to receive a blood transfusion during the screening period and are eligible if a repeat hemoglobin test is >7 g/dL prior to randomization.	This change is made to minimize a patient entering the study meeting the criteria for a blood transfusion at the outset and to facilitate the determination of endpoint achievement for transfusion avoidance	Section 7.2.2 Exclusion Criteria, #31
Clarified in the primary objective and hypothesis that patients will be switching from eculizumab or ravulizumab therapy to the pozelimab/cemdisiran combination treatment.	This change is requested by an ethics committee for clarity.	Clinical Study Protocol Synopsis: Objectives Section 2.1 Primary Objective Section 3.1 Hypothesis
Modified the text in the rationale for dose selection section to indicate that the PK/PD modeling that was performed to support the dose rationale [redacted]	This is a correction. [redacted]	Section 3.2.2 Rationale for Dose Selection
Added clarification that patients who discontinue study treatment (including those who complete the study but decline to participate in the next study) will proceed to the follow-up period. For study diagram, added clarification that the transition period is for patients who plan to enroll into the extension study.	These changes clarify the intended next steps for patients who discontinue study drug and those who complete the open-label treatment period.	Section 6.1 Study Description and Duration Figure 1 Study Diagram Section 6.1.4 Post-Open-Label Treatment Period (Post-OLTP)

Description of Change	Brief Rationale	Section # and Name
Provide guidance regarding the timing of screening visit 1, visit 2e/2r, and day 1. • For patients taking eculizumab, screening visit 1 should be scheduled on the day of or the day prior to an eculizumab dose and visit 2e should be scheduled when all information are available to assess eligibility. Day 1 should be scheduled on or up to 2 days prior to an eculizumab dose. Last dose of eculizumab will be at day 15 (week 2) visit • For patients taking ravulizumab, screening visit 1 should be scheduled about 6 weeks after the last administered ravulizumab dose and visit 2r should be scheduled on the day of or up to 2 days before the patient's next scheduled ravulizumab dose. Day 1 should be scheduled 26 to 28 days after the last ravulizumab dose at visit 2r.	Language is revised for emphasis/clarity, to ensure that sites are aware of the timing of drug administration relative to treatment visits.	Clinical Study Protocol Synopsis: Study Design Section 6.1.1 Screening Period Section 6.1.3 Open-Label Treatment Period (OLTP) Section 9.1.1.1 Table 1 Schedule of Events for the Open-Label Treatment Period, footnote #2, #3, #36 Section 9.2.1 Procedures Performed Only at the Screening Period
Moved language [redacted] from Section 6.1.1 to Sections 7.2 and 8.5.	This is a reorganization. Text was originally located in Section 6.1.1 and moved to Sections 7.2 and 8.5 for clarity. There is no change to the enrollment process or sample size.	Clinical Study Protocol Synopsis: Study Design, Population Section 6.1.1 Screening Period Section 7.2 Study Population Section 8.5 Method of Treatment Assignment
Revised the wording of stratification factors to be based on the time of randomization. Removed details regarding stratification from Sections 6.1.2 and 7.2 to reduce redundancy.	Because randomization occurs on day 1, there is no change to study conduct. This change clarifies that patients are stratified at the time of randomization.	Section 6.1.1 Randomization Section 11.4.2 Demography and Baseline Characteristics
Included language regarding the timing of screening visits for patients who plan to enroll into the next clinical study.	This change provides guidance for patients who are near completion of this study to initiate the screening process for the next study.	Section 6.1.4 Post-Open-Label Treatment Period (Post-OLTP) Section 9.1.1.1 Table 1 Schedule of Events for the Open-Label Treatment Period, footnote #1
Added study stopping rules, in which the independent data monitoring committee will review unblinded data on a regular basis and may recommend changes in study conduct including halting the study	This change addresses a comment from a health authority to include study stopping rules	Section 6.1.5 Study Stopping Rules [new]

Description of Change	Brief Rationale	Section # and Name
For the transfusion algorithm, clarified that transfusions may be performed as clinically indicated. However, to meet the endpoint criteria for the evaluation of blood transfusion, patients with hemoglobin >7 to ≤9 g/dL should have onset of new or worsening signs/symptoms of anemia *after day 1*.	This change was made to ensure that a patient that is counted as a non-responder for transfusion avoidance has experienced a change in clinical status and is not receiving a transfusion on the basis of a hemoglobin value and symptoms that remain unchanged from baseline.	Section 6.4 Transfusion Algorithm
Clarified that enrollment will continue until approximately 140 patients have been randomized and received at least 1 dose of study treatment.	The revised language assures that sufficient data from treated patients will be collected for the statistical analysis. There is no change to the study sample size.	Clinical Study Protocol Synopsis: Study Design, Population Section 7.1 Number of Patients Planned Section 8.5 Method of Treatment Assignment
Clarified that study treatment refers only to the investigational medicinal products (ie, pozelimab, cemdisiran, eculizumab, and ravulizumab) provided for use in this study.	This change is to differentiate study drug provided for use in this study from the patient's standard of care treatment (eculizumab or ravulizumab) that they receive.	Section 8.1 Investigational and Reference Treatments Table 1 Schedule of Events for the Open-Label Treatment Period
Clarified that eculizumab and ravulizumab will be provided by the study sponsor but may be sourced locally by the study site in exceptional circumstances	This update clarifies that eculizumab and ravulizumab will be provided by the study sponsor but allows the flexibility of local sourcing by sites.	Section 8.1.3 Eculizumab Section 8.1.4 Ravulizumab
Added citations to the approved prescribing information for eculizumab and ravulizumab (such as the summary of product characteristics)	This provides additional reference information for the comparator drugs used in this study.	Section 8.1.3 Eculizumab Section 8.1.4 Ravulizumab
Added language to clarify that no interaction is expected between antibiotic prophylaxis and cemdisiran or pozelimab.	This change aligns with language from other studies in the pozelimab/ cemdisiran combination program.	Section 8.2.4 Oral Antibiotics for Meningococcal Infection
Added language to clarify that investigators should use their clinical judgment when resuming study treatment after a temporary discontinuation and encourages investigators to discuss with the Sponsor's medical monitor.	The study medical monitor should be involved upon resumption of the study treatment after a period of treatment interruption [redacted]	Section 8.3.2.2 Reasons for Temporary Discontinuation of Study Drug

Description of Change	Brief Rationale	Section # and Name
Suggested that vaccination against COVID-19 may be given 2 to 3 weeks after a dose of pozelimab/cemdisiran or ravulizumab, or up to 1 week after administration of eculizumab.	This change clarifies the suggested timing of COVID-19 vaccination for patients on eculizumab, which is dosed every 2 weeks.	Section 8.8.2 Permitted Medications and Procedures
Added a timepoint to review inclusion/exclusion criteria at screening visit 2.	This change allows patients to be excluded earlier if they do not meet the eligibility requirements for this study.	Table 1 Schedule of Events for the Open-Label Treatment Period
• Separate Tables were included to describe the transition from eculizumab or ravulizumab to the combination of pozelimab and cemdisiran for patients participating in the follow-up open label extension study (R3918-PNH-2050). – New Table 2 to describe the transition period for patients included in the eculizumab arm – New Table 3 to describe the transition period for patients included in the ravulizumab arm • Added monthly urine pregnancy testing at week 8t during the transition period for ravulizumab arm (Table 3)	The original table describing the transition period is separated into two individual tables for patients in the eculizumab arm or the ravulizumab arm for clarity. Monthly pregnancy testing was clarified to address a comment from a health authority.	Table 2 Schedule of Events for the Transition Period: Patients on Eculizumab in OLTP who Plan to Enroll in the OLE Table 3 Schedule of Events for the Transition Period: Patients on Ravulizumab in OLTP who Plan to Enroll in the OLE
Renumbered visits in the safety follow up period to start at follow-up visit 1 (rather than follow-up visit 0) for consistency with other study periods.	This is a minor change for alignment with the visit numbering system for other study periods.	Table 4 Schedule of Events for the Safety Off-Treatment Follow-up Period Section 9.1.4.1 Table 4 Schedule of Events for the Safety Off-Treatment Follow-up Period, footnote #1 , #2

Description of Change	Brief Rationale	Section # and Name
• Added D-dimer as part of coagulation panel for laboratory analysis as well as for any suspected drug hypersensitivity event • Added drug concentration and anti-pozelimab antibodies assessments in the event of a suspected drug hypersensitivity or a suspected event of breakthrough hemolysis • Added magnesium as an analyte to blood chemistry to monitor electrolytes per request from a health authority • Added immunogenicity sample (anti-pozelimab antibodies) as part of laboratory analysis for any suspected breakthrough hemolysis event • Added urobilinogen to list of analytes for urinalysis and noted when to perform macroscopy, microscopy, and urine culture • Clarified the assessments to be performed for bilirubin	These changes clarify details regarding sample collection.	Section 6.2 Large Drug-Target-Drug Immune Complexes Section 9.1.1.1 Table 1 Schedule of Events for the Open-Label Treatment Period, Footnote #23, #31 Section 9.1.2.1 Table 2 Schedule of Events for the Transition Period: Patients on Eculizumab in OLTP who Plan to Enroll in the OLE, Footnote #8 Section 9.2.4.7 Laboratory Testing
For Open label treatment period (OLTP, Table 1): • Added time points for D-dimer • Added time points for immunoglobulin G in order to assess protein catabolism • Reorganized the collection of samples for drug concentration, ADA, and total C5 to separate the schedule by treatment arm. For transition period (Table 2): • Removed anti-drug antibody (ADA) time points from the transition period • Updated the time points for total C5 • Reorganized the collection of samples for drug concentration, ADA, and total C5 to separate the schedule by treatment arm.	These changes describe updates made to sample collection.	Table 1 Schedule of Events for the Open-Label Treatment Period Table 2 Schedule of Events for the Transition Period: Patients on Eculizumab in OLTP who Plan to Enroll in the OLE Section 9.1.2.1 Table 2 Schedule of Events for the Transition Period: Patients on Eculizumab in OLTP who Plan to Enroll in the OLE, Footnote #14 [removed] Section 9.2.4.7 Laboratory Testing

Description of Change	Brief Rationale	Section # and Name
Removed specification that C5 mutation (if needed during study) must be performed by a local laboratory. This test may also be done by a central laboratory.	This change allows flexibility for C5 mutation testing to be performed by a central laboratory.	Section 9.1.1.1 Footnotes for Table 1, Schedule of Events for the Open-Label Treatment Period, #4
Included in the schedule of events the labs that are required to be conducted for patients taking ravulizumab prior to the dose of ravulizumab at week -4 (visit 2r). Removed information about baseline laboratory assessments from Section 9.2.1 and Section 9.1.1.1 (footnote #16) because the timing and details for these assessments are incorporated into Table 1.	This change was added to clarify that for patients taking ravulizumab, laboratory samples are to be collected at visit 2r (week -4, the day of or prior to ravulizumab dosing), to ensure that pre-dose assessments are obtained before randomization.	Table 1 Schedule of Events for the Open-Label Treatment Period Section 9.1.1.1 Table 1 Schedule of Events for the Open-Label Treatment Period, footnote #16 Section 9.2.1 Procedures Performed Only at the Screening Period
Added footnote in schedule of events to clarify additional sampling: • Added footnote to collect samples at week 36 visit to assess ADA in patients randomized to the pozelimab/cemdisiran combination arm as well as patients randomized to the standard-of-care arm who will be continuing in the transition period • Sample for the measurement of concentrations of cemdisiran and its metabolites will be collected at the week 36 visit only for patients who are receiving eculizumab treatment and willing to continue in the transition period and into the open-label extension (OLE)	This change clarifies additional sampling that is needed	Table 1 Schedule of Events for the Open-Label Treatment Period Section 9.1.1.1 Table 1 Schedule of Events for the Open-Label Treatment Period, Footnote #32 [new], #33 [new]
Revised language to ask that an LDH assessment be repeated if it is ≥2 × ULN in association with a potassium ≥6 mmol/L.	This change provides guidance on when laboratory assessments may need to be repeated.	Section 9.1.1.1 Table 1 Schedule of Events for the Open-Label Treatment Period, Footnote #24
Added footnote to clarify that a dose is only given at week 36 to patients who plan to continue into the OLE study.	This change clarifies the requirements for receiving study drug at week 36.	Section 9.1.1.1 Table 1 Schedule of Events for the Open-Label Treatment Period, Footnote #37

Description of Change	Brief Rationale	Section # and Name
Added the following screening procedures to align with changes to the schedule of events: • Added a bullet for a blood sample to measure titers for *Neisseria meningitidis* if required by local practice/regulations (this procedure is described in the schedule of events and was inadvertently omitted in this section) •	These changes are made to align with the schedule of events.	Section 9.2.1 Procedures Performed Only at the Screening Period
Clarified that electronic devices for recording patient-reported questionnaires during the study will be provided to the patients at Screening Visit 2e or 2r (instead of Screening Visit 2).	This is a minor clarification to align with the schedule of events since Screening Visit 2 was separated into 2 visits, one for patients taking eculizumab at entry and one for patients taking ravulizumab at entry.	Section 9.2.1 Procedures Performed Only at the Screening Period Section 9.2.3 Clinical Outcome Assessments
Removed language indicating that laboratory samples will be obtained in countries where sample collection and export are permitted.	This change allows the collection of laboratory samples even in countries where export of samples is not permitted. This provides flexibility for the samples to be collected and analyzed locally.	Section 9.2.4.7 Laboratory Testing Section 9.2.5.1 Concentrations of Total Pozelimab, Total Eculizumab, Total Ravulizumab and Total C5 Section 9.2.5.2 Concentrations of Cemdisiran and Cemdisiran Metabolites Section 9.2.6 Immunogenicity Measurements and Samples Section 9.2.7 Pharmacodynamic Biomarker Procedures
Added procedure for distribution of a patient safety brochure for participants randomized to the standard-of-care arm (for eculizumab or ravulizumab, respectively) and provision of prescriber safety brochures to all investigators	As part of the commitment to centrally source eculizumab and ravulizumab, provision of the patient safety brochure is required for all patients randomized to receive standard-of-care treatment. Prescriber safety brochures for eculizumab and ravulizumab will also be provided to investigators	Section 6.1.3 Open-Label Treatment Period (OLTP) Section 8.1.3 Eculizumab Section 8.1.4 Ravulizumab Section 8.2.3 Monitoring for Meningococcal Infection Table 1 Schedule of Events for the Open-Label Treatment Period Section 9.2.1 Procedures Performed Only at the Screening Period Section 9.2.4.6 Safety Monitoring
Removed language related to Risk Evaluation and Mitigation Strategy (REMS) for eculizumab and ravulizumab	REMS is related to post-marketing use and is not applicable for clinical trials. Risk mitigation strategies for this study are described in the protocol Section 3.3	Section 6.1.1 Screening Period

Description of Change	Brief Rationale	Section # and Name
Removed fasting requirement for blood chemistry sample	This change reduces study complexity as the results of the endpoints should not be impacted in a meaningful way by fasting status	Section 9.2.4.7 Laboratory Testing
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 (FACIT-Fatigue)
Removed the collection of pregnancy data for the female partner of a male patient from protocol	This is an error. The collection of safety data for the pregnant partner of a male study patient is not needed given that the study does not require male contraception	Section 10.1.3 Events that Require Expedited Reporting to Sponsor
Added details on metrics that will be collected for patient disposition	Changes are made to provide additional details and to align with the analysis plan	Section 11.3.1 Patient Disposition
Updated descriptions of analysis sets to provide additional details	This change provides additional details regarding analysis sets defined in the study	Section 11.3.1 Full Analysis Set Section 11.3.2 Safety Analysis Set Section 11.3.3 Pharmacokinetic Analysis Set Section 11.3.4 Immunogenicity Analysis Set Section 11.3.5 Per-Protocol Set Section 11.3.6 Biomarker Endpoint Analysis Set [new]
Revisions were made to align the description of the efficacy analysis with the planned approach. The statistical analysis plan is referenced for additional details	Brief descriptions of the analyses are included for endpoints, with full details planned for the analysis plan	Section 11.4.3.1 Primary Efficacy Analysis Section 11.4.3.2 Secondary Efficacy Analysis
Removed details regarding the control of multiplicity. The statistical analysis plan is referenced for additional details	This change reduces the level of detail on the control of multiplicity. A robust description will be provided in the analysis plan	Section 11.4.4 Control of Multiplicity
Provided additional details on safety analysis	This change describes additional tabular summaries planned as part of the safety analysis	Section 11.4.5 Safety Analysis Section 11.4.5.1 Adverse Events
• Removed description of study duration from section on Study Design and to include the follow-up period in the Study Duration section for completeness • Included a description of the pozelimab ■ mg/kg IV dose in the Treatment section to align with the regimen for the transition period	These are editorial changes to align the synopsis with the protocol body and to avoid repetition of details that are presented elsewhere in the synopsis	Clinical Study Protocol Synopsis: Study Design, Study Duration, Treatments

Description of Change	Brief Rationale	Section # and Name
Removed program-level details that are provided in the investigator's brochure	This change removes details that are already provided in the investigator's brochure to avoid repetition and the potential for discrepancy	Section 1 Introduction
Removed "total" in reference to drug concentration for cemdisiran	This is a correction. The mechanism of action of cemdisiran is not by binding, and hence there is no free and bound or total cemdisiran.	Throughout document
Updated name of the global principal investigator	This is an administrative update	Clinical Study Protocol Synopsis: Principal Investigator
Included "non-inferiority" in the study title.	This change addresses a request from a health authority	Title page Clinical Study Protocol Synopsis: Title Section 20 Investigator's Agreement Signature of Sponsor's Responsible Officers
Added study name	ACCESS-2 is the official study name	Title page
Editorial and formatting changes	These are minor changes including clarifications, corrections, reorganization, and template updates	Throughout document

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
[redacted]	[redacted]
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BW	Body weight
C3	Complement component 3
C5	Complement factor 5
CBC	Complete blood count
C9	Complement component 9
CH50	Complement hemolytic activity
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
DTD	Drug-target-drug
Dxt	Day x of transition period
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EOS	End of study
EOT	End-of-treatment
EORTC-QLQ-C30	European organization for research and treatment of cancer quality-of-Life questionnaire core 30 items
EOS	End of study
[redacted]	[redacted]
EU	European Union
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full analysis set
FBR	Future biomedical research
FDA	U.S. Food and Drug Administration

FIH	First-in-human
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GHS	Global health status
GPI	Glycophosphatidylinositol
HCP	Health care provider
HRQoL	Health-related quality of life
HSC	Hematopoietic stem cell
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent data monitoring committee
IgG4P	Immunoglobulin G4P
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
LTBI	Latent tuberculosis infection
mAbs	Monoclonal antibodies
MAC	Membrane-attack complex
MAVE	Major adverse vascular events
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
mRNA	Messenger ribonucleic acid
NAb	Neutralizing antibody
NIM	Non-Inferiority Margin
NSAIDs	Non-steroidal anti-inflammatory drugs
OLE	Open-label extension
OLTP	Open label treatment period
PCSV	Potentially clinically significant value
PD	Pharmacodynamic
PF	Physical function
[redacted]	[redacted]
[redacted]	[redacted]
PIGA	Phosphatidylinositol glycan anchor
PK	Pharmacokinetic

PNH	Paroxysmal nocturnal hemoglobinuria
PPS	Per-protocol set
PRO	Patient-reported outcomes
PT	Preferred Term
Q2W	Every 2 weeks
Q4W	Every 4 weeks
Q8W	Every 8 weeks
QoL	Quality of life
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
RBQM	Risk-Based Quality Monitoring
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous
SD	Standard deviation
siRNA	Small interfering ribonucleic acid
SOC	System organ class
Spp	Species
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
[redacted]	[redacted]
ULN	Upper Limit of Normal
US	United States
Vxt	Visit x of transition period
WBC	White blood cell
WOCBP	Women of childbearing potential

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Randomized, Open-Label, Eculizumab and Ravulizumab Controlled, Non-Inferiority Study to Evaluate the Efficacy and Safety of Pozelimab and Cemdisiran Combination Therapy in Patients with Paroxysmal Nocturnal Hemoglobinuria Who are Currently Treated with Eculizumab or Ravulizumab
Site Location(s)	Globally at multiple sites.
Principal Investigator	Morag Griffin, MBChB, FRCPath
Objectives	The primary objective of the study is: • To evaluate the effect on hemolysis, as assessed by lactate dehydrogenase (LDH), of pozelimab and cemdisiran combination therapy after 36 weeks of treatment in Paroxysmal Nocturnal Hemoglobinuria (PNH) patients who switch from eculizumab or ravulizumab therapy to the combination treatment versus patients who continue their eculizumab or ravulizumab therapy. The secondary objectives of the study are to: • Evaluate the effect of pozelimab and cemdisiran combination treatment versus anti-complement factor 5 (C5) standard-of-care treatment (eculizumab or ravulizumab) on the following: – Transfusion requirements and transfusion parameters – Measures of hemolysis: LDH control, breakthrough hemolysis, and inhibition of complement hemolytic activity (CH50) – Hemoglobin levels – Fatigue as assessed by clinical outcome assessments (COAs) – Health-related quality of life (HRQoL) as assessed by COAs – Safety and tolerability • To assess the concentrations of total pozelimab and either total eculizumab or total ravulizumab in serum and cemdisiran and total C5 protein in plasma • To assess the immunogenicity of pozelimab and cemdisiran
Study Design	This study is a randomized, open-label, eculizumab and ravulizumab-controlled, non-inferiority study. The study plans to enroll patients with PNH who are currently treated with either eculizumab or ravulizumab at the labeled posology. **Screening Period (up to 6 weeks)** The first screening visit should take place up to 6 weeks prior to day 1. Screening visit 1 should be scheduled based on the patient's eculizumab or ravulizumab dosing regimen prior to the study. For patients taking eculizumab at screening: • Screening visit 1 should be scheduled on the day of or the day prior to an eculizumab dose and may take place up to 6 weeks prior to day 1. • At visit 2e, patients will be provided with an eCOA device to take home. • Day 1 shall be scheduled on the day of or up to 2 days prior to the patient's scheduled eculizumab administration. For patients taking ravulizumab at screening:

- Screening visit 1 should be scheduled ~6 weeks after a ravulizumab dose
- Visit 2r should be scheduled on the day of or up to 2 days prior to the patient's next scheduled ravulizumab dose. This will be the last non-study ravulizumab dose. Additional laboratory samples (including for baseline LDH assessment) will be taken at this visit and eCOA device will be provided to the patient to take home.
- The day 1 visit should be scheduled 26 to 28 days after the last administration of ravulizumab at visit 2r.

Additional interim screening visit(s) may take place as needed.

Due to the risk of *Neisseria meningitidis* infection, patients will require administration of meningococcal vaccination(s) in accordance with the local eculizumab or ravulizumab prescribing information (where applicable) and in accordance with current national vaccination guidelines for vaccination use with complement inhibitors or local practice and at the very least, within a period of 5 years prior to screening.

In addition to *Neisseria meningitidis* infection, fatal or serious infections with *Neisseria gonorrhea* have been reported in patients taking complement inhibitor therapy. Patients should therefore undergo a risk assessment and counseling regarding the potential risk of *Neisseria gonorrhea* as per local practice or national guidelines.

Patients who have not been vaccinated against *Streptococcus pneumoniae* and *Haemophilus influenzae* type B may receive these vaccinations during the screening period or on the day of randomization based on investigator discretion and taking into consideration the available national guidelines.

Patients will be assessed for active or latent tuberculosis (TB) infection based on local practice or applicable guidelines.

Open-Label Treatment Period (OLTP, 36 weeks)

On day 1, after all baseline assessments have been performed, eligible patients will be randomized in a 1:1 ratio to continue their current anti-C5 standard-of-care (eculizumab or ravulizumab, as applicable) or switch to treatment with pozelimab and cemdisiran. The treatment period is 36 weeks. Treatment administration is based on a patient's PNH treatment prior to screening as well as their treatment assignment and is described in the section on Treatments below.

After the first administration with the study drugs, subsequent administrations may be continued by the site personnel or a healthcare professional at the patient's home (if possible and approved by the sponsor) or additionally, for the combination of pozelimab and cemdisiran, administered by the patient or designated person, at the patient's preferred location (in which case, the patient shall be contacted by the study site to ensure study drug administration, as planned).

Patients should be closely monitored for infusion reactions, potential drug-target-drug complexes, and early signs and symptoms of meningococcal infection. Patients should be evaluated immediately if an infection is suspected. Consideration should be given to the use of antimicrobial prophylaxis for meningococcal infection, to be initiated at the start of the study treatment and continued for the duration of the study, unless the risks outweigh the benefits, or such use is inconsistent with local practice. In this study, antibiotic use will be at the discretion of the investigator.

Assessments for the primary analysis will be completed at week 36.

	Post-OLTP Patients who complete the OLTP will be offered the opportunity to enroll in another study, a follow-on OLE study. For patients who complete the 36-week OLTP on the pozelimab and cemdisiran arm, the transition of treatment from the current study to the OLE study is planned to be uninterrupted, whereby the day 1 visit of the OLE will correspond to the end-of-treatment (EOT) period/end of study (EOS) visit (week 36) in the current study. Patients who complete the 36-week OLTP on the anti-C5 standard-of-care arm and plan to participate in the OLE study will undergo a transition period in order to switch to cemdisiran and pozelimab combination treatment in the same manner as those switching to the combination at study initiation. Patients who discontinue treatment as well as patients who decline enrollment into the follow-on study of the OLE will undergo a safety off-treatment follow up period of up to 52 weeks. Patients discontinuing the combination treatment should be treated in accordance with local standards of care while continuing to be monitored in the 52-week off-treatment safety follow-up period. Investigators switching patients from the combination treatment to another anti-C5 mAb should have a heightened awareness for possible adverse events resulting from the formation of large DTD immune complexes.
Study Duration	The duration of the study including the screening period (up to 6 weeks), and the OLTP period (36 weeks) may be up to 42 weeks. Patients who complete the 36-week OLTP on the anti-C5 standard-of-care arm and plan to participate in the OLE study will undergo a transition to switch to cemdisiran and pozelimab combination treatment in the same manner as those switching to the combination at study initiation. Patients who discontinue study treatment as well as patients who decline enrollment into the OLE study will undergo a safety off-treatment follow-up period of up to 52 weeks.
End of Study Definition	The EOS is defined as the date the last patient completes the last study visit, withdraws from the study, or is lost to follow-up (ie, the study patient can no longer be contacted by the investigator).
Population	The study will consist of adult male and female patients with a confirmed diagnosis of PNH currently being treated at the labeled dose regimen with either eculizumab for the past 12 weeks or ravulizumab for at least 24 weeks with any level of LDH control.
Sample Size:	Enrollment will continue until approximately 140 patients have been randomized and received at least 1 dose of study treatment. Patients will be randomized in a 1:1 ratio to the combination arm (pozelimab and cemdisiran) or continue their anti-C5 standard-of-care therapy with either eculizumab 900 mg intravenous (IV) or IV ravulizumab. Randomization will be stratified based on screening visit LDH, history of RBC/whole blood transfusion in the past year, and anti-C5 standard-of-care therapy at screening. Enrollment of patients who have a screening visit LDH level >1.5 × Upper Limit of Normal (ULN) [redacted]
Target Population:	Eligible patients will consist of adult male and female patients with a confirmed diagnosis of PNH who are currently treated with either eculizumab or ravulizumab at the labeled dose for the past 12 or 24 weeks, respectively.

Treatments	Study treatment refers only to drugs (pozelimab, cemdisiran, eculizumab, and ravulizumab) provided for use in this study.
Study Drug (eculizumab at screening)	**Pozelimab + cemdisiran arm (patients on eculizumab at screening)**
Dose/Route/Schedule:	[redacted]
Study Drug (ravulizumab at screening)	**Pozelimab + cemdisiran arm (patients on ravulizumab at screening)**
Dose/Route/Schedule:	[redacted]
Reference Drug (eculizumab at screening)	Eculizumab
Dose/Route/Schedule:	Eculizumab 900 mg IV every 2 weeks (Q2W)
Reference Drug (ravulizumab at screening)	Ravulizumab
Dose/Route/Schedule:	Ravulizumab IV every 8 weeks (Q8W) per labeled weight-based dosage
Endpoints	
Primary:	The primary endpoint is the percent change in LDH from baseline to EOT period at week 36 (day 253)
Key Secondary:	The key secondary endpoints are: • Transfusion avoidance after day 1 through week 36, inclusive (defined as not requiring an RBC transfusion as per protocol algorithm based on hemoglobin values after day 1)

	• Breakthrough hemolysis, in patients with a baseline LDH ≤1.5 × ULN, after day 1 through week 36, inclusive • Hemoglobin stabilization (defined as patients who do not receive an RBC transfusion and have no decrease in hemoglobin level from baseline of ≥2 g/dL) after day 1 through week 36, inclusive • Maintenance of adequate control of hemolysis, defined as LDH ≤1.5 × ULN from week 8 through week 36, inclusive • Adequate control of hemolysis (defined as LDH ≤1.5 × ULN) from week 8 through week 36, inclusive • Normalization of LDH (defined as LDH ≤ 1.0 × ULN) from week 8 through week 36, inclusive • Change in fatigue as measured by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT)-Fatigue Scale from baseline to week 36 • Change in physical function (PF) score on the European organization for research and treatment of cancer quality-of-Life questionnaire core 30 items (EORTC QLQ-C30) from baseline to week 36 • Change in global health status (GHS)/QoL scale score on the EORTC QLQ-C30 from baseline to week 36
Other Secondary:	Other secondary endpoints are: • Transfusion avoidance from week 4 through week 36, inclusive (defined as not requiring an RBC transfusion as per protocol algorithm based on hemoglobin values after day 1) • Breakthrough hemolysis, in patients with a baseline LDH ≤1.5× ULN, from week 4 through week 36, inclusive • Hemoglobin stabilization (defined as patients who do not receive an RBC transfusion and have no decrease in hemoglobin level from baseline of ≥2 g/dL) from week 4 through week 36, inclusive • Maintenance of adequate control of LDH, defined as LDH ≤1.5 × ULN after day 1 through week 36, inclusive • Adequate control of hemolysis (defined as LDH ≤1.5 × ULN) after day 1 through week 36, inclusive • Normalization of LDH (defined as LDH ≤1.0 × ULN) after day 1 through week 36, inclusive • Rate and number of units of RBCs transfused per protocol algorithm after day 1 through week 36, and from week 4 through week 36 • Change in hemoglobin levels from baseline to week 36 • Incidence and severity of treatment-emergent serious adverse events (SAEs), treatment-emergent adverse events (TEAEs) of special interest and TEAEs leading to treatment discontinuation over 36 weeks • Change and percent change in total CH50 from baseline to week 36 • Concentration of total C5 in plasma assessed throughout the study • Concentrations of total pozelimab in serum assessed throughout the study • Concentrations of cemdisiran in plasma assessed throughout the study • Concentrations of total eculizumab or ravulizumab in serum assessed throughout the study

	• Incidence of treatment emergent anti-drug antibodies (ADAs) to pozelimab assessed throughout the study • Incidence of treatment emergent ADAs to cemdisiran assessed throughout the study
Procedures and Assessments	Efficacy assessments include laboratory evaluations of LDH and hemoglobin, as well as blood transfusions. Efficacy as measured by certain COAs including FACIT-Fatigue and EORTC-QLQ-C30. 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). Adverse events and concomitant medications and procedures will be monitored throughout the study. Other procedures include collection of blood samples for the measurement of drug concentrations, biomarkers, immunogenicity, and exploratory assessments. In addition, an exploratory research serum and plasma sample should be collected. Patients may participate in up to 2 optional sub-studies: for future biomedical research and for pharmacogenomic analysis.
Statistical Plan	**Justification of the Sample Size** The primary endpoint is percent change from baseline to EOT period (week 36) in LDH. [redacted]

[redacted]

1. INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is a chronic, progressive, life-threatening, and rare multisystem disease. It is characterized by uncontrolled complement activation on red blood cells (RBCs), resulting in intravascular hemolysis (Sahin, 2016), and on white blood cells (WBCs) and platelets, resulting in an increased risk of thrombosis. The estimated incidence of PNH is 1.3 cases per million individuals per year, and the estimated prevalence is 15.9 cases per million individuals (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 and that becomes numerous enough so that the effects of its mutation are symptomatic. The PIGA gene product is required for the biosynthesis of the glycophosphatidylinositol (GPI) anchor, a glycolipid moiety that attaches dozens of proteins to the plasma membrane of cells. Consequently, the PNH stem cell and all of its progeny have a reduction or absence of GPI-anchored proteins. The mature blood cells derived from the hematopoietic clone can have a complete deficiency (type III) or a partial deficiency (type II) of GPI-linked proteins (Hillmen, 2004). Two of the proteins that are affected by the absence of GPI anchors are CD55 and CD59, complement regulatory proteins. CD55 regulates complement activation by inhibiting complement component 3 (C3) convertases, whereas CD59 inhibits the assembly of the membrane-attack complex (MAC) C5b–complement component 9 (C9) by interacting with complement component 8 (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. Symptoms of PNH include, abdominal pain, dysphagia, erectile dysfunction. Longer term complications include chronic kidney disease and pulmonary hypertension (Hillmen, 2006). Thromboembolism is the most common cause of mortality in patients with PNH and accounts for approximately 40% to 67% of attributable deaths. Potential mechanisms for thromboembolism include platelet activation, toxicity of free hemoglobin, nitric oxide depletion, absence of other GPI-linked proteins, and endothelial dysfunction (Hill, 2013). PNH usually arises on the background of bone marrow dysfunction (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). In this manner, the PNH clone becomes predominant.

An accepted definition of active disease is lactate dehydrogenase (LDH) ≥1.5 × upper limit of normal (ULN) in 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 (Almeida, 2017). Alternatively, activity can be established by a history of RBC transfusion due to PNH within 3 months.

Eculizumab and Ravulizumab

The benefit of blocking complement factor 5 (C5) complement activity in PNH has been clearly established by eculizumab (Soliris® Eculizumab (Prescribing information)) and ravulizumab (Ultomiris® (Prescribing information)), (Kulasekararaj, 2019) (Lee, 2019) which are humanized monoclonal antibodies directed against C5. Their effectiveness has been evidenced by reduction

of LDH levels and transfusion requirements. In addition, long-term data in eculizumab treated patients have shown a reduction in the need for blood transfusion, decrease in the incidence of thrombosis, improvement in anemia, quality of life (QoL), and survival (Hillmen, 2004), (Griffin, 2017) (Hillmen, 2007) (Hillmen, 2013) (Brodsky, 2008). Eculizumab is approved for use in complement-mediated serious ultra-rare conditions (prevalence of 1 to 5 per million), including PNH. Ravulizumab is modified from eculizumab to have 4 amino-acid substitutions that act to prolong its half-life (Kulasekararaj, 2019). Ravulizumab is also approved in PNH. While eculizumab has been demonstrated to be an effective therapy for these patients, it is administered by intravenous (IV) infusion every 2 weeks and has been described as being burdensome for patients and may negatively impact QoL (Groth, 2017). Also, 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. Up to 20% of patients on eculizumab therapy require significant increases in dose or dose frequency due to insufficient efficacy (Hill, 2013) (Nakayama, 2016) (Peffault de Latour, 2015). Twenty-five percent of patients still need recurrent, albeit less frequent, blood transfusions. The heterogeneity in these hematological responses may be related to underlying aplastic anemia, C3b-mediated extravascular hemolysis or incomplete pharmacologic blockade of C5 (Al-Ani, 2016). While the regulatory approval of ravulizumab (Ultomiris® (Prescribing information)) for PNH in the United States (US) in December 2018 and the European Union (EU) in July 2019 has improved convenience with an IV dosing frequency of every 8 weeks, patients still experience some hemolytic breakthrough. In head-to-head studies of ravulizumab versus eculizumab in both complement inhibitor naïve and complement inhibitor experienced PNH patients, ravulizumab was found to be non-inferior to eculizumab on all primary and key secondary endpoints. Demonstration of superiority was not achieved (Ultomiris® (Prescribing information)) (Lee, 2019) (Kulasekararaj, 2019). Additionally, 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 monoclonal antibodies (mAbs) (Nishimura, 2014). Although ravulizumab is not approved in many countries around the world, regulatory approval and utilization of ravulizumab is increasing over time.

Pozelimab

Pozelimab is a human monoclonal immunoglobulin G4P (IgG4P) 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 the MAC – C5b-9, a structure mediating cell lysis. Pozelimab can be administered by IV or subcutaneous (SC) administration. Additionally, pozelimab binds to polymorphic variations in C5 due to differences in binding sites compared to eculizumab and ravulizumab.

A phase 1 study in healthy volunteers evaluated single ascending IV and SC doses of up to 30 mg/kg and 600 mg, respectively, and a repeat dose regimen of pozelimab 400 mg SC weekly for 4 weeks preceded by a loading dose of 15 mg/kg one week before. Dose dependent inhibition of C5 as measured by complement hemolytic activity assay (CH50) was established and the repeat dosing regimen was shown to completely inhibit CH50 throughout the dosing period. A regimen of 30 mg/kg IV loading dose followed by 800 mg SC weekly was effective in a phase 2 study in complement treatment naïve patients with PNH (R3918-PNH-1852) at reducing serum LDH to <1.5 × ULN in all patients and <1.0 × ULN in most patients. However, the regimen 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 3600 mg IV Q8W for eculizumab and ravulizumab, respectively). The requirement for such high dosing is driven by 2 factors. First, the objective is to have sufficient coverage of participants with very high serum concentrations of C5 (80 µg/mL to 120 µg/mL) even during intercurrent illness such as infection. Second, it is necessary to have near 100% inhibition of C5 at all times to achieve the desired therapeutic effect in PNH (Peffault de Latour, 2015).

Study R3918-PNH-1852 in patients with PNH who are naïve to complement inhibitor therapy or have not recently received complement inhibitor therapy in the past 6 months has been completed. Patients received pozelimab as an IV loading dose of 30 mg/kg followed by weekly administration of 800 mg SC. 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 was 6.1 × ULN, hemoglobin was 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 study day 29 in all 17 patients, including a patient with a C5 variant known to be resistant to blockade by eculizumab/ravulizumab (Jang, 2020). LDH reduction was sustained <1.5 × ULN until study 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 (hemoglobin levels from a subset of 9 patients were available at the time of the analysis and used for the calculation). Following the pozelimab treatment, an improvement in the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) score (a 13-item, 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 was 100% as measured by CH50 and was sustained post pozelimab IV infusion on day 1 throughout day 183 (N=9).

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

Cemdisiran

Cemdisiran is a synthetic small interfering ribonucleic acid (siRNA) targeting C5 messenger ribonucleic acid (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. Complement factor 5 is encoded by a single gene and is expressed and secreted predominantly by hepatocytes. Through the ribonucleic acid (RNA) interference pathway, cemdisiran leads to the degradation of C5 mRNA by RNases, thereby reducing C5 protein production, leading to reduced levels of circulating C5 protein. In study ALN-CC5-001 (Badri, 2021) (Cemdisiran IB), 32 healthy volunteers were treated with single SC doses of cemdisiran ranging from 50 mg to 900 mg, 24 healthy volunteers were treated with multiple doses of cemdisiran ranging from 100 mg to 600 mg (dosing weekly, every other week or monthly), 6 patients with PNH were treated with cemdisiran at cumulative doses of 3200 mg to 4200 mg (eculizumab-naïve patients) and 1200 mg to 2400 mg (patients on background eculizumab treatment). A single dose of 600 mg cemdisiran achieved a C5 concentration of 12.3 ± 1.47 µg/mL by day 14 and nadir at 2.3 ± 0.76 µg/mL by day 56. The reduction in C5 protein was durable, with >90% knockdown of C5 beginning on day 21 and persisting through day 238. The relationship between C5 concentrations and complement activity is non-linear, such that, even with greater than 90% reduction in C5 levels, there is still incomplete inhibition of complement

activity and >90% suppression of C5 expression was not sufficient in achieving adequate reduction of LDH in PNH patients. Cemdisiran monotherapy in patients not receiving eculizumab was ineffective as a monotherapy treatment for PNH. However, patients with PNH who were receiving eculizumab were able to reduce their eculizumab dose and/or increase the interval between eculizumab doses while maintaining clinically meaningful inhibition of complement activity and LDH level control. These data support the efficacy and clinical utility of combining an siRNA and a mAb targeting C5 and lend support to the current study design.

Additional background information on cemdisiran and the development program can be found in the IB for cemdisiran.

Pozelimab/Cemdisiran Combination Treatment in Patients with PNH

By reducing the production of C5 with cemdisiran, the pharmacological goal of the pozelimab/cemdisiran combination therapy is to reduce concentration of active C5 in circulation to biologically inactive levels, while concurrently slowing the rate of pozelimab:C5 complex formation, thus allowing for an extended dosing interval at a lower pozelimab dose level. Pharmacokinetic/pharmacodynamic (PK/PD) modeling based on observed data from both pozelimab and cemdisiran first-in-human (FIH) studies in healthy subjects and patients with PNH who are naïve to anti-C5 treatment or on a background therapy of eculizumab suggests that by combining cemdisiran and pozelimab, the dose of both agents may be significantly reduced and the interval for SC dosing of pozelimab may be significantly increased from once weekly to every 4 weeks, while still maintaining desired C5 suppression.

The biologic mechanism that drives clinical efficacy of an anti-C5 therapy is the ability to completely and durably suppress the cell lytic activity of terminal portion of the complement pathway, the MAC. This biology is measured using the CH50 assay and other assays measuring complement pathway activity. The relationship of CH50, as a pharmacodynamic measure of active C5, with clinical efficacy has been demonstrated for pozelimab and for cemdisiran in patients with PNH. In separate studies of pozelimab and cemdisiran in active patients with PNH, clinical efficacy, as measured by reduction in LDH, a marker of hemolysis, correlated with reduction in CH50 or other complement activity assays. In the cemdisiran study, incomplete CH50 inhibition was associated with suboptimal LDH reduction. In the pozelimab study, complete CH50 inhibition was associated with optimal LDH reduction. Therefore, the CH50 assay can be reliably used to follow the degree of inhibition of the complement pathway and should translate into reduction in LDH which is a marker of hemolysis.

The combination treatment of cemdisiran and pozelimab is being developed in patients with PNH for the following reasons; 1) both drugs work via a complementary approach on a validated pathway with the possibility of complete inhibition of the pathway over a longer duration, which may translate into optimal efficacy in nearly all patients and anticipated better control of breakthrough hemolysis, 2) cemdisiran is insufficient to treat PNH as monotherapy, 3) pozelimab was effective as monotherapy in treatment of PNH in a Phase 2 study, however, the weekly higher volume injection regimen was considered potentially burdensome, 4) the pozelimab and cemdisiran combination therapy will address significant unmet needs for patients by providing a self-administered Q4W dosing regimen for patients who require chronic long-term treatment, 5) efficacy is expected in patients with polymorphic variant C5 protein (eg, p.Arg885His and p.Arg885Cys) for which eculizumab and presumably ravulizumab are ineffective 6) the combination therapy may be associated with an improved safety profile for adverse events (AEs)

related to injection site reactions as the combination is expected to allow for a lower volume and less frequent dosing of pozelimab compared to that associated with pozelimab monotherapy regimens required for the treatment of PNH, and 7) with respect to other safety events, the risk of C5 inhibition is shared by all anti-C5 agents. The pozelimab/cemdisiran combination is not expected to be associated with risks beyond that of the individual agents.

Ongoing Clinical Studies and Study Design

The combination of pozelimab and cemdisiran is being evaluated in the following phase 2 studies:

REGN-PNH-2092: 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 approximately 24 patients with PNH who had been receiving treatment with pozelimab monotherapy in study R3918-PNH-1868. Eligible patients will be randomized 1:1 to 1 of 2 dose regimens with the pozelimab and cemdisiran combination. Pozelimab [redacted] mg will be administered subcutaneously either every 4 weeks (Q4W) or Q2W in combination with cemdisiran [redacted] mg Q4W subcutaneously.

REGN-PNH-20105: A single-arm, open-label, 32-week study to evaluate the safety, efficacy, and PD effects of pozelimab and cemdisiran combination therapy in approximately 12 patients with PNH who are currently receiving eculizumab and who will be switched to pozelimab and cemdisiran combination therapy.

Additional background information on the combination of pozelimab and cemdisiran and the development program can be found in the respective IB.

This study is being performed to evaluate whether treatment with the combination of pozelimab and cemdisiran in patients who switch from eculizumab or ravulizumab treatment is non-inferior to continued treatment with anti-C5-standard-of-care therapy (eculizumab or ravulizumab) in the control of intravascular hemolysis, as assessed by the change in LDH over time.

This study is a randomized, eculizumab and ravulizumab controlled study with a 36-week open-label treatment period (OLTP). The choice of primary endpoint is an accepted, objective laboratory measure that reflects control of intravascular hemolysis (LDH). Key secondary endpoints were selected in order to evaluate stabilization of the patient's hemolysis over time (ie, transfusion avoidance, the avoidance of clinically important breakthrough hemolysis events, hemoglobin stabilization, measures of LDH control), as well as to evaluate changes in parameters central to the QoL of patients with PNH (ie, fatigue, physical function [PF] and other health-related quality of life [HRQoL] assessments).

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is:

- To evaluate the effect of pozelimab and cemdisiran combination therapy on hemolysis, as assessed by LDH, after 36 weeks of treatment, in patients with PNH who switch from eculizumab or ravulizumab therapy to the combination treatment versus patients who continue their eculizumab or ravulizumab therapy.

2.2. Secondary Objectives

The secondary objectives of the study are to:

- Evaluate the effect of pozelimab and cemdisiran combination treatment versus anti-C5 standard-of-care treatment (eculizumab or ravulizumab) on the following:
  - Transfusion requirements and transfusion parameters
  - Measures of hemolysis: LDH control, breakthrough hemolysis, and inhibition of CH50
  - Hemoglobin levels
  - Fatigue as assessed by Clinical Outcome Assessments (COAs)
  - HRQoL as assessed by COAs
  - Safety and tolerability
- To assess the concentrations of total pozelimab and either total eculizumab or total ravulizumab in serum and cemdisiran and total C5 protein in plasma
- To assess the immunogenicity of pozelimab and cemdisiran

2.3. Exploratory Objectives

The exploratory objectives of the study are:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]
- [redacted]

3. HYPOTHESIS AND RATIONALE

3.1. Hypothesis

The primary hypothesis is that PNH disease control as assessed by LDH after a 36-week treatment period with pozelimab and cemdisiran combination therapy in patients with PNH who switch from their current eculizumab or ravulizumab treatment to the combination treatment is not inferior to continued eculizumab or ravulizumab treatment.

3.2. Rationale

3.2.1. Rationale for Study Design

The study is a randomized, open-label, eculizumab and ravulizumab-controlled, non-inferiority study.

This study is open-label and thus patients and investigators will be aware of treatment allocation. The study is not blinded for patients and investigators, as it would require double-dummy administration which would lead to a large number of sham IV infusions to patients receiving pozelimab and cemdisiran combination along with sham IV and SC injections for patients assigned to the anti-C5 standard-of-care arm. An open-label design is deemed acceptable by the sponsor as the primary endpoint of the study is an objective laboratory-based parameter (ie, LDH) that is unlikely to be biased by knowledge of treatment assignment.

The use of eculizumab and ravulizumab as the two comparators is justified as these options are considered as standard-of-care treatment for PNH. As the trial will recruit patients who are currently being treated with either eculizumab or ravulizumab, a reasonable comparison is the continued use of their prior standard-of-care therapy (eculizumab or ravulizumab) versus pozelimab and cemdisiran combination therapy. It is believed that the combination of pozelimab and cemdisiran will have similar efficacy to eculizumab and ravulizumab in patients with PNH.

Rationale for Primary Objective and Primary Endpoints

The primary objective of this study is an assessment of the control of hemolysis, as measured by LDH, which is central to the clinical monitoring of PNH (Rother, 2005), including during eculizumab or ravulizumab therapy. An LDH of at least 1.5 × ULN along with related clinical symptoms is considered a criterion for diagnosis of PNH, and for treatment with complement inhibition (Sahin, 2016). Furthermore, reductions in LDH below the 1.5 × ULN threshold with complement inhibitor therapy have been shown to correlate with improvement in patient's symptoms, QoL measures, and transfusion requirements (Brodsky, 2008).

The primary endpoint is the percent change in LDH from baseline to end-of-treatment (EOT) period. Baseline and EOT LDH assessments will be performed at the end of dosing period for each treatment, ensuring a fair comparison across arms.

Lactate dehydrogenase (LDH), as a measure of hemolysis allows for an objective and precise means to gauge if the control in hemolysis with eculizumab and ravulizumab is sustained when patients switch to pozelimab and cemdisiran treatment. If anti-C5 therapy were to be discontinued, patients would experience a return of their manifestations of PNH prior to week 36. Thus, the absence of a clinically significant rise in LDH in patients switching from eculizumab or

ravulizumab to pozelimab and cemdisiran treatment supports the efficacy of the combination approach.

In the clinical trial of ravulizumab vs eculizumab in C5-inhibitor–experienced adult patients with PNH (Kulasekararaj, 2019), patients treated with eculizumab were either switched to ravulizumab or continued eculizumab. The percent change in LDH from baseline to week 26, the primary endpoint of the study, in the eculizumab arm was 8.4% relative to -0.8% in the ravulizumab arm (95% confidence interval [CI] for the difference, -0.42, 18.84).

Rationale for Treatment Duration

The study treatment duration of 36 weeks is considered sufficient to provide an adequate understanding of the efficacy and safety of pozelimab and cemdisiran. It is expected that by week 36, there will be no contribution of eculizumab or ravulizumab in pozelimab and cemdisiran combination treated patients towards efficacy on LDH based on the known dosing interval and half-lives of these drugs. By the EOT period, the effect on LDH in the pozelimab and cemdisiran combination arm will be due to the sole contribution of the combination maintenance regimen. The long-term safety and efficacy of pozelimab and cemdisiran combination therapy will be assessed by enrolling patients from this study into an open-label extension (OLE) study.

Rationale for Study Population

The study population includes patients with PNH currently being treated at the labeled dose regimen with either eculizumab for at least the prior 12 weeks or ravulizumab for at least the prior 24 weeks with any level of LDH control. Eculizumab and ravulizumab are both administered as an IV infusion. IV administration places a burden on the health care system as it requires administration in an infusion center or by a healthcare professional at the patient's home. Pozelimab and cemdisiran combination maintenance therapy is expected to remove the requirement for resource consuming visits to infusion centers or home nurse visits and time off for the patient from their work/school and away from their families. In addition, the inconvenience and interruptions associated with IV infusions may impact compliance, which is expected to be addressed with every 4 weeks self-administered pozelimab and cemdisiran combination therapy. Disruptions due to the coronavirus disease 2019 (COVID-19) pandemic and requirements from governments on travel restrictions, stay-at-home orders and maintaining social distancing can impact any infusion therapy such as eculizumab or ravulizumab administration whereas this impact would be minimized with self-administered pozelimab and cemdisiran combination therapy. These disruptions are particularly impactful in PNH where continuous inhibition of complement is important to avoid breakthrough hemolysis events. Additionally, the PK/PD profile of the combination is expected to provide advantages in dosing flexibility; a delayed dose is expected to have less negative clinical impact compared to patients treated with current anti-C5 standard-of-care. Intravenous (IV) access issues may be encountered with eculizumab or ravulizumab infusions making it difficult to complete its administration.

3.2.2. Rationale for Dose Selection

The dosage regimen of pozelimab/cemdisiran combination therapy in patients with PNH who switch from eculizumab or ravulizumab treatment is as follows:

Eculizumab switch to combination therapy:

- [redacted]
- [redacted]
- [redacted]

Ravulizumab switch to combination therapy:

- [redacted]
- [redacted]

The proposed dosage regimen was selected based on safety, efficacy, and PK/PD data from completed and on-going studies for each individual agent in healthy subjects and in patients with PNH. The primary objective of the chosen regimen is to ensure complete suppression of hemolysis after the initiation of the combination treatment and throughout the dosing intervals. More information regarding the results of the completed and on-going studies of pozelimab and cemdisiran is provided in the pozelimab IB and cemdisiran IB, respectively.

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 FIH data. PK/PD modeling of observed data from both pozelimab and cemdisiran FIH 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 durable with significantly lower doses of both agents and a longer dosing interval. [redacted]

Mitigation of Potential High Molecular Weight Complex Formation During Treatment Switch

While the overall goal of the proposed dosing regimen is to prevent hemolysis, the initiation of therapy is also designed to mitigate the potential for the formation of large drug-target-drug (DTD) immune complexes of eculizumab-C5-pozelimab or ravulizumab-C5-pozelimab during the treatment switch. [redacted] Refer to the Pozelimab IB and Cemdisiran IB for details.

[redacted]

3.3. Risk-Benefit

A risk-benefit statement with respect to the overall development program is provided in the IB for pozelimab and the IB for cemdisiran. The following sections describe potential risks and strategies for mitigation.

3.3.1. Risk Benefit for Eculizumab and Ravulizumab Active Comparators

Eculizumab and ravulizumab have been selected as the active comparators in this study as they are the current standard-of-care therapy in the treatment of adult patients with PNH. In countries where eculizumab and ravulizumab have been granted marketing authorization, the regulatory bodies have considered that the benefit of therapy has outweighed the risk for the indications granted. When left untreated, PNH is a life-threatening condition with a median survival time of 10 years from diagnosis (Hillmen, 1995). Long-term treatment with complement inhibition has demonstrated an improvement/normalization in survival with eculizumab (Kelly, 2011). While anticipated to behave similarly to eculizumab due to the same mechanism of action and structural similarities, longer term data for ravulizumab including its impact on survival is still unknown given that ravulizumab has only recently been granted marketing authorization (first approval 2018).

Since pozelimab shares the same mechanism of action as eculizumab and ravulizumab, the risk profile for these agents is expected to be similar, as outlined below.

The following sections describe potential risks and strategies for mitigation.

3.3.2. Potential Risk of *Neisseria* Infection

An established risk of blocking C5 complement activity with eculizumab or ravulizumab 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 (ie, pozelimab and cemdisiran) 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 C5.

Experience with eculizumab and ravulizumab suggests that pretreatment with appropriate vaccinations covering multiple serotypes is effective at substantially mitigating this risk (Hillmen, 2013) (McNamara, 2017) (NHS England, 2013) (Soliris® Eculizumab (Prescribing information)) (Ultomiris® (Prescribing information)). Concurrent therapy with oral antibiotics is also recommended. Current treatment guidelines for PNH and the eculizumab and ravulizumab package inserts 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 infections with 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 8.2.3), 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 8.2.4) 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* spp (other than *N. meningitidis*), including disseminated gonococcal infections, have been reported during eculizumab treatment (Soliris® Eculizumab (Prescribing information)). 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 8.2.5).

3.3.3. Liver Function Test Abnormalities

[redacted]

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. Patients who develop abnormalities in liver function tests should undergo additional investigations or consultation (Section 8.2.6). 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 8.3.2). These mitigation steps are considered sufficient to address this potential risk.

3.3.4. Infusion Reactions

[redacted] In the 13- and 26-week toxicology studies dosed up to 100 mg/kg/week in cynomolgus monkeys, no adverse effects were reported. Infusion reactions may occur with ravulizumab and eculizumab. In clinical trials, no patients experienced

infusion-related reactions requiring discontinuation of therapy. Additional details may be found in the IB for pozelimab and the respective prescribing information for eculizumab and ravulizumab.

3.3.5. Other Risks

Other risks are described under Safety Considerations in Section 6.1.3.

3.3.6. Study Conduct in Response to Coronavirus Disease 2019

Recognizing that the COVID-19 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.

For additional information related to the continuity of clinical study conduct and oversight during the COVID-19 pandemic, see Section 6.1.3.

For information regarding the permitted timing of COVID-19 vaccinations, see Section 8.8.2 Permitted Medications.

4. ENDPOINTS

4.1. Primary and Secondary Endpoints

The definition of baseline for efficacy variables is provided in Section 11.4.3.

4.1.1. Primary Endpoint

Percent change in LDH from baseline to EOT period at week 36 (day 253).

4.1.2. Key Secondary Endpoints

The key secondary endpoints are:

- Transfusion avoidance after day 1 through week 36, inclusive (defined as not requiring an RBC transfusion as per protocol algorithm based on hemoglobin values after day 1)
- Breakthrough hemolysis, in patients with a baseline LDH ≤ 1.5× ULN, after day 1 through week 36, inclusive
- Hemoglobin stabilization (defined as patients who do not receive an RBC transfusion and have no decrease in hemoglobin level from baseline of ≥2 g/dL) after day 1 through week 36, inclusive
- Maintenance of adequate control of hemolysis, defined as LDH ≤1.5 × ULN from week 8 through week 36, inclusive
- Adequate control of hemolysis (defined as LDH ≤1.5 × ULN) from week 8 through week 36, inclusive
- Normalization of LDH, defined as LDH ≤1.0 × ULN from week 8 through week 36, inclusive
- Change in fatigue as measured by the FACIT-Fatigue Scale from baseline to week 36
- Change in PF score on the EORTC-QLQ-C30 from baseline to week 36
- Change in global health status (GHS)/QoL scale score on the EORTC-QLQ-C30 from baseline to week 36

4.1.3. Other Secondary Endpoints

Other secondary endpoints are:

- Transfusion avoidance from week 4 through week 36, inclusive (defined as not requiring an RBC transfusion as per protocol algorithm based on hemoglobin values after day 1)
- Breakthrough hemolysis, in patients with a baseline LDH ≤1.5× ULN, from week 4 through week 36, inclusive
- Hemoglobin stabilization (defined as patients who do not receive an RBC transfusion and have no decrease in hemoglobin level from baseline of ≥2 g/dL) from week 4 through week 36, inclusive

- Maintenance of adequate control of hemolysis, defined as LDH ≤1.5 × ULN after day 1 through week 36, inclusive
- Adequate control of hemolysis (defined as LDH ≤1.5 × ULN) after day 1 through week 36, inclusive
- Normalization of LDH (defined as LDH ≤1.0 × ULN) after day 1 through week 36, inclusive
- Rate and number of units of RBCs transfused per protocol algorithm after day 1 through week 36, and from week 4 through week 36
- Change in hemoglobin levels from baseline to week 36
- Incidence and severity of treatment-emergent SAEs, TEAEs of special interest and TEAEs leading to treatment discontinuation over 36 weeks
- Change and percent change in total CH50 from baseline to week 36
- Concentration of total C5 in plasma assessed throughout the study
- Concentrations of total pozelimab in serum assessed throughout the study
- Concentrations of cemdisiran in plasma assessed throughout the study
- Concentrations of total eculizumab or ravulizumab in serum assessed throughout the study
- Incidence of treatment emergent anti-drug antibodies (ADAs) to pozelimab assessed throughout the study
- Incidence of treatment emergent ADAs to cemdisiran assessed over 36 weeks

4.1.4. Exploratory Endpoints

The exploratory endpoints are:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

5. STUDY VARIABLES

5.1. Demographic and Baseline Characteristics

Baseline characteristics will be collected and will include standard demography (eg, age, sex, race, ethnicity, weight, height, etc), disease characteristics, medical history, and medication history for each patient. 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 is required by certain regulatory agencies, such as the US Food and Drug Administration (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

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
- [redacted]
- [redacted]
- [redacted]

5.3. Safety Variables and Anthropometric Variables

Safety and anthropometric variables in this study include:

- Vaccination/revaccination for *Neisseria meningitidis*,
- Vaccination against *Streptococcus pneumoniae* and *Haemophilus influenzae* type B (if needed)

- Concomitant medications and procedures
- Height
- Body weight
- Vital Signs
- Physical Examination
- Electrocardiogram (ECG)
- AEs
- Breakthrough hemolysis assessment
- Routine safety laboratory tests (hematology, chemistry, coagulation parameters, direct antiglobulin test, urinalysis, and pregnancy testing [for women of childbearing potential or WOCBP])

5.4. Pharmacokinetic Variables

The PK variables are the concentrations of total pozelimab, total C5 (target), cemdisiran, cemdisiran metabolites, total eculizumab, total ravulizumab, 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 biomarker variables are:

- CH50 (an assay assessing the activity of the classical pathway of complement) will be used to measure C5 activity. This is the principal PD marker for the study.
- [redacted]
- [redacted]
- [redacted]
- [redacted]

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

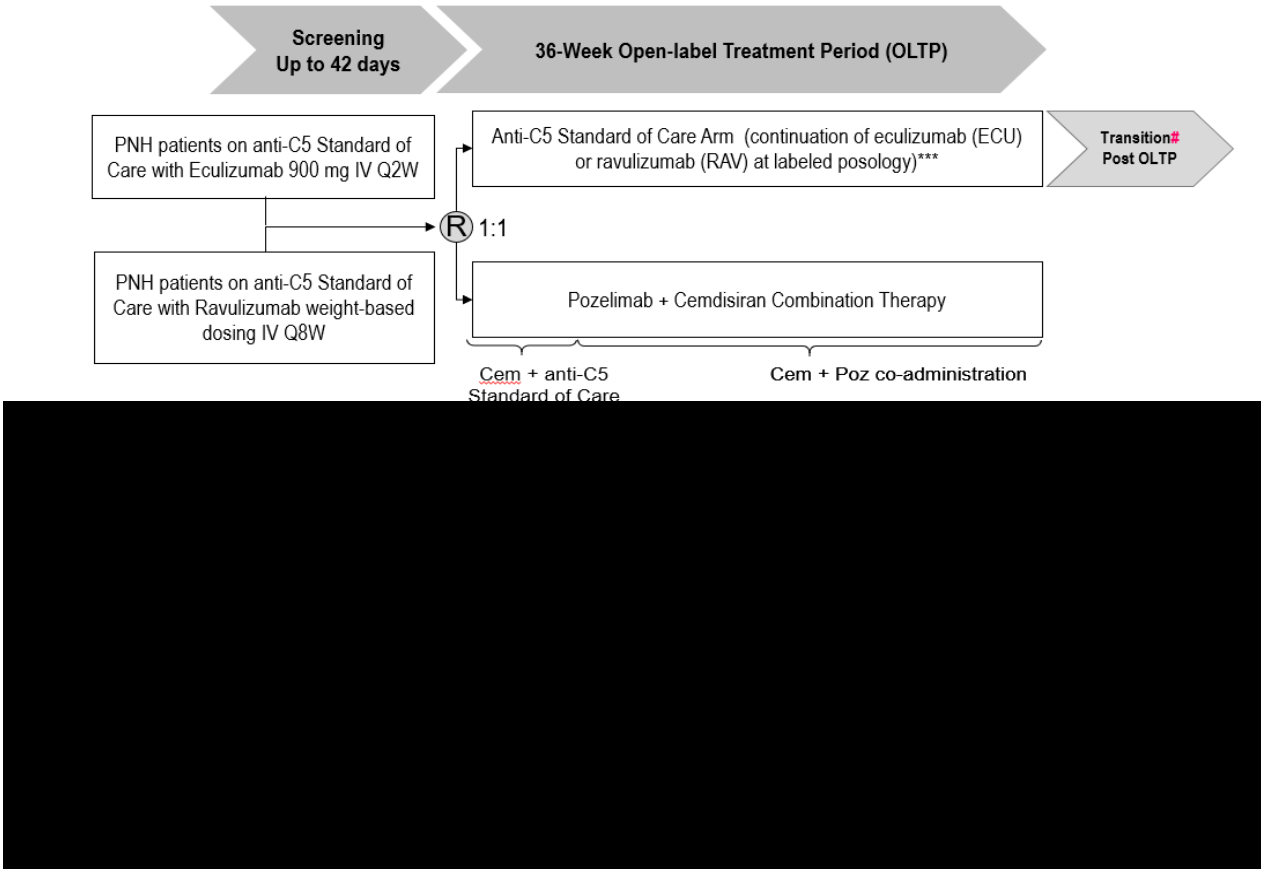
6.1. Study Description and Duration

The study is a randomized, open-label, eculizumab and ravulizumab-controlled, non-inferiority study:

- Patients treated with eculizumab will be eligible if they are taking eculizumab at the labeled posology of 900 mg IV Q 14 days for at least 12 weeks prior to screening visit.
- Patients treated with ravulizumab will be eligible if they are taking IV ravulizumab at the labeled posology Q8W based on body weight (BW) as follows: 3000 mg for BW ≥40 kg to <60 kg, 3300 mg for BW ≥60 kg to <100, 3600 mg for BW ≥100 kg for at least 24 weeks prior to screening visit.

The study (Figure 1) consists of the following periods: a 6-week screening period and a 36-week open label treatment period (OLTP). Patients who complete the OLTP in the anti-C5 standard-of-care arm and plan to enroll in the follow-on open-label long-term extension study with pozelimab and cemdisiran combination must participate in a post-OLTP transition period. Patients who discontinue study treatment as well as patients who decline enrollment into the OLE study will undergo a safety off-treatment follow-up period of up to 52 weeks.

Figure 1: Study Diagram



Patients who complete anti-C5 Standard of Care arm and plan to enroll into the open-label extension with pozelimab and cemdisiran combination will undergo a transition period to phase in combination treatment

6.1.1. Screening Period

The first screening visit should take place up to 6 weeks prior to day 1 (Table 1). Screening visit 1 should be scheduled based on the patient's eculizumab or ravulizumab dosing regimen prior to the study.

For patients taking eculizumab at screening:

- Screening visit 1 should be scheduled on the day of or the day prior to an eculizumab dose and may take place up to 6 weeks prior to day 1.
- At visit 2e, patients will be provided with an eCOA device to take home.
- Day 1 shall be scheduled on the day of or up to 2 days prior to the patient's scheduled eculizumab administration.

For patients taking ravulizumab at screening:

- Screening visit 1 should be scheduled about 6 weeks after a ravulizumab dose
- Visit 2r should be scheduled on the day of or up to 2 days prior to the patient's next scheduled ravulizumab dose. This will be the last non-study ravulizumab dose. Additional laboratory samples for baseline assessments will be taken at this visit and eCOA device will be provided to the patient to take home.
- The day 1 visit should be scheduled 26 to 28 days after the last administration of ravulizumab at visit 2r.

Additional interim screening visit(s) may take place as needed, for instance, for repeat blood collection.

Historical data will be collected such as but not limited to eculizumab or ravulizumab administration, concomitant medications, hemolytic parameters, and RBC transfusions.

Due to the risk of *Neisseria meningitidis* infection, patients will require administration of meningococcal vaccination(s) in accordance with the local eculizumab or ravulizumab prescribing information, where applicable, and in accordance with current national vaccination guidelines for vaccination use with complement inhibitors or local practice and at the very least, within a period of 5 years prior to screening. For patients who require administration with meningococcal vaccination(s) during the screening period, administration should occur preferably at least 2 weeks prior to day 1, or at another time point according to local practice or national guidelines/local eculizumab or ravulizumab prescribing information (as applicable). 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 as described in Section 8.2.4.

In addition to *Neisseria meningitidis* infection, fatal or serious infections with *Neisseria gonorrhea* have been reported in patients taking complement inhibitor therapy. Patients should therefore undergo a risk assessment and counseling regarding the potential risk of *Neisseria gonorrhea* as per local practice or national guidelines.

Patients who have not been vaccinated against *Streptococcus pneumoniae* and *Haemophilus influenzae* type B may receive these vaccinations during the screening period or on the day of

randomization, based on investigator discretion and taking into consideration the available national guidelines.

Patients will be assessed for active or latent tuberculosis (TB) infection based on local practice or applicable guidelines. Based on the risk assessment, the need for screening with either tuberculin skin test or T-cell interferon-gamma release assay will be made. The interpretation of these results, as applicable, will be made by the investigator. Further management and treatment of TB will be the responsibility of the investigator.

6.1.2. Randomization

Day 1 (randomization) must take place on the day of the patient's scheduled eculizumab administration or 4 weeks (ie, 26 to 28 days) after the last administration of ravulizumab, as applicable. If the day of randomization cannot be scheduled on the day of the patient's next eculizumab dose or exactly 4 weeks after the last ravulizumab dose, a window of 1 to 2 days is allowed such that the day of randomization may take place 1 to 2 days prior to the next scheduled eculizumab dose or 26-28 days after the last ravulizumab dose, as applicable.

Patients who fulfill all the eligibility criteria will be randomized in a 1:1 ratio to anti-C5 standard-of-care (ie, continue existing treatment with eculizumab or ravulizumab) or treatment with pozelimab and cemdisiran.

Randomization will be stratified based on the criteria described in 8.5.

6.1.3. Open-Label Treatment Period (OLTP)

The treatment period is 36 weeks. Treatment administration is based on a patient's PNH treatment prior to screening as well as their treatment assignment:

- Pozelimab and cemdisiran arm:
  - Patients who were on eculizumab at screening will receive the following during the study:

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

  - Patients who were on ravulizumab at screening will receive the following during the study:

[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]

- Anti-C5 standard-of-care arm:
  - Patients who were on eculizumab at screening will continue to receive eculizumab during the study:

[redacted]	[redacted]
[redacted]	[redacted]

  - Patients who were on ravulizumab at screening will continue to receive ravulizumab during the study:

[redacted]	[redacted]

Administration of Pozelimab and Cemdisiran

[redacted] After the first administration with the study drugs, subsequent administrations may be continued by the site personnel or a healthcare professional at the patient's home (if possible and approved by the sponsor) or additionally, for the combination of pozelimab and cemdisiran administered by the patient or designated person, at the patient's preferred location. These various options for administration will depend on preference of the investigator and patient, local regulations as well as availability of healthcare professional with sponsor endorsement. If self-administration/ administration by patient/designated person is undertaken for the combination of pozelimab and cemdisiran, then sufficient injection training at the scheduled administration(s) with pozelimab and cemdisiran maintenance regimen will be provided. After training, observation of self-administration/administration by patient/designated person will be conducted by clinical site personnel or visiting healthcare professional/virtual visit (if available). Once this observation is considered satisfactory, the pozelimab and cemdisiran maintenance regimen can be subsequently administered independently by patient/designated person for the remainder of the study. Patients who self-administer/have the study drug administered by a designated person shall complete a patient diary to collect information on study treatment administration. They shall also be contacted by the study site to ensure study drug administration as planned.

Safety Considerations

During the transition of therapy from eculizumab or ravulizumab to pozelimab, investigators should have heightened awareness for possible AEs as a result of the risk of formation of large multimers of complexes of eculizumab-C5-pozelimab (ie, large DTD immune complexes) (see Section 6.2).

Breakthrough hemolysis is assessed by the investigator throughout the study and is defined in Section 6.3.

The decision to transfuse with RBCs during the study should proceed according to the predefined criteria in Section 6.4.

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 8.2.3 and Section 8.2.5). 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 (HCP) for awareness. Patients should be instructed to carry the patient safety card at all times and to show this card to any HCP involved in their treatment. Additionally, patients who are randomized to standard-of-care will receive a patient safety brochure for eculizumab or ravulizumab, as applicable, prior to treatment initiation. Daily oral antibiotic prophylaxis is recommended (Section 8.2.4).

COVID-19

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 in response 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.

A patient who has a documented, positive reverse transcriptase polymerase chain reaction (RT-PCR) or antigen test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on-study should follow protocol guidance regarding interruption and discontinuation of study treatment (see Section 8.3.2). The investigator, with possible input from the sponsor, should determine what is most appropriate to do with the study treatment in accordance with the protocol.

6.1.4. Post-Open-Label Treatment Period (Post-OLTP)

Patients who complete the OLTP (ie, end of study [EOS] visit at day 253) will be offered the opportunity to enroll in another study, a follow-on OLE study. Screening for the next study may be conducted while the patient is in the OLTP, as described in Section 9.1.1.1 footnote #1.

For patients who complete the 36-week OLTP on the pozelimab and cemdisiran arm, the transition of treatment from the current study to the OLE is planned to be uninterrupted, whereby day 1 visit of the OLE will correspond to the EOT period/EOS visit in the current study.

Patients who complete the 36-week OLTP on the anti-C5 standard-of-care arm and plan to participate in the OLE study will undergo a transition period in order to switch to cemdisiran and pozelimab combination treatment in the same manner as those switching to the combination at study initiation as follows:

[redacted]

- [redacted]
- [redacted]

- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

This approach for patients randomized to the anti-C5 standard-of-care arm and who plan to enroll in the OLE study, ensures a consistent dosing approach when switching from eculizumab or ravulizumab to pozelimab and cemdisiran combination therapy and has no impact on study efficacy analysis for the randomized treatment period. Patients who discontinue treatment as well as patients who decline enrollment into the follow-on study of the OLE will undergo a safety off-treatment follow up period (FUP) of up to 52 weeks according to Table 4. Patients discontinuing the study treatment should be treated in accordance with local standards of care while continuing to be monitored in the 52-week off-treatment safety FUP. Investigators switching patients from the combination treatment to another anti-C5 mAb should have a heightened awareness for possible adverse events resulting from the formation of large DTD immune complexes.

The main study is considered finished, when all patients either complete the 36-week treatment period or prematurely discontinue the study. Additional data collected during the transition period and safety off-treatment FUP will be described separately.

6.1.5. Study Stopping Rules

The independent data monitoring committee (IDMC), which may also be referred to as Data and Safety Monitoring Board (DSMB), will monitor unblinded data on a regular basis to assess the benefit-risk profile of the combination regimen of pozelimab and cemdisiran. If at any time the IDMC has significant concerns regarding a meaningful imbalance in TEAEs or treatment-emergent SAEs, the IDMC may make a recommendation to the sponsor to halt the study or make recommendations for other changes in the study conduct. This will prompt a review by the sponsor. Applicable regulatory procedures will be adhered to as required by local laws in relation to any decisions related to a change in study conduct, temporary halt, study termination, or study restart.

6.1.6. End of Study Definition

The EOS is defined as the date the last patient completes the last study visit withdraws from the study, or is lost to follow-up (ie, the study patient can no longer be contacted by the investigator).

6.2. Large Drug-Target-Drug Immune Complexes

During the transition of therapy from eculizumab or ravulizumab to pozelimab, investigators should have heightened awareness for possible AEs as a result of the risk of formation of large

multimers of complexes of eculizumab-C5-pozelimab or ravulizumab-C5-pozelimab (ie, large DTD immune complexes). Patients may present with a variety of signs and symptoms such as fever, malaise, rash, and polyarthralgia. Investigators should also consider meningococcal infection as the cause of the aforementioned symptoms. If a rash does develop, the site may consider taking pictures of the skin lesions as allowed based on local requirements and/or perform a skin biopsy if clinically indicated. If photos are obtained, then copies should be kept as source documents, which may later be collected by the sponsor. If there is a suspicion of an AE potentially due to large DTD immune complexes, unscheduled laboratory tests should be obtained as described in "Other Laboratory Tests" (Section 9.2.4.7). It is recommended that the investigator consult with a rheumatologist or nephrologist if needed and inform the Sponsor. However, further investigations are at the discretion of the investigator. Investigators should administer an additional dose of pozelimab ■ mg/kg IV if systemic corticosteroids are administered for a type III hypersensitivity reaction (see below), with Sponsor approval. This additional dose will likely establish conditions of pozelimab excess in the circulation and thereby minimize the risk of further formation of immune complexes. Further management should be based on clinical experience with type III hypersensitivity reactions (ie, serum sickness) which includes antihistamines, non-steroidal anti-inflammatory drugs (NSAIDs), topical corticosteroids for localized skin rash, and systemic corticosteroids for generalized skin rash or systemic manifestations.

6.3. Breakthrough Hemolysis

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 baseline LDH is ≤1.5 × ULN or
  - LDH ≥2 × ULN after initial achievement of LDH ≤1.5 × ULN if baseline LDH is >1.5 × ULN

  Note: Baseline is defined in Section 11.4.3.
- The signs or symptoms are 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).

6.4. Transfusion Algorithm

Transfusions with RBCs during the study (including during the screening period) may proceed according to the following predefined criteria that will trigger a transfusion, as clinically indicated, however, the actual number of units to be transfused is at the discretion of the investigator:

- Transfuse with RBCs if hemoglobin level is >7 to ≤9 g/dL with new onset or worsening signs or symptoms resulting from anemia that are of sufficient severity to warrant transfusion (Note: the onset of new or worsening signs/symptoms of anemia must occur post-baseline after day 1 to be considered as meeting the endpoint criteria for transfusion), or

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

6.5. Planned Interim Analysis

No interim analysis is planned.

6.6. Study Committees

6.6.1. Independent Data Monitoring Committee

Given the concern of monitoring for suspected immune AEs potentially related to suspected high molecular weight complex formation, an IDMC will be used for safety monitoring. In addition to formal safety reviews throughout the study, the IDMC will review the safety data from first 12 patients treated for 8 weeks.

The IDMC will monitor unblinded data on an ongoing basis to assess the risk/benefit profile of pozelimab/cemdisiran. If at any time the IDMC has significant concerns regarding TEAEs, treatment-emergent SAEs, or treatment-emergent adverse events of special interest (AESIs), the IDMC may make a recommendation to sponsor to halt the study or make other changes in the study conduct. This will prompt a review by sponsor who will decide to implement, modify, or reject the recommendation. Applicable regulatory procedures will be adhered to as required by local laws in relation to any decisions related to a change in study conduct, temporary halt, study termination, or study restart.

The makeup of the IDMC will be at least 3 members who will be external to the sponsor; 1 immunologist or rheumatologist, 1 statistician and 1 hematologist. This may be modified based on availability of specialists to participate to the IDMC.

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

7.1. Number of Patients Planned

Enrollment will continue until approximately 140 patients have been randomized and have received at least 1 dose of study treatment.

7.2. Study Population

The study population will consist of adult male and female patients with a confirmed diagnosis of PNH currently being treated at the labeled dose regimen with either eculizumab for at least the prior 12 weeks or ravulizumab for at least 24 weeks with any level of LDH control. Treatment assignment and stratification factors are described in Section 8.5.

[redacted]

7.2.1. Inclusion Criteria

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

1. Male or female ≥18 years of age or legal age of majority, whichever is greater, at the time of consent
2. Diagnosis of PNH confirmed by a history of high-sensitivity flow cytometry from prior testing
3. Ongoing treatment with eculizumab* 900 mg IV Q 14 days for at least 12 weeks prior to screening visit.

   or

   Ongoing treatment with ravulizumab* IV Q8W based on BW as follows; 3000 mg for BW ≥40 kg to <60 kg, 3300 mg for BW ≥60 kg to <100, 3600 mg for BW ≥100 kg for at least 24 weeks prior to screening visit.

   Note: Patients opting to participate from the R3918-PNH-2021 trial (A Randomized, Open-Label, Ravulizumab-Controlled Study to Evaluate the Efficacy and Safety of Pozelimab and Cemdisiran Combination Therapy in Patients with Paroxysmal Nocturnal Hemoglobinuria who are Complement Inhibitor Treatment-Naive or Have Not Recently Received Complement Inhibitor Therapy) who were randomized to the ravulizumab arm must complete the open-label treatment period to be considered for eligibility in this study.

   *Biosimilars are not permitted, unless approved by the Sponsor.
4. Provide informed consent signed by study patient.
5. Willing and able to comply with clinic/remote visits and study-related procedures.
6. Able to understand study-related questionnaires.

7.2.2. Exclusion Criteria

Note: If a patient screen fails, and if the study is still ongoing, they may be rescreened (up to 2 times) if the Principal Investigator determines the patient may be eligible upon rescreening.

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

1. Patients with a screening LDH >1.5 × ULN who have not taken their C5 inhibitor within the labeled dose interval at the dose prior to the screening LDH assessment.
2. Receipt of an organ transplant, history of bone marrow transplantation or other hematologic transplant.
3. Body weight < 40 kilograms at screening visit.
4. Current plans for modification (initiation, discontinuation, or dose/dosing interval change) of the following background concomitant medications, as applicable, during screening and treatment period: erythropoietin, immunosuppressive drugs, corticosteroids, anti-thrombotic agents, anticoagulants, iron supplements, and folic acid.
5. Any use of complement inhibitor therapy other than eculizumab or ravulizumab in the 26 weeks prior to the screening visit or planned use during the study with the exception of study treatments.
6. Any of the following abnormalities at the screening visit (two repeat measurements are allowed per parameter during screening period):
    a. Peripheral blood absolute neutrophil count (ANC) <500/μL (<0.5 × 10^9/L) or
    b. Peripheral blood platelet count <30,000/μL or
    c. Peripheral blood reticulocyte count abnormality defined as <60,000/μL (<0.06 × 10^6/μL, <60 × 10^9/L)

    Note: a patient will not be excluded if upon repeat testing the parameter no longer meets the exclusion criterion.

    Note: Patients receiving acute treatment (eg, platelet transfusions, granulocyte colony stimulating factors) for these conditions during screening and in the 1-month preceding screening will not be eligible.
7. Not meeting meningococcal vaccination requirements for eculizumab or ravulizumab according to the current local prescribing information (where available) and at a minimum documentation of meningococcal vaccination within 5 years prior to screening visit.

    Note: Patients without prior vaccination will be eligible provided they are willing to undergo vaccination prior to initiation of study treatment and vaccination is documented prior to randomization.
8. Any contraindication for receiving *Neisseria meningitidis* vaccination.
9. Unable to take antibiotics for meningococcal prophylaxis (if required by local eculizumab or ravulizumab prescribing information, where applicable or national guidelines/local practice or if vaccination is less than 2 weeks from study treatment initiation).

10. Any active, ongoing infection or a recent infection requiring ongoing systemic treatment with antibiotics, antivirals, or antifungals within 2 weeks prior to screening or during the screening period.
11. Documented history of systemic fungal disease or unresolved tuberculosis, or evidence of active or latent tuberculosis infection (LTBI) (ie, if not having completed treatment for LTBI) during screening period. Assessment for active TB and LTBI should accord with local practice or guidelines, including those pertaining to risk assessment, and the use of tuberculin skin test or T-cell interferon gamma release assay.
12. Positive hepatitis B surface antigen or hepatitis C virus RNA during screening.

    Note: Cases with unclear interpretation should be discussed with the medical monitor.
13. Patients with known HIV with history of opportunistic infections in the last 1 year, any history of HIV related malignancy, documented history of CD4 count <500 cells/µL or detectable viral load within the last 6 months (note: CD4 count and viral load must be available within the last 6 months, and may be conducted by a local laboratory during screening if needed).

    Note: Local testing for HIV may be conducted in patients if required locally or by local regulations.
14. Documented* history of positive RT-PCR, antigen or serology test, or other health authority authorized test for SARS-CoV-2 and:
    a. Have not recovered from COVID-19 (all COVID-19-related symptoms and major clinical findings which can potentially affect the safety of the patient should be resolved to baseline), and
    b. Did not have 2 negative results from a health authority-authorized nucleic acid amplification (RT-PCR) test or other health authority authorized test for COVID-19 taken at least 48 hours apart prior to day 1.

    *Note: Screening for COVID-19 will not be performed as part of eligibility assessments for this study
15. Known hereditary complement deficiency
16. Documented history of active, uncontrolled, ongoing systemic autoimmune diseases
17. Documented history of liver cirrhosis or patients with liver disease with evidence of current impaired liver function or patients with ALT or AST (unrelated to PNH or its complications) greater than 3 × ULN at the screening visit (if the AST or ALT returns >3 × ULN, one repeat assessment of the abnormal parameter(s) is allowed during screening).
18. Patients with an eGFR of < 30 mL/min/1.73m^2 (according to Chronic Kidney Disease - Epidemiology Collaboration equation 2009) at screening visit (one repeat assessment allowed during screening).
19. Recent, unstable medical conditions, excluding PNH and PNH related complications, within the past 3 months prior to screening visit (eg, myocardial infarction, congestive heart failure with New York Heart Association Class ≥ III or IV, serious uncontrolled cardiac arrhythmia, cerebrovascular accident, active gastrointestinal bleed)

20. Anticipated need for major surgery during the study
21. History of cancer within the past 5 years, except for adequately treated basal cell skin cancer, squamous cell skin cancer, or in situ cervical cancer
22. Participation in another interventional clinical study (except R3918-PNH-2021) or use of any experimental therapy within 30 days before screening visit or within 5 half-lives of that investigational product, whichever is greater, with the exception of eculizumab or ravulizumab.
23. Known hypersensitivity to eculizumab or ravulizumab (as applicable), pozelimab, cemdisiran or to any components of their respective formulations.
24. Patients with functional or anatomic asplenia
25. Any clinically significant abnormality identified at the time of screening that in the judgment of the Investigator or sub-Investigator(s) would preclude safe completion of the study or constrain endpoints assessment such as major systemic diseases, or patients with short life expectancy
26. Considered by the Investigator or sub-Investigator(s) as inappropriate for this study for any reason, eg,
    a. Deemed unable to meet specific protocol requirements, such as scheduled visits.
    b. Deemed unable to administer or tolerate need for chronic injections
    c. Presence of any other conditions (eg, geographic, social etc.) actual or anticipated, that the Investigator feels would restrict or limit the patient's participation for the duration of the study.
    d. Part of a vulnerable population such as the institutionalized (this may also include patients who are committed to an institution by order issued either by the judicial or the administrative authorities, as applicable)
    e. Patient ineligible for clinical trial participation due to local regulations (eg, under legal protection measures [such as L1121-8 or L1121-8-1 in France], etc).
27. Members of the clinical site study team and/or his/her immediate family, unless prior approval granted by the Sponsor.
28. Pregnant or breastfeeding women.
29. Women of childbearing potential (WOCBP)* who are unwilling to practice highly effective contraception prior to the initial dose/start of the first study 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 or tubal occlusion;

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.

Pregnancy testing and contraception are required for WOCBP. Pregnancy testing and contraception are not required for women who are post-menopausal or permanently sterile.

†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 subject.

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

30. Non-responsive to eculizumab or ravulizumab treatment (note: non-responsive refers to patients with no reduction in LDH after receiving treatment with eculizumab or ravulizumab; patients with a response to eculizumab or ravulizumab that is sub-optimal are not excluded provided all other eligibility criteria are satisfied)
31. Hemoglobin ≤7 g/dL (Note: A patient may receive a blood transfusion during the screening period and is eligible if repeat hemoglobin returns >7 g/dL prior to randomization. More than 2 repeat measurements are allowed.)

7.3. Premature Withdrawal from the Study

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

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

Patients who are withdrawn prematurely from the study will be asked to complete the early termination visit, as described in Section 9.1.5.

Rules for discontinuation of study treatment (permanent or temporary) are discussed in Section 8.3.2.

7.4. Replacement of Patients

Patients enrolled and withdrawn from study any time prior to first dose of study drug will not be considered evaluable for assessment and will be replaced with another patient. All patients who have received a dose of study drug will be included in an as treated analysis.

8. STUDY TREATMENTS

8.1. Investigational and Reference Treatments

Study treatment refers only to investigational medicine product (IMP, ie. pozelimab, cemdisiran, eculizumab, and ravulizumab) provided for use in this study.

8.1.1. Pozelimab

[redacted]

8.1.2. Cemdisiran

[redacted]

8.1.3. Eculizumab

30 mL of concentrate (10 mg/mL) in a Type I glass vial.

Eculizumab will be provided to the study sites by the sponsor (but may be sourced locally by the study site in exceptional circumstances).

Biosimilars are not permitted unless approved by the sponsor.

Instructions on dose preparation are provided in the pharmacy manual.

Please see the latest approved prescribing information for eculizumab (where available) for additional information (Soliris® Eculizumab (Prescribing information)), Summary of Product Characteristics. A prescriber safety brochure for eculizumab will be provided to all investigators.

8.1.4. Ravulizumab

Ravulizumab 11 mL of concentrate (100 mg/mL) or 3 mL of concentrate (100 mg/mL) in a single-dose vial.

Ravulizumab will be provided to the study sites by the sponsor (but may be sourced locally by the study site in exceptional circumstances).

Biosimilars are not permitted unless approved by sponsor.

Instructions on dose preparation are provided in the pharmacy manual.

Please see the latest approved prescribing information for ravulizumab (where available) for additional information (Ultomiris® (Prescribing information)), (Ultomiris® (Summary of Product Characteristics)). A prescriber safety brochure for ravulizumab will be provided to all investigators.

8.2. Risk Mitigation and Background Treatments

8.2.1. Meningococcal Vaccinations

Patients will require administration of meningococcal vaccination unless there is documentation of prior immunization within the past 5 years, or a shorter duration as required by current national vaccination guidelines for vaccination use with complement inhibitors or local practice.

For patients requiring vaccination, administration should occur, preferably, at least 2 weeks prior to initiation of study treatment, or at another time point according to local practice or regional guidelines. If administration of the vaccine is less than 2 weeks of receiving study treatment, then antibiotic prophylaxis is required for a period of at least 2 weeks from the date of vaccine administration. Patients should undergo vaccination for serotypes A, C, Y, W, and serotype B if available. The vaccinations will be generally sourced locally by the investigator or designee and reimbursed by the Sponsor.

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 revaccination during the course of the study should receive the vaccination and continue study treatment.

8.2.2. *Streptococcus Pneumoniae* and *Haemophilus Influenzae Type B* Vaccination

Patients who have not been vaccinated against *Streptococcus pneumoniae and Haemophilus influenzae* type B may receive these vaccinations during the screening period or on the day of randomization based on investigator discretion and taking into consideration the available national guidelines.

8.2.3. 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 and investigators will be provided with educational materials describing signs and symptoms of meningococcal infection, along with instructions to follow in case of a potential meningococcal infection.

Information will also be provided for the non-investigator healthcare provider for awareness.

8.2.4. Oral Antibiotics for Meningococcal Infection

It is recommended that antimicrobial prophylaxis for meningococcal infection be initiated at the start of study treatment, unless the risks outweigh the benefits, or such treatment is inconsistent with local practice. It is recommended that prophylaxis be continued for up to 52 weeks after the last dose of pozelimab and cemdisiran combination treatment, including for patients who prematurely discontinue pozelimab/cemdisiran. For post-treatment prophylaxis for eculizumab or ravulizumab, follow the local prescribing information/national guidelines/local practice. 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. No interaction is expected between antibiotic prophylaxis and cemdisiran or pozelimab. Based on a mechanistic understanding of antibiotics and antibodies, as well as

nonclinical data on cemdisiran, neither the study treatments nor the prophylactic antibiotics are expected to interact with clearance pathways of either cemdisiran or pozelimab.

Ultimately, the decision to administer prophylaxis with oral antibiotics, the start day of administration, the duration of prophylaxis, the choice and dosage regimen of antibiotics will be at the discretion of the investigator in accordance with national guidelines/local practice/eculizumab or ravulizumab prescribing information (as applicable), unless the patient receives vaccination within 2 weeks from day 1, in which case the patient must receive antibiotic prophylaxis for a minimum of 2 weeks from day of vaccination. Patients who require revaccination against *Neisseria meningitidis* during the study should receive the vaccination and continue the study treatment.

8.2.5. Risk Management of *Neisseria Gonorrhea*

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

Risk 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 HCP) 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.

8.2.6. Guidance on Abnormalities in Transaminases and Other Liver Function Tests

Patients who develop any of the following abnormalities below should undergo additional investigations or consultation, as clinically indicated, if considered by the investigator not due to PNH. Also refer to the criteria set forth with specific thresholds for ALT, AST, total bilirubin, and INR in Reasons for Permanent Discontinuation of Study Treatment (Section 8.3.2) and Events that Require Expedited Reporting to Sponsor (Section 10.1.3).

- ALT ≥3 × ULN if baseline ALT < ULN
- ALT ≥2 × baseline if baseline ALT ≥ ULN
- Total bilirubin ≥2 × ULN considered hepatic in origin, as per investigator

Additional investigations or consultation, as clinically indicated, should be undertaken as follows:

- The above abnormalities should be confirmed by repeat testing, generally within 72 hours, including ALT, AST, alkaline phosphatase, total bilirubin, and INR with continued monitoring every 48 to 72 hours as clinically indicated until stabilization. Hematology and chemistry may also be obtained as well as other assessments or evaluations per investigator discretion, as appropriate.
- Consider the following alternative causes with focused history, and, as indicated, specialized laboratory tests and imaging (abdominal ultrasound with Doppler flow [or computed tomography or magnetic resonance imaging] including right upper quadrant):

  - Acute viral hepatitis types A, B, C, D, and E
  - Other causes of infection such as cytomegalovirus, Epstein Barr virus, herpes simplex virus 1 and 2, and herpes zoster
  - Autoimmune hepatitis
  - Alcoholic hepatitis
  - Hepatic injury due to concomitant medications, supplements, or environmental exposures
  - Non-alcoholic steato-hepatitis (NASH)
  - Hypoxic/ischemic hepatopathy
  - Biliary tract disease
  - Cardiovascular disease such as heart failure
- Consider gastroenterology or hepatology consultations

Completion of case report forms with more detailed information will be collected (eg, focused history of symptoms, travel history, use of any potentially hepatotoxic concomitant medications, work-related exposures, alcohol consumption, etc.).

8.2.7. Guidance on Large Drug-Target-Drug Immune Complexes

During the transition of therapy from eculizumab or ravulizumab to pozelimab, investigators should have heightened awareness for possible AEs as a result of the risk of formation of large multimers of complexes of eculizumab-C5-pozelimab or ravulizumab-C5-pozelimab (ie, large DTD immune complexes, see Section 6.2).

8.3. Dose Modification and Study Treatment Discontinuation Rules

8.3.1. Dose Modification

Dose modification for an individual patient is not allowed.

8.3.2. Study Drug Discontinuation

Patients who permanently discontinue from study drug 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.

Patients who permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete study assessments, per Section 6.1.5 and Section 9.1.4.1.

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

8.3.2.1. Reasons for Permanent Discontinuation of Study Drug

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

- Evidence of pregnancy

- Patient withdraws 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

Study drug dosing will also be permanently stopped for patients receiving pozelimab and cemdisiran in the event of:

- Serious or severe allergic reactions considered related to study drug
  - Note that AEs potentially due to large DTD immune complexes are not considered as an automatic reason for permanent treatment discontinuation. The investigator should review the particular case and consult with the medical monitor prior to deciding on permanent treatment discontinuation.
- 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 (Section 8.2.6):
  - 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)

Study drug dosing will also be permanently stopped for patients receiving eculizumab or ravulizumab in the event of:

- Any additional reasons for mandatory drug discontinuation outlined in the local prescribing information for eculizumab or ravulizumab, as applicable

Note: A documented, positive RT-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 study drug is deemed unfavorable.

8.3.2.2. Reasons for Temporary Discontinuation of Study Drug

Temporary discontinuation may be considered by the investigator because of suspected AEs. After the condition leading to temporary discontinuation of study treatment resolves, study treatment dosing may resume. 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 temporary discontinuation with pozelimab/cemdisiran, consultation with the medical monitor should take place prior to re-initiation of study drug [redacted].

In general, after a decision is made that it is safe to reinitiate study treatment, the patient should receive any missed dose as soon as possible. It is recommended that the patient returns to the original dosing schedule with administration of the next scheduled dose at the end of the respective dosing window. Ultimately, the investigator should exercise their clinical judgment as it relates to the exact timing of the dose administration after treatment re-initiation. In all cases, discussion with the Sponsor's medical monitor is advised [redacted].

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 or eculizumab/ravulizumab (as applicable) until the patient recovers from SARS-CoV-2, then it is advisable that two repeat COVID-19 RT-PCR tests, or equivalent tests depending on regional recommendations, be conducted to confirm the patient is negative for SARS-CoV-2. If COVID-19 RT-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 pozelimab/cemdisiran 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' medical monitor regarding the permissible duration of interruption to allow resumption of treatment should be sought.

8.4. Management of Acute Reactions

8.4.1. Acute Intravenous Infusion Reactions

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.

8.4.1.1. Interruption of the Intravenous Infusion

The pozelimab 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 pozelimab infusion may be restarted at 50% of the original rate.

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

Management of infusion reactions related to eculizumab or ravulizumab should follow the approved local prescribing information/local standards of care.

8.4.1.2. Termination of the Intravenous Infusion

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

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

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

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

8.4.2. Acute Injection Reactions

8.4.2.1. Systemic Injection Reactions

Emergency equipment and medication for the treatment of systemic reactions must be available at the clinical site for immediate use. All injection reactions must be reported as AEs (as defined in Section 10.2.1) and graded using the grading scales as instructed in Section 10.2.5.

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

8.4.2.2. Local Injection Site Reactions

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

8.5. Method of Treatment Assignment

Eligible patients will be randomized in a 1:1 ratio to receive either the combination treatment with SC pozelimab [redacted] mg and cemdisiran [redacted] mg Q4W or continue their anti-C5 standard-of-care therapy with either eculizumab 900 mg IV Q2W or IV ravulizumab according to the labeled weight-based dosing algorithm according to a central randomization scheme provided by an Interactive Web Response System (IRWS) to the designated study pharmacist (or qualified designee). Randomization will be stratified according to the following factors:

- [redacted]
- [redacted]
- [redacted]

8.6. Blinding

This is an open-label study. The sponsor considers this open-label design as acceptable since the primary endpoint of the study is an objective laboratory-based parameter (ie, LDH) that is unlikely to be biased by knowledge of treatment assignment. Efforts will be made by the Sponsor to minimize bias due to the open-label study design. These efforts will be detailed in a separate study-related document/study plan.

8.7. Treatment Logistics and Accountability

8.7.1. Packaging, Labeling, and Storage

Open-label study drug (pozelimab, cemdisiran, ravulizumab, and eculizumab) will display the product lot number on the label.

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

Ravulizumab and eculizumab will be stored at the site at a temperature of 2ºC to 8ºC; storage instructions will be provided in the pharmacy manual and the package insert.

8.7.2. Supply and Disposition of Treatments

Pozelimab and cemdisiran 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 pozelimab and cemdisiran will be returned to the sponsor or designee or destroyed with sponsor's approval.

Ravulizumab and eculizumab will either be shipped at a temperature of 2ºC to 8ºC to the investigator or designee at regular intervals or as needed during the study by the Sponsor's depot, or it will be sourced locally by the sites. 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 centrally sourced opened and unopened ravulizumab and eculizumab will be returned to the sponsor or designee or destroyed with sponsor's approval.

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 pozelimab, cemdisiran, ravulizumab, and eculizumab. 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 the first dose of study drug to the final study visit will be considered concomitant medication. This includes medications that were started before the study and are ongoing during the study. Any medication that the patient has taken within 3 months of the screening visit or during the screening period shall be collected in the electronic case report form (eCRF). In addition, to the extent that it is possible, any complement inhibitor therapy taken at any time prior to screening or during the screening period should be recorded along with any vaccinations against the following: *Neisseria meningitidis, Haemophilus influenzae* type B*, Streptococcus pneumoniae*, and SARS-CoV-2.

8.8.1. Prohibited Medications and Procedures

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

- 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. It is suggested that strenuous exercise be avoided 24 hours prior to obtaining samples for laboratory assessments, 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 for meningococcal infection, per the investigator, as described in Section 8.2.4
- 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.
- Vitamin and electrolyte supplementation as needed
- Any other medication required for the treatment of patient's background medical conditions
- COVID-19 vaccination and influenza vaccination can be administered as deemed necessary per the investigator based on his/her practice, standard-of-care or as required based on mandatory vaccination programs. Vaccination is suggested to be administered preferably 2 to 3 weeks after a dose of pozelimab/cemdisiran combination or ravulizumab, or up to 1 week after administration of eculizumab.
- Other vaccinations against *Streptococcus pneumoniae* and *Haemophilus influenzae* type B may be administered based on investigator discretion and taking into consideration the available national guidelines

8.9. Poststudy Treatments and Procedures

All patients who complete the study without having prematurely discontinued the study treatment will be offered to participate in the follow on long-term, OLE study of the combination treatment.

Patients randomized to the anti-C5 standard-of-care arm, who complete the 36-week OLTP and plan to enroll into the OLE study, will enter into a transition period (Table 2).

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 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 in Table 1 (OLTP), Table 2 (transition period for eculizumab arm), Table 3 (transition period for ravulizumab arm), and Table 4 (FUP).

9.1.1. Open-Label Treatment Period

Table 1: Schedule of Events for the Open-Label Treatment Period

Study Procedure (Visit)[1]	Screening			Open Label Treatment Period (OLTP)												
		For ravu	For ecu													EOS
Visit #	**V1[2]**	**V2r**	**V2e**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Week	Up to -6	-4	-4 to -2	0	2	4	6	8	10	12	16	20	24	28	32	36
Day	Up to -42	-28	-28 to -14	1[3]	15	29	43	57	71	85	113	141	169	197	225	253
Window (day)		+2			±2	±3	±3	±3	±3	±3	±7	±7	±7	±7	±3	±3
Screening/Baseline[2]:																
eCOA device dispensation		X	X													
Inclusion/Exclusion	X	X	X	X												
Informed consent	X															
FBR informed consent (optional)	X															
Genomics informed consent (optional)	X															
Medical history[4]	X															
Prior medications[5]	X															
Demographics	X															
Height	X															
Hepatitis B and C testing	X															
Vaccination / revaccinate for *Neisseria meningitidis*[6]	<---------- X ---------->															
Vaccination against *Streptococcus pneumoniae* and *Haemophilus influenzae* type B (if needed) [7]	<---------- X ---------->															
Tuberculosis history and assessment[8]	X															
Risk assessment for *Neisseria gonorrhea*[9]	X															
Randomization				X												

Study Procedure (Visit)[1]	Screening			Open Label Treatment Period (OLTP)												
		For ravu	For ecu													EOS
Visit #	**V1[2]**	**V2r**	**V2e**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Week	Up to -6	-4	-4 to -2	0	2	4	6	8	10	12	16	20	24	28	32	36
Day	Up to -42	-28	-28 to -14	1[3]	15	29	43	57	71	85	113	141	169	197	225	253
Window (day)		+2			±2	±3	±3	±3	±3	±3	±7	±7	±7	±7	±3	±3
Treatment:																
IVRS/IWRS	X			X	X	X	X	X	X	X	X	X	X	X	X	X
Timing of ecu/ravu (non-IMP) during screening	[redacted]															
Pozelimab and cemdisiran arm																
Anti-C5 SOC: Eculizumab IMP arm																
Anti-C5 SOC: Ravulizumab IMP arm																
Injection Training/patient instructions[17]						X		X		X	X	X	X	X	X	
Patient diary[18]								X	X	X	X	X	X	X	X	X
Concomitant meds and treatment	X	X	X	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	X	X	X

Study Procedure (Visit)[1]	Screening			Open Label Treatment Period (OLTP)												
		For ravu	For ecu													EOS
Visit #	**V1[2]**	**V2r**	**V2e**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Week	Up to -6	-4	-4 to -2	0	2	4	6	8	10	12	16	20	24	28	32	36
Day	Up to -42	-28	-28 to -14	1[3]	15	29	43	57	71	85	113	141	169	197	225	253
Window (day)		+2			±2	±3	±3	±3	±3	±3	±7	±7	±7	±7	±3	±3
Antibiotics prophylaxis (recommended)[19]				<----------X---------->												
Clinical outcome assessments (COAs):																
FACIT-Fatigue				X	X	X		X		X	X	X	X	X	X	X
EORTC-QLQ-C30				X	X	X		X		X	X	X	X	X	X	X
[redacted]																
Safety and Anthropometric:																
Patient safety card for *Neisseria meningitidis*[10]				X	X	X	X	X	X	X	X	X	X	X	X	X
For ravulizumab arm only: Provide patient safety brochure for ravulizumab				X												
For eculizumab arm only: Provide patient safety brochure for eculizumab				X												
Body weight	X					X		X		X	X	X	X	X	X	X
Vital signs[21]	X			X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[22]	X					X		X		X				X		X
Electrocardiogram	X									X						X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Breakthrough hemolysis assessment[23]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Procedure (Visit)[1]		Screening			Open Label Treatment Period (OLTP)												
			For ravu	For ecu													EOS
Visit #		V1[2]	V2r	V2e	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
Week		Up to -6	-4	-4 to -2	0	2	4	6	8	10	12	16	20	24	28	32	36
Day		Up to -42	-28	-28 to -14	1[3]	15	29	43	57	71	85	113	141	169	197	225	253
Window (day)			+2			±2	±3	±3	±3	±3	±3	±7	±7	±7	±7	±3	±3
Laboratory Testing[24]:																	
Titers to measure *N. meningitidis* (only if required per local practice/regulations)		X															
For patients receiving ravulizumab prior to screening: Additional samples (drawn pre-ravu dose)	Blood chemistry		X														
	Hematology		X														
	Coagulation panel		X														
	Free hemoglobin		X														
	Haptoglobin		X														
Hematology[25]		X			X	X	X		X		X	X	X	X	X	X	X
Coagulation panel		X			X	X	X	X	X	X	X	X	X	X	X	X	X
Blood chemistry (long panel) including LDH[26]		X			X	X	X	X	X	X	X	X	X	X	X	X	X
D-dimer					X							X					X
Immunoglobulin G					X		X				X						
Pregnancy test (applicable patients)[27]		X			X		X		X		X	X	X	X	X	X	X
Urinalysis		X			X	X	X		X		X	X	X	X		X	X
Direct antiglobulin test (DAT or Coombs test)					X		X		X		X	X	X	X		X	X
Pharmacokinetics, ADA and Total C5 Sampling[28]:																	
Pozelimab and cemdisiran arm	Blood samples for conc. of pozelimab				X		X[29]		X		X	X	X	X	X	X	X
	Blood samples for conc. of cemdisiran and metabolites[30]				X						X			X		X	
	Blood samples for ADA of pozelimab[31]				X						X			X			X
	Blood samples for ADA of cemdisiran[31]				X						X			X			X
	Blood samples for conc. of total C5				X	X	X		X		X	X	X	X	X	X	X

Study Procedure (Visit)[1]		Screening			Open Label Treatment Period (OLTP)												
			For ravu	For ecu													EOS
Visit #		V1[2]	V2r	V2e	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
Week		Up to -6	-4	-4 to -2	0	2	4	6	8	10	12	16	20	24	28	32	36
Day		Up to -42	-28	-28 to -14	1[3]	15	29	43	57	71	85	113	141	169	197	225	253
Window (day)			+2			±2	±3	±3	±3	±3	±3	±7	±7	±7	±7	±3	±3
Anti-C5 standard-of-care arm	Blood samples for conc. of eculizumab (for patients taking eculizumab only)				X	X	X				X			X			X
	Blood samples for conc. of ravulizumab (for patients taking ravulizumab only)				X	X	X				X				X		X
	Blood samples for conc. of cemdisiran and metabolites[30]																X[32]
	Blood samples for ADA of pozelimab[31]																X[33]
	Blood samples for ADA of cemdisiran[31]																X[33]
	Blood samples for conc. of total C5				X	X	X		X		X	X	X	X	X	X	X
Biomarkers:																	
[redacted]																	
Optional pharmacogenomics (DNA AND RNA):																	
Whole blood for DNA isolation (optional)[35]					X												
Whole blood for RNA isolation (optional)					X						X						X

9.1.1.1. Table 1 Schedule of Events for the Open-Label Treatment Period

1. Study Procedures visits on days 15, 43, 71, 141, 169, and 225 may be at the clinical site, or another preferred location such as patient's home. The location will be dependent on availability (and if approved by the sponsor) of home healthcare visiting professional, and preferences of the investigator and patient. Visits may also be conducted at another preferred location depending on extenuating circumstances such as due SARSCoV2 infection, in all cases, provided that the home healthcare professional is able to conduct all required assessments for that visit. Also, when multiple procedures are performed on the same day, the sequence of procedures is as follows: Clinical outcome assessments, electrocardiogram (ECG) and/or vital signs, blood collection, and study treatment administration. Patients who are being screened in this study (R3918-PNH-2022) who complete the R3918-PNH-2021 study will have all assessments performed as indicated in the SOE. This implies that the Screening Visit 1 in the R3918-PNH-2022 study may take place at week 24 of the R3918-PNH-2021 study and V2r of the R3918-PNH-2022 study take place at the time of week 26 of the R3918-PNH-2021 study prior to the ravulizumab dose administration. Assessments that are common to both studies should not be duplicated.
2. Screening visit 1 should be scheduled based on the patient's dosing regimen prior to the study. For patients taking eculizumab, screening visit 1 should be scheduled on the day of or the day prior to an eculizumab dose. For patients taking ravulizumab, screening visit 1 should be scheduled about 6 weeks after the last ravulizumab dose. Additional screening visits may be scheduled as needed.
3. For patients taking ravulizumab, the day 1 visit should occur 4 weeks (ie, 26 to 28 days) after the last administration of ravulizumab.
4. Medical history including, 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 infections of the *Neisseria* spp. will be collected. Patients who have a C5 mutation confirmed while the study is ongoing should have the information included as part of the patient's medical history. Patients who are poor responders to eculizumab or ravulizumab treatment during the study may be asked for a mutation analysis to be conducted as part of the study, if the patient agrees to such testing.
5. Including detailed eculizumab or ravulizumab administration history and *Neisseria meningitidis* vaccination and other vaccinations as applicable.
6. Patients will require administration with meningococcal vaccination unless documentation is provided of prior immunization in the past 5 years, or less than 5 years if required according to current national vaccination guidelines for vaccination use with complement inhibitors/local eculizumab or ravulizumab prescribing information. For patients who require administration with meningococcal vaccination(s) during the screening period, administration should occur preferably at least 2 weeks prior to day 1, or at another time point according to local eculizumab or ravulizumab prescribing information/national guidelines.

7. Vaccination for *Streptococcus pneumoniae* and *Haemophilus influenzae* type B should be initiated per current national/local vaccination guidelines.
8. Tuberculosis history and assessment: Screening by tuberculin skin test or T-cell interferon-gamma release assay may be performed according to local practice or guidelines at the discretion of the investigator
9. A risk factor assessment for *Neisseria gonorrhea* will be performed in accordance with local practice/national guidelines, and regular testing and counseling is advised for at-risk patients.
10. Patient safety card: provide the patient safety card for *Neisseria meningitidis* infection to the patient on day 1 and any other visit when needed. Site should review the instructions on the safety card with the patient at each visit.
11. [redacted]
12. [redacted]
13. [redacted]
14. [redacted]

15. [redacted]
16. [redacted]
17. If the sponsor has endorsed self-injection, injection training will be provided to patients randomized/enrolled to pozelimab and cemdisiran combination therapy and who desire self-injection or injection by a designated person. Site should observe patient syringe preparation and self-injection or injection by a designated person and confirm adequacy. Patient instruction materials will be provided.
18. Patient diary: If needed, for self-administration or administration by a designated person with pozelimab and cemdisiran combination treatment only, a patient diary may be provided to collect information on study treatment administration. Patient diary may be provided at day 57 visit or a subsequent visit. 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.
19. Daily oral antibiotic prophylaxis against *Neisseria meningitidis* is recommended starting on the first day of dosing with study treatment and continuing until up to 52 weeks after discontinuation of pozelimab/cemdisiran. For post-treatment prophylaxis for eculizumab or ravulizumab follow the local prescribing information/national guidelines/local practice. If vaccination for *Neisseria meningitidis* occurs less than 2 weeks prior to day 1, then antibiotic prophylaxis must be administered for at least 2 weeks from the day of vaccination.
20. [redacted]
21. Vital signs include temperature, sitting blood pressure, and pulse. Vital signs will be obtained pre-dose after the patient has been sitting quietly for at least approximately 5 minutes, where applicable.
22. 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.

23. 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 CBC, coagulation parameters (including D-dimer), chemistry, reticulocyte count, total C5, CH50, drug concentrations of pozelimab/cemdisiran/eculizumab/ravulizumab (depending on the patient's randomization/enrollment), ADA (against pozelimab), and exploratory research serum and plasma 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 CBC, coagulation parameters (including D-dimer), chemistry, reticulocyte count, total C5, CH50, drug concentrations of pozelimab/cemdisiran/eculizumab/ravulizumab, and ADA (against pozelimab), as applicable, and exploratory research serum and plasma.
24. 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, consideration should be given to repeat the lab sample if clinically warranted, and in all cases where an LDH is ≥2 × ULN in association with a potassium ≥6 mmol/L. Blood collection should always be obtained prior to study treatment administration, unless otherwise noted. The coagulation blood sample must always be collected first, followed immediately by the blood chemistry sample.
25. Hemoglobin will be assessed as part of the hematology analysis. Hematology sample should be collected before study treatment administration.
26. Serum LDH, CRP, and bilirubin will be assessed as part of the blood chemistry analysis. During the screening period, obtain chemistry including LDH on the day of (or if not possible, one day before) eculizumab or ravulizumab administration. On day 1 and all subsequent visits, obtain chemistry including LDH prior to any study treatment administration, as applicable.
27. Pregnancy test: A serum test will be done at screening visit and a urine test will be done at all other visits.
28. [redacted]
29. For patients who receive pozelimab IV infusion: obtain blood samples where permitted, prior to IV administration of pozelimab and also within 15 minutes after the end of the IV infusion.

30. Blood samples for concentrations of cemdisiran and its metabolites will be collected, where permitted, prior to any study treatment administration (pre-dose) and at 1 to 4 hours post dose. The post dose sample may be collected at the clinic or by a visiting health care professional (if available).
31. Blood samples for ADA will be collected, where permitted, before the administration of any study drug (pre-dose). In the event of suspected SAEs, such as anaphylaxis or hypersensitivity, additional blood samples may be collected at or near the onset of the event for PK, ADA, and other analyses.
32. Samples for the measurement of concentrations of cemdisiran and its metabolites will be collected at this visit only for patients who are receiving eculizumab treatment and willing to continue in the transition period and into the OLE
33. Pozelimab and cemdisiran ADA samples will also be collected predose at this visit for patients who are received eculizumab or ravulizumab treatment and willing to continue in the transition period and into the OLE.
34. [redacted]
35. Whole blood samples for DNA extraction (optional) should be collected on day 1 (predose) but can be collected at a later study visit.
36. [redacted]
37. [redacted]

9.1.2. Transition Period: Patients on Eculizumab in OLTP who Plan to Enroll in the OLE

Table 2: Schedule of Events for the Transition Period: Patients on Eculizumab in OLTP who Plan to Enroll in the OLE

Study Procedure (Visit) [1]		Transition period for patients on eculizumab in OLTP (only for patients who complete OLTP and plan to enroll in OLE)	
Visit #		(2 weeks after last dose of eculizumab at OLTP week 36) TV1e[2]	TV2e
Weeks (after last dose of study treatment at OLTP week 36)		2t	4t
Day		15t	29t
Window (day)		±2	±2
Baseline:			
Patient safety card for *Neisseria meningitidis*[3]		X	X
Treatment:			
IVRS/IWRS		X	X
Anti-C5 standard-of-care arm: Eculizumab[4]	[redacted]		
Concomitant meds and treatment		X	X
Transfusion record update		X	X
Antibiotics prophylaxis (recommended)[7]		X	X
Safety and Anthropometric:			
Body Weight		X	X
Vital signs		X	X
Adverse events		X	X
Breakthrough hemolysis assessment[8]		X	X
Laboratory Testing[9]:			
Hematology[10]		X	X
Coagulation panel		X	X
Blood chemistry (long panel) including LDH[11]		X	X
Pregnancy test (applicable patients)[12]			X
Pharmacokinetics and Total C5 Sampling:			
Patients previously taking eculizumab	Blood samples for conc. of pozelimab[13]		X
	Blood samples for conc. of eculizumab		X
	Total C5 sample[14]		X
CH50		X	X

9.1.2.1. Table 2 Schedule of Events for the Transition Period: Patients on Eculizumab in OLTP who Plan to Enroll in the OLE

1. When multiple procedures are performed on the same day, the sequence of procedures is as follows: vital signs, blood collection (first coagulation draw then chemistry draw followed by all other labs) and study drug administration. It is particularly important that the scheduled blood draws are obtained prior to the administration of study treatment, especially efficacy parameters such as LDH (ie, measurements reflect a time point at the end of the dosing interval).
2. Transition period day 1 is the day of the week 36 eculizumab dose given in the OLTP. During the transition period, eculizumab may be administered within 2 days of all visits where eculizumab administration applies. If eculizumab administration does not coincide with the day of clinic visit, as applicable, then the clinic visit should always precede the infusion of eculizumab.
3. Patient safety card: provide the patient safety card for *Neisseria meningitidis* infection to the patient at any visit when needed. Site should review the instructions on the safety card with the patient at each visit.
4. [redacted]
5. [redacted]
6. *Intentionally left blank*
7. Daily oral antibiotic prophylaxis against *Neisseria meningitidis* is recommended starting on the first day of dosing with study treatment and continuing until up to 52 weeks after discontinuation of pozelimab/cemdisiran. For post-treatment prophylaxis for eculizumab or ravulizumab follow the local prescribing information/national guidelines/local practice.
8. If a patient is suspected of having a breakthrough hemolysis event, then in addition to the required laboratory collection, additional samples for CBC, coagulation parameters (including D-dimer), chemistry, reticulocyte count, total C5, CH50 and drug concentrations of pozelimab, cemdisiran, eculizumab or ravulizumab, ADA (against pozelimab), and exploratory research serum and plasma 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 to evaluate the patient and to collect CBC, coagulation parameters (including D-dimer), chemistry, reticulocyte count, total C5,

CH50 and drug concentrations of eculizumab or ravulizumab/pozelimab/cemdisiran, and ADA (against pozelimab) as applicable, and exploratory research serum and plasma.

9. 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, consideration should be given to repeating the lab sample if clinically warranted and, in all cases, where an LDH is ≥2 × ULN in association with potassium ≥6 mmol/L. Blood collection should always be obtained prior to study treatment administration, unless otherwise noted.
10. Hemoglobin will be assessed as part of the hematology analysis. Hematology sample should be collected before study treatment administration.
11. Serum LDH, CRP, and bilirubin will be assessed as part of the blood chemistry analysis. Obtain chemistry including LDH prior to any study treatment administration.
12. Pregnancy test: A urine test will be done.
13. For patients who receive pozelimab IV infusion: obtain blood samples prior to IV administration of pozelimab and also within 15 minutes after the end of the IV infusion.
14. Blood sample for CH50 and total C5 will be collected pre-dose.

9.1.3. Transition Period: Patients on Ravulizumab in OLTP who Plan to Enroll in the OLE

Table 3: Schedule of Events for the Transition Period: Patients on Ravulizumab in OLTP who Plan to Enroll in the OLE

Study Procedure (Visit) [1]		Transition period for patients on ravulizumab in OLTP (only for patients who complete OLTP and plan to enroll in OLE)	
Visit #		(4 weeks after last dose of ravulizumab at OLTP week 36) TV1r[2]	TV2r
Weeks (after last dose of study treatment at OLTP week 36)		4t	8t
Day		29t	57t
Window (day)		±2	±2
Baseline:			
Patient safety card for *Neisseria meningitidis*[3]		X	X
Treatment:			
IVRS/IWRS		X	X
Anti-C5 standard-of-care arm: Ravulizumab[6]	[redacted]		
Concomitant meds and treatment		X	X
Transfusion record update		X	X
Antibiotics prophylaxis (recommended)[7]		X	X
Safety and Anthropometric:			
Body Weight		X	X
Vital signs		X	X
Adverse events		X	X
Breakthrough hemolysis assessment[8]		X	X
Laboratory Testing[9]:			
Hematology[10]		X	X
Coagulation panel		X	X
Blood chemistry (long panel) including LDH[11]		X	X
Pregnancy test (applicable patients)[12]		X	X
Pharmacokinetics and Total C5 Sampling:			
Patients previously taking ravulizumab	Blood samples for conc. of pozelimab[13]		X
	Blood samples for conc. of ravulizumab		X
	Total C5 sample[14]		X
CH50		X	X[14]

9.1.3.1. Table 3 Schedule of Events for the Transition Period: Patients on Ravulizumab in OLTP who Plan to Enroll in the OLE

1. When multiple procedures are performed on the same day, the sequence of procedures is as follows: vital signs, blood collection (first coagulation draw then chemistry draw followed by all other labs) and study drug administration. It is particularly important that the scheduled blood draws are obtained prior to the administration of study treatment, especially efficacy parameters such as LDH (ie, measurements reflect a time point at the end of the dosing interval).
2. Transition period day 1 is the day of the week 36 ravulizumab dose given in the OLTP.
3. Patient safety card: provide the patient safety card for *Neisseria meningitidis* infection to the patient at any visit when needed. Site should review the instructions on the safety card with the patient at each visit.
4. *Intentionally left blank*
5. [redacted]
6. [redacted]
7. Daily oral antibiotic prophylaxis against *Neisseria meningitidis* is recommended starting on the first day of dosing with study treatment and continuing until up to 52 weeks after discontinuation of pozelimab/cemdisiran. For post-treatment prophylaxis for eculizumab or ravulizumab follow the local prescribing information/national guidelines/local practice.
8. If a patient is suspected of having a breakthrough hemolysis event, then in addition to the required laboratory collection, additional samples for CBC, coagulation parameters (including D-dimer), chemistry, reticulocyte count, total C5, CH50 and drug concentrations of pozelimab, cemdisiran, eculizumab or ravulizumab, ADA (against pozelimab), and exploratory research serum and plasma 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 to evaluate the patient and to collect CBC, coagulation parameters (including D-dimer), chemistry, reticulocyte count, total C5, CH50 and drug concentrations of eculizumab or ravulizumab/pozelimab/cemdisiran, and ADA (against pozelimab) as applicable, and exploratory research serum and plasma.

9. 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, consideration should be given to repeating the lab sample if clinically warranted and in all cases where an LDH is ≥2 × ULN in association with potassium ≥6 mmol/L. Blood collection should always be obtained prior to study treatment administration, unless otherwise noted.
10. Hemoglobin will be assessed as part of the hematology analysis. Hematology sample should be collected before study treatment administration.
11. Serum LDH, CRP, and bilirubin will be assessed as part of the blood chemistry analysis. Obtain chemistry including LDH prior to any study treatment administration.
12. Pregnancy test: A urine test will be done.
13. For patients who receive pozelimab IV infusion: obtain blood samples prior to IV administration of pozelimab and also within 15 minutes after the end of the IV infusion.
14. Blood sample for CH50 and total C5 will be collected pre-dose.

9.1.4. Safety Off-Treatment Follow-up Period

The FUP is for patients who discontinue treatment for any reason, including those who complete the OLTP but decline enrollment into the OLE.

- Patients in the ravulizumab arm who complete OLTP (ie, last dose of study drug at week 28 and EOS at week 36) will enter FUP at visit FU-3 (ie, 12 weeks after last dose of study drug)
- Patients in the eculizumab arm who complete OLTP (ie, last dose of study drug at week 32 and EOS at week 36) will enter FUP at visit FU-2 (ie, 8 weeks after last dose of study drug)
- Patients in the pozelimab/cemdisiran arm who complete OLTP (ie, last dose of study drug at week 32 and EOS at week 36) will enter FUP at visit FU-2 (ie, 8 weeks after last dose of study drug)
- For patients who discontinue and did not complete OLTP, they will have an ET visit. Thereafter, their entry point into the FUP will depend on the number of weeks that have elapsed after their final dose of study treatment

Table 4: Schedule of Events for the Safety Off-Treatment Follow-up Period

Visit	**FU-1**	**FU-2**	**FU-3**	**FU-4**	**FU-5**	**Phone visit FU-6**	**Phone visit FU-7**
Weeks (after the last dose of study drug)	4	8	12	16	26	38	52
Window (day)	±10	±10	±10	±10	±10	±10	±10
Body weight	X	X	X	X	X		
Vital signs	X	X	X	X	X		
Physical examination			X		X		
Concomitant meds/treatment	X	X	X	X	X	X	X
Adverse event reporting	X	X	X	X	X	X	X
Pregnancy reporting	X	X	X	X	X	X	X
Antibiotics prophylaxis (recommended)[1]	X	X	X	X	X	X	X
Patient safety card for *Neisseria meningitidis*[2]	X	X	X	X	X	X	X
Laboratory Testing							
Hematology	X	X	X	X	X		
Blood chemistry	X	X	X	X	X		
Monthly urine pregnancy test (WOCBP)[3]	<----------X---------->						
Pharmacokinetics, and ADA Sampling:							
Pozelimab PK sample					X		
ADA sample for pozelimab					X		
ADA sample for cemdisiran					X		
Total C5 (plasma)					X		

9.1.4.1. Table 4 Schedule of Events for the Safety Off-Treatment Follow-up Period

1. Antibiotics prophylaxis (recommended): Daily oral antibiotic prophylaxis against *Neisseria meningitidis* is recommended starting at FU-1 and continuing until up to 52 weeks after discontinuation of pozelimab/cemdisiran. For post-treatment prophylaxis for eculizumab or ravulizumab follow the local prescribing information/national guidelines/local practice.
2. Patient safety card for *Neisseria meningitidis*: Patient safety card: provide the patient safety card for *Neisseria meningitidis* infection to the patient at FU-1 or any other visit when needed. Site should review the instructions on the safety card with the patient at each visit.
3. Pregnancy testing: Monthly urine pregnancy testing will be conducted for WOCBP only. If performed via at-home testing kits, patients should be reminded to call the study staff each month with the results of their pregnancy test, and as soon as possible if their pregnancy test result is positive.

9.1.5. Early Termination Visit

Patients who are withdrawn from the study before the primary endpoint visit (week 36) will be asked to return to the clinic: once for an early termination visit consisting of the end of study assessments described in Table 1.

9.1.6. Unscheduled Visits

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

Screening visit 1 must be scheduled based on the patients' dosing regimen prior to study: please see scheduling requirements in Section 6.1.1.

- eCOA device dispensation at visit 2e (for eculizumab patients) or visit 2r (for ravulizumab patients)
- Informed consent (including optional sub-studies)
- Medical history, including disease characteristics
- Height
- Demographics
- Prior medications
- Vaccination against *Streptococcus pneumoniae* and *Haemophilus influenza type B* (if needed)

- Hepatitis B and C testing
- Tuberculosis history and assessment
- Titers to measure *N. meningitidis* (only if required per local practice/regulations)
- Risk assessment for *Neisseria gonorrhea*
- Other assessments as described in Table 1

9.2.2. Efficacy Procedures

9.2.2.1. Laboratory Assessments of Efficacy

Laboratory assessments of efficacy will be performed at scheduled visits according to Table 1 (OLTP), Table 2 (Transition Period [eculizumab arm]), and Table 3 (Transition Period [ravulizumab arm]).

9.2.2.1.1. Lactate Dehydrogenase

Samples for LDH testing are collected as part of the blood chemistry panel (Section 9.2.4.5) and will be collected prior to study drug administration at scheduled visits. Levels of LDH in serum will be analyzed by a central laboratory. Care must be taken with the collection of LDH as it is the primary endpoint in the study. [redacted]

9.2.2.1.2. Hemoglobin

Samples for hemoglobin testing are collected as part of the hematology panel (Section 9.2.4.5) and will be collected prior to study drug administration at scheduled visits.

9.2.3. Clinical Outcome Assessments

The following clinical outcome assessments are self-reported and will be completed by the patient at time points according to Table 1 (OLTP). Questionnaires will be completed using electronic devices, pre-loaded with COA questionnaires, that will be supplied to patients at Screening Visit 2e (for eculizumab patients) or Visit 2r (for ravulizumab patients).

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 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 originally designed to assess HRQoL in patients with cancer (Stead, 1999) (Cocks, 2007). The EORTC-QLQ-C30 assesses HRQoL across multiple domains, including GHS/global QoL, functioning (physical, role, emotional, cognitive, and social functioning), symptom scales (fatigue, nausea and vomiting, pain), and single items (dyspnea, insomnia, appetite loss, 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).

[redacted]

[redacted]

[redacted]

9.2.4. Safety Procedures

9.2.4.1. Body-Weight

Body weight will be assessed using calibrated scales. Subjects should void (empty bladder) prior to weight assessment. Subjects should be wearing light clothing/undergarments and no shoes during weight assessments. Body weight will be recorded to the nearest 0.1 kg.

9.2.4.2. Vital Signs

Vital signs, including temperature, sitting blood pressure, and pulse will be collected pre-dose at time points according to Table 1 (OLTP), Table 2 (Transition Period [eculizumab arm]), and Table 3 (Transition Period [ravulizumab arm]), and Table 4 (FUP).

9.2.4.3. Physical Examination

A thorough and complete physical examination including an evaluation of the head and neck, lungs, heart, abdomen, extremities, and skin will be performed at time points according to Table 1 (OLTP), Table 2 (Transition Period [eculizumab arm]), and Table 3 (Transition Period [ravulizumab arm]), and Table 4 (FUP). 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

A standard 12-lead ECG will be performed at time points according to Table 1 (OLTP), Table 2 (Transition Period [eculizumab arm]), and Table 3 (Transition Period [ravulizumab arm]), and Table 4 (FUP). Heart rate will be recorded from the ventricular rate and the PR, QRS, and QT (QTcF) intervals 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 6.4. Any blood transfusion will be captured in the transfusion record CRF.

9.2.4.6. Safety Monitoring

For all patients, a patient safety card for *Neisseria meningitidis* infection will be provided to the patient on day 1 and any other visit when needed. Site should review the instructions on the safety card with the patient at each visit. Additionally, for patients randomized into the anti-C5 standard-of-care arm only, a patient safety brochure for eculizumab or ravulizumab will be provided on day 1, as applicable.

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 9.1.6).

In addition, at each visit during the OLTP (Table 1) or Transition Period (Table 2 [eculizumab arm] or Table 3 [ravulizumab arm]) or FUP (Table 4), changes to concomitant medications or procedures will be recorded (Section 8.8).

9.2.4.7. Laboratory Testing

Samples for laboratory testing will be collected at scheduled visits according to Table 1 (OLTP), Table 2 (Transition Period [eculizumab arm]), and Table 3 (Transition Period [ravulizumab arm]), and Table 4 (FUP). **The coagulation blood sample must always be collected first, followed immediately by the blood chemistry sample.**

During blood collection, handling, and processing, the same methodology will be applied across study visits, as best as possible, to preserve the quality of the sample and avoid hemolysis (Section 9.2.2.1).

Detailed instructions for blood sample collection, including the sequence in which blood draws must be performed, are in the laboratory manual provided to study sites. Unscheduled visits may be scheduled to collect blood samples as part of safety monitoring (Section 9.2.4.6).

Hematology, chemistry, and urinalysis samples are planned to be analyzed by a central laboratory whenever possible. A 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 (eg, total C5, CH50, AH50) will be done by a specialized laboratory as outlined in study-related documents provided to the site.

Samples will be obtained on the specified days where permitted. Tests will include:

Blood Chemistry

Sodium	Total protein, serum	Bilirubin*
Potassium	Creatinine**	Uric acid
Chloride	Blood urea nitrogen (BUN)/blood urea	C-reactive protein
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 (RBCs)	Lymphocytes
White blood cells (WBCs)	Monocytes
Red cell indices	Basophils
Platelet count	Eosinophils
Reticulocyte count	

Urinalysis

Color	Glucose	RBC
Clarity	Blood	Hyaline and other casts
pH	Bilirubin	Bacteria
Specific gravity	Leukocyte esterase	Epithelial cells
Ketones	Nitrite	Crystals
Protein	WBC	Yeast
Hemosiderin	Urobilinogen	

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 the Investigator judgment.

Other Laboratory Tests

Other laboratory tests include:

- Coagulation panel: prothrombin time/international normalized ratio (INR) and activated partial thromboplastin time (aPTT)
- D-dimer: This will be collected as part of the coagulation panel
- Immunoglobulin G
- Direct antiglobulin test
- Hepatitis B and C testing
- 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.
- FSH level (only if needed per the investigator to help assess post-menopausal status)
- Unscheduled blood collection for suspected drug hypersensitivity events including suspicion of an AE potentially due to large DTD immune complexes. At minimum to include: CBC, CRP, chemistry, D-dimer, C3, C4, drug concentration, ADA (against pozelimab), and urinalysis (including microscopic evaluation). In addition, an exploratory research serum and plasma sample should be collected.
- Unscheduled blood collection for suspected breakthrough hemolysis events should include, at a minimum, CBC, reticulocyte count, chemistry, coagulation parameters (including D-dimer), total C5, CH50, ADA (against pozelimab), and drug concentrations of pozelimab/cemdisiran and eculizumab or ravulizumab, as applicable. In addition, an exploratory research serum and plasma sample should be collected.
- Titers to measure *N. meningitidis* (only if required per local practice/regulations)

- Drug concentration measurements (Section 9.2.5)
- Immunogenicity measurements (Section 9.2.6)
- Pharmacodynamic and exploratory biomarkers (Section 9.2.7)
- Optional: pharmacogenomic and future biomarker research (Section 9.2.8 and Section 9.2.9)

Abnormal Laboratory Values and Laboratory Adverse Events

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

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

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

Criteria for reporting laboratory values as an AE are provided in Section 10.1.1.

9.2.5. Drug Concentration and Measurements

9.2.5.1. Concentrations of Total Pozelimab, Total Eculizumab, Total Ravulizumab and Total C5

Samples to measure the concentration of total pozelimab, total eculizumab, total ravulizumab and total C5 will be collected prior to any IV or SC study drug administration at time points specified in Table 1 (OLTP), Table 2 (transition period for eculizumab), Table 3 (transition period for ravulizumab), and Table 4 (FUP).

Samples will be obtained on the specified days prior to eculizumab, ravulizumab or the combination administration, as applicable where permitted.

9.2.5.2. 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 (transition period for eculizumab), and Table 3 (transition period for ravulizumab). At each time point, blood samples will be collected prior to any SC study drug administration and 1 to 4 hours after study drug administration.

Samples will be obtained on the specified days prior to ravulizumab or the combination administration where permitted.

9.2.6. 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 (transition period for eculizumab), and Table 3 (transition period for ravulizumab).

Samples that are positive in the pozelimab ADA assay will be banked for the analysis of NAb, until the pozelimab NAb assay is available. Samples that are positive in the cemdisiran ADA assay will not be analyzed for anti-cemdisiran neutralizing activity.

Samples will be obtained on the specified days prior to ravulizumab or the combination administration where permitted.

9.2.7. Pharmacodynamic Biomarker Procedures

Samples for biomarkers will be collected at time points specified in Table 1 (OLTP), Table 2 (transition period for eculizumab), and Table 3 (transition period for ravulizumab). Biomarker variables are described in Section 5.6 and include:

- CH50 (serum)
  - Samples for CH50 testing will be collected prior to study drug administration at scheduled visits. The CH50 tests the function of the terminal complement pathway by assessing the ability of the patient's serum to lyse antibody coated sheep red blood cells (RBC sensitized with rabbit immunoglobulin M). The CH50 value/titer is reported as the reciprocal of the dilution of serum required to lyse 50% of antibody coated sheep red blood cells.

[redacted]

The results of analysis performed on these samples will be presented in the clinical study report (CSR).

Samples will be obtained on the specified days where permitted.

9.2.7.1. Exploratory Biomarkers

[redacted]

9.2.8. 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. Residual

biomarker samples for study-related research, as well as unused PK and ADA samples, will be stored for up to 15 years after the final date of the database lock (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.

9.2.9. 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. Whole blood samples for RNA extraction will be collected at time points according to Table 1 (OLTP). DNA and RNA samples will be collected for pharmacogenomics analyses to understand the genetic determinants of efficacy and safety 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 for 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 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 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 (see Section 11.4.5.1). Medical conditions that existed or were diagnosed prior to the signing of the Informed Consent will be recorded as part of medical history. Abnormal laboratory values and vital signs observed at the time of Informed Consent should also be recorded as medical history. Any subsequent worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug should also be recorded as an AE.

At each visit, the investigator will determine whether any AEs have occurred by evaluating the patient. Adverse events may be directly observed, reported spontaneously by the patient, or by questioning the patient at each study visit. Patients should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 10.2. The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature. The Investigator should follow up on SAEs (and AESIs) until they have resolved or are considered clinically stable; AEs should be followed until they are resolved or last study visit, whichever comes first.

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

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

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the serious adverse event (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 Informed Consent Form) 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 on-treatment period) that the Investigator assesses as related to study drug should also be reported.

All AEs, serious adverse events (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 potentially related to study treatment
  - Suspected *Neisseria* infection
  - Any 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)
  - Adverse events potentially related to suspected large DTD immune complexes (Section 3.2.2 [Mitigation of Potential High Molecular Weight Complex Formation During Treatment Switch])
  - 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 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 treatment 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 may involve the collection of additional details in separate CRFs:

- Injection Site Reactions (ISRs) potentially related to study treatment administration
- Mild infusion reactions potentially related to study treatment
- Mild hypersensitivity reactions potentially related to study treatment

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**. Inpatient 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.

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 subject's health. Treatment for symptom may be given and/or patient hospitalized.

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

Infusion Reactions

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

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

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

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

Injection Site Reactions

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

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

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

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

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, GPS; 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, IECs/IRBs, and the participating investigators of any SUSARs (Suspected Unexpected Serious Adverse Reactions) occurring in other study centers or other studies of the active study drug (pozelimab and cemdisiran) and comparators (eculizumab and ravulizumab), as appropriate

per local reporting requirements. In addition, the sponsor and/or CRO will comply with any additional local safety reporting requirements.

Upon receipt of the sponsor's notification of a SUSAR that occurred with the study drug, the investigator will inform the Institutional Review Board (IRB)/Ethics Committee (EC) unless delegated to the sponsor.

Event expectedness for study drug (pozelimab and cemdisiran), are assessed against the Reference Safety Information section of the Investigator's Brochure that is effective for expedited safety reporting. Event expectedness for comparators (eculizumab and ravulizumab) are assessed against the summary of product characteristics (SmPC).

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

11. STATISTICAL PLAN

This section provides a high-level description of the planned analysis and will serve as the basis for the statistical analysis plan (SAP) for the study.

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

11.1. Statistical Hypothesis

For the primary endpoint of percent change in LDH from baseline to EOT period at week 36 (day 253), the statistical hypotheses being tested in this study are: the null hypothesis is that treatment with pozelimab and cemdisiran combination therapy in patients with PNH who switch from eculizumab or ravulizumab treatment is inferior to treatment with anti-C5 standard-of-care on the primary endpoint, [redacted]. The alternative hypothesis is that treatment with pozelimab and cemdisiran combination therapy is non-inferior to anti-C5 standard-of-care, [redacted].

11.2. Justification of Sample Size and Non-Inferiority Margins

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

11.3. Analysis Sets

The following analysis sets will be utilized in the analysis of this study.

11.3.1. Full Analysis Set

The full analysis set (FAS) includes all patients who are randomized and have received at least one dose of any investigational study drug (pozelimab, cemdisiran, eculizumab, or ravulizumab). The FAS is the main analysis set used for the efficacy analysis in this study. For analyses utilizing the FAS, the treatment assignments are defined to be those assigned via the randomization (as randomized).

11.3.2. Safety Analysis Set

The safety analysis set (SAF) includes all patients who received at least one dose of any investigational study drug (pozelimab, cemdisiran, eculizumab, or ravulizumab). The SAF is the main analysis set used for the safety analysis in this study. For analyses utilizing the SAF, the treatment assignments are determined to be as-treated.

11.3.3. Pharmacokinetic Analysis Set

The PK analysis population includes all patients who received any amount of study drug (pozelimab, cemdisiran, eculizumab, and ravulizumab) and who had 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 (as-treated).

11.3.4. Immunogenicity Analysis Sets

The ADA analysis set includes all patients who received any study drug (pozelimab and/or cemdisiran as applicable) and have at least 1 non-missing ADA result following the first dose of study drug.

The NAb analysis set includes all patients who received any study drug (pozelimab and/or cemdisiran as applicable) and who are negative in the ADA assay or positive in the ADA assay 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].

11.3.5. Per-Protocol Set

The per-protocol set (PPS) includes all patients in the FAS who do not experience any important protocol deviations throughout the course on or prior to week 36 of the study that significantly impact the reliability and/or interpretability of the primary efficacy analysis. Protocol deviations that lead to exclusion for the PPS will be identified prior to database lock.

11.3.6. Biomarker Endpoint Analysis Set

The biomarker endpoint (pharmacodynamic) analysis set includes all patients who received any amount of study drug (pozelimab, cemdisiran, eculizumab, or ravulizumab) and who had at least 1 non-missing analyte measurement following the first dose of study drug.

11.4. Statistical Methods

Continuous variables will be summarized within each treatment group, presenting the following descriptive statistics: the sample size (ie, number of observations with an available value of the variable), mean, standard deviation, median, minimum, maximum, 1st quartile and 3rd quartile.

Categorical data will be summarized within each treatment group by presenting the frequency (ie, total number of observations within each level of the categorical variable within a given treatment group). All levels of the categorical variable will be included. For categorical variables that are ordinal in nature, the order in which the levels of the categories are displayed will be consistent with their natural ordering. Percentages will also be calculated for each level of the categorical variables with respect to the total sample size of the respective treatment arm. Category levels with frequencies of 0 will have the corresponding percentage displayed as 0%.

11.4.1. Patient Disposition

Patient disposition for this study will be summarized by reporting metrics describing patients' status at major milestone throughout the study. The following metrics will be collected:

- Number of patients screened (defined as having signed the ICF)
- Number of screen failed patients categorized by reason for screen failing
- Number of randomized patients (defined as having received a randomization number per IWRS)
- Number of non-randomized but treated patients (if applicable)
- Number of randomized but not treated patients (if applicable)
- Number of patients completing the OLTP
  - Number of patients who took study medication until the end of the OLTP
  - Number of patients discontinuing the treatment early during the OLTP along with reasons for early treatment discontinuation
- Number of patients who withdrew from the study early along with reasons for early study withdrawal.

11.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group and overall using the FAS. The demographic and baseline characteristics variables are:

- Age at screening (year)
- Age category (<35, 35 to 65, ≥65)

- Sex (Male, Female)
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White and Other)
- Ethnicity (Hispanic or Latino, non-Hispanic or Latino, Not Reported, Unknown)
- Baseline Weight (kg)
- Baseline Height (cm)
- Baseline Body mass index (BMI)

Baseline disease characteristics will be summarized descriptively by treatment group and overall using the FAS. The baseline disease characteristics variables are:

- Duration of PNH at screening
- Age at onset of PNH
- Stratification factors as indicated in the IWRS system for presence of RBC/whole blood transfusion within the past year prior to randomization (yes/no)
- Stratification factor as indicated in the IWRS system for LDH levels (≤1.5 × ULN or >1.5 × ULN)
- Stratification factor as indicated in the IWRS system for anti-C5 standard-of-care therapy taken at screening (eculizumab versus ravulizumab)
- Number of RBC/whole blood transfusion within the past year prior to randomization (0, 1 to 14; >14)
- Number of units of RBC transfused (0, 1 to 14, >14)
- Baseline LDH level
- PNH clone size
- History of aplastic anemia
- History of venous thromboembolism
- Baseline hemoglobin level
- Baseline renal function

Patient medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be descriptively summarized by treatment group and overall using the FAS, showing patient counts and percentages by primary System Organ Class (SOC) and Preferred Term (PT).

11.4.3. Efficacy Analyses

Unless stated otherwise, analysis of all efficacy variables will be performed using the FAS. Treatment differences are defined as taking the value of the relevant summary statistic in the pozelimab + cemdisiran treatment arm minus the corresponding value in the anti-C5 standard-of-care arm.

For LDH, the baseline value is defined as follows:

- For patients entering the study who were previously treated with eculizumab: the last value of the assessment in the screening period immediately preceding randomization.
- For patients entering the study who were previously treated with ravulizumab: last value of the assessment immediately preceding their last dose of ravulizumab in the screening period.

For all other efficacy variables, baseline is the last value of assessment immediately preceding randomization.

11.4.3.1. Primary Efficacy Analysis

[redacted]

11.4.3.2. Secondary Efficacy Analysis

Secondary Efficacy Analysis:

[redacted]

[redacted]

11.4.4. Control of Multiplicity

Details of the testing strategy will be specified in the SAP.

11.4.5. Safety Analysis

Unless stated otherwise, analysis of all safety variables will be performed using the SAF.

The baseline value of a safety parameter is defined to be the value of its last available assessment prior to randomization.

In addition to the study periods defined in Section 6.1, the following observation periods are also defined and will be utilized for analysis as applicable:

- The pretreatment period is defined as the time from signing the ICF up to the time of randomization.
- The on-treatment period is defined as from the time of randomization to either:
  - the last dose of IMP plus 52 weeks for those not continuing into R3918-PNH-2050 (the OLE study).
  - the End of the OLTP Visit for those continuing into R3918-PNH-2050.
- The mono-treatment period is defined as starting at the time of randomization and concludes at the initiation of study drug administration during the week 4 visit.

- The combination-treatment period is defined as starting after study drug administration at week 4 up until the end of the OLTP.
- The post-treatment period applies to all patients who are not continuing into R3918PNH-2050 and is defined as any time after the end of the on-treatment period.
- The transition period applies to patients receiving anti-C5 standard-of-care who plan on continuing into R3918-PNH-2050 and is defined as the period after the on-treatment period to the first dose of IMP in R3918-PNH-2050.

11.4.5.1. Adverse Events

Adverse events summaries will be presented with incidence tables. Adverse event incidence tables will present the number (n) and percentage (%) of patients in each treatment arm experiencing an AE, sorted by decreasing frequency of SOC and PT in the anti-C5 standard-of-care arm. Multiple occurrences of the same event in a patient will only be counted once in the tables within a treatment period. In AE incidence tables by severity, the worst severity will be counted for multiple events occurring in a patient. The denominator for percentage computation is the number of patients in the SAF receiving the respective treatment. An AE will be considered as occurring in a respective period if either:

- The onset of the initial instance of that AE was within the time period
- The AE was already present/occurred and then worsened in severity within the time period
- The AE was already present/occurred and then became serious within the time period

Treatment-emergent adverse events (TEAEs) are defined as follows for patients allocated to:

- Combination Therapy
  - Adverse events that develop or worsen after the first dose of investigational medicinal product (IMP) administered in the R3918-PNH-2022 study
- Anti-C5 SOC therapy
  - Eculizumab
    - Adverse events that develop or worsen after the first dose of IMP administered in the R3918-PNH-2022 study
  - Ravulizumab
    - Adverse events that develop or worsen post-randomization on or after day 1 in the R3918-PNH-2022 study

Please note that the definition of the start of the TEAE period for patients randomized to anti-C5 SOC therapy taking ravulizumab differs from the start of the TEAE period for patients randomized to anti-C5 SOC therapy taking eculizumab and those randomized to the combination therapy given that the first day of IMP for those randomized to Anti-C5 SOC therapy taking ravulizumab will start at week 4 given the Q8W administration of ravulizumab and not on day 1.

Summaries of AE incidence by treatment arm will include:

- Overview of TEAEs during the OLTP, summarizing number of events and percentage of patients within the specified category
  - Total number of TEAEs
  - Total number of serious TEAEs
  - Total number of treatment-emergent AESIs
  - Total number of severe TEAEs
  - Total number of patients with any TEAEs
  - Total number of patients with any serious TEAEs
  - Total number of patients with any treatment-emergent AESIs
  - Total number of patients with any severe TEAEs
  - Patients with any TEAEs leading to permanent discontinuation of study drug
  - Patients with any TEAEs leading to withdrawal from study
  - Patients with any TEAEs leading to death
- TEAEs during the OLTP by SOC and PT
  - TEAEs
  - TEAEs by maximum severity: mild, moderate, or severe
  - TEAEs resulting in permanent study treatment discontinuation
- Serious TEAEs during the OLTP by SOC and PT
- AESIs by SOC and PT
  - Treatment-emergent AESIs during the OLTP
  - AESIs resulting in permanent study treatment discontinuation
  - Treatment-emergent AESIs during the transition period
- All pretreatment AEs by SOC and PT
- All AEs during the Transition Period by SOC and PT (for anti-C5 standard-of-care patients continuing into the OLEs study)
- All TEAEs during the FUP by SOC and PT (for patients not continuing into either R3918-PNH-2022 or the R3918-PNH-2050)
- TEAEs leading to death

11.4.5.2. Other Safety

Vital Signs

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

Laboratory Tests

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

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

11.4.5.3. Treatment Exposure

Study treatment exposure is measured by the total number of complete and incomplete injections administered for infusions and SCs. SC injection location is also recorded.

The total number of complete and incomplete injections during the on-treatment period administered for IV infusions and SC, will be summarized by treatment group using descriptive statistics.

The duration of study participation will be calculated as: [date of last study contact] – [first dose day] + 1, where the 'date of last study contact' is taken from the respective Study Completion CRF. The duration of study participation will be summarized by treatment group using descriptive statistics.

11.4.5.4. Treatment Compliance

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

Treatment Compliance=(Number of investigational study drug doses taken during the on-treatment period)/(Number of investigational study drug doses planned for the on-treatment period) × 100%.

The number of planned investigational study drug doses does not include doses that were missed because study drug was temporarily withheld. Similarly, doses at timepoints subsequent to when a patient discontinues study treatment or withdraws from the study will not be counted in the number of planned doses.

Treatment compliance will be summarized via descriptive statistics for each interventional study drug administered in this study using for the appropriate treatment arm.

11.4.6. Pharmacokinetics

11.4.6.1. Analysis of Drug Concentration Data

The concentrations of total pozelimab, cemdisiran, cemdisiran metabolites, total ravulizumab, total eculizumab and total C5 over time and selected pharmacokinetic parameters will be summarized by descriptive statistics for each of the treatment groups for the purpose of estimating exposures in these groups. This descriptive statistical assessment will include the geometric means and ratios of the geometric means for selected PK parameters, as deemed appropriate.

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 less than 9-fold for anti-pozelimab antibody assay over baseline titer levels
- Treatment-emergent ADA response, defined as any post-dose positive ADA assay response when the baseline results are negative
  - Treatment-emergent ADA response may be further characterized as persistent, transient, or indeterminate
- Treatment boosted ADA response, defined as any post-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 values
  - Low (titer <1,000)
  - Moderate (1,000≤ titer ≤10,000)
  - High (titer >10,000)
- NAb status in the 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 dose group will be provided. Incidence of treatment-emergent ADA and NAb will be assessed as absolute occurrence (N) and percent of patients (%), grouped by study cohorts and ADA titer level.

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

11.4.8. Analysis of Pharmacodynamic and Exploratory Biomarker Data

Analysis of PD and exploratory 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. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program 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/surgical 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) Medidata Rave.

12.1.2. Electronic Systems

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

- IVRS/IWRS system – randomization, study drug supply
- EDC system – data capture – Medidata Rave
- Statistical Analysis System (SAS) – statistical review and analysis
- Pharmacovigilance safety database
- Electronic Clinical Outcome Assessment (eCOA) system – electronic device.

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

12.2.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic Case Report Forms (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 eCRF must be signed electronically by the investigator. This signed declaration accompanies each set of patient final eCRF 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 '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 CLOSEOUT OF A SITE

15.1. Premature Termination of the Study

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

15.2. Close-out of a Site

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

Investigator's Decision

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

Sponsor's Decision

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

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

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

16. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

17. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

18. PUBLICATION POLICY

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

19. REFERENCES

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20. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A Randomized, Open-label Eculizumab and Ravulizumab Controlled, Non-Inferiority Study to Evaluate the Efficacy and Safety of Pozelimab and Cemdisiran Combination Therapy in Patients with Paroxysmal Nocturnal Hemoglobinuria who are Currently Treated with Eculizumab or Ravulizumab 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 Eculizumab and Ravulizumab Controlled, Non-Inferiority Study to Evaluate the Efficacy and Safety of Pozelimab and Cemdisiran Combination Therapy in Patients with Paroxysmal Nocturnal Hemoglobinuria Who are Currently Treated with Eculizumab or Ravulizumab

Protocol Number: R3918-PNH-2022

Protocol Version: R3918-PNH-2022 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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