REGENERON
Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN
VERSION: 1.0

Clinical Study Protocol 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

Compound:	Pozelimab (REGN3918) Cemdisiran (ALN-CC5)
Protocol Number:	R3918-PNH-2022
Clinical Phase:	Phase 3
Sponsor:	Regeneron Pharmaceuticals, Inc.
Study Biostatistician:	[redacted]
Clinical Trial Manager:	[redacted]
Study Medical Director:	[redacted]
Version/Date:	1.0 / 18JUL2023

The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
ATC	Anatomical Therapeutic Chemical
CH50	Total Complement hemolytic activity assay
COA	Clinical outcome assessment
CRF	Case report form (electronic or paper)
ECG	Electrocardiogram
EORTC	European Organisation for Research and Treatment of Cancer
EoS	End of study
eGFR	Estimated glomerular filtration rate
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full analysis set
HRQoL	Health-related quality of life
ICF	Informed consent form
ICH	International Council for Harmonisation
IV	Intravenous
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
OLE	Open-label extension
[redacted]	[redacted]
[redacted]	[redacted]
PK	Pharmacokinetic
PNH	Paroxysmal nocturnal hemoglobinuria
PRO	Patient reported outcome
PT	Preferred term
Q2W	Every 2 weeks
Q4W	Every 4 weeks
Q8W	Every 8 weeks
QLQ-C30	Quality of life questionnaire-core 30
QW	Once weekly

RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SC	Subcutaneous
SOC	System organ class
TEAE	Treatment-emergent adverse event
[redacted]	[redacted]
ULN	Upper limit of normal
WBC	White blood cell
WHODD	World Health Organization Drug Dictionary

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to support the credibility of the study results by pre-specifying the statistical approaches for the analysis of data generated from the R3918-PNH-2022 (ACCESS-2) clinical trial as described in Amendment 1 of the corresponding protocol, dated 21JUN22.

Due to feasibility challenges related to enrollment and not due to any efficacy or safety reasons, the sponsor decided to cease enrollment for the study effective 20DEC2022. As a result, only three patients were enrolled. As the study was terminated prematurely the objectives stated in the protocol will not be analyzed as planned but instead, will be summarized descriptively as outlined in this plan.

1.1. Study Description and Objectives

The objective of the study was to evaluate the efficacy, safety, PK and immunogenicity of pozelimab and cemdisiran (combination therapy) in adult patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) who switch from eculizumab or ravulizumab therapy to the combination treatment versus patients who continue their eculizumab or ravulizumab therapy. Additional information can be found in the study protocol. Due to early termination and small sample size, the original primary and secondary objectives will not be analyzed as planned.

1.1.1. Primary Objective

The primary objective of the study was to evaluate the effect of pozelimab and cemdisiran combination therapy on hemolysis, as assessed by LDH (lactate dehydrogenase), after 36 weeks of treatment, in patients with PNH who switch from eculizumab or ravulizumab therapy versus patients who continue their eculizumab or ravulizumab therapy.

1.1.2. Secondary Objectives

The secondary objectives of the study were 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 CH50
  - Hemoglobin levels
  - Fatigue as assessed by Clinical Outcome Assessment (COA)
  - Health-related quality of life (HRQoL) as assessed by COA
  - Safety and tolerability
- To assess the concentrations of total pozelimab and either total eculizumab or total ravulizumab in serum and total cemdisiran and total C5 protein in plasma

- To assess the immunogenicity of pozelimab and cemdisiran

Exploratory objectives are considered out of scope of this SAP. Additional details on exploratory objectives can be found in the protocol Section 2.3.

1.2. Statistical Hypothesis

The primary hypothesis was 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. Due to early termination and small sample size, no hypothesis testing will be conducted.

1.3. Interim Analysis

No interim analysis was planned for this study.

1.4. Modifications from the Statistical Section in the Final Protocol

As this study was terminated prematurely, the study objectives stated in the study protocol will not be analyzed as planned. Demographic, safety and efficacy data will be provided in the listings.

The efficacy analysis as specified in Protocol Amendment 1 for this study (dated 21JUN2022) as well as country specific amendment 2 for Germany (dated 03NOV2022) is modified to remove the following primary and secondary endpoints:

Primary Endpoints to be removed:

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

Key Secondary Endpoints to be removed:

- 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 to 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

Other Secondary Endpoints to be removed:

- 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

1.5. Revision History for SAP Amendments

This section is not applicable as this is the original version of the SAP.

2. INVESTIGATION PLAN

2.1. Study Design

This was an open-label, active-controlled (ravulizumab or eculizumab), non-inferiority study of pozelimab in combination with cemdisiran in patients with a confirmed diagnosis of PNH who were currently being treated with anti-C5 standard of care (SOC) (either ravulizumab or eculizumab).

The study consisted of the following periods: up to 6-week screening period and a 36-week open-label treatment period (OLTP) with either anti-C5 SOC or the combination of pozelimab and cemdisiran.

On day 1 (the day of randomization), patients who complete the screening period and were deemed eligible for enrollment, were randomized in a 1:1 ratio to one of the following treatment regimens:

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

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

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

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

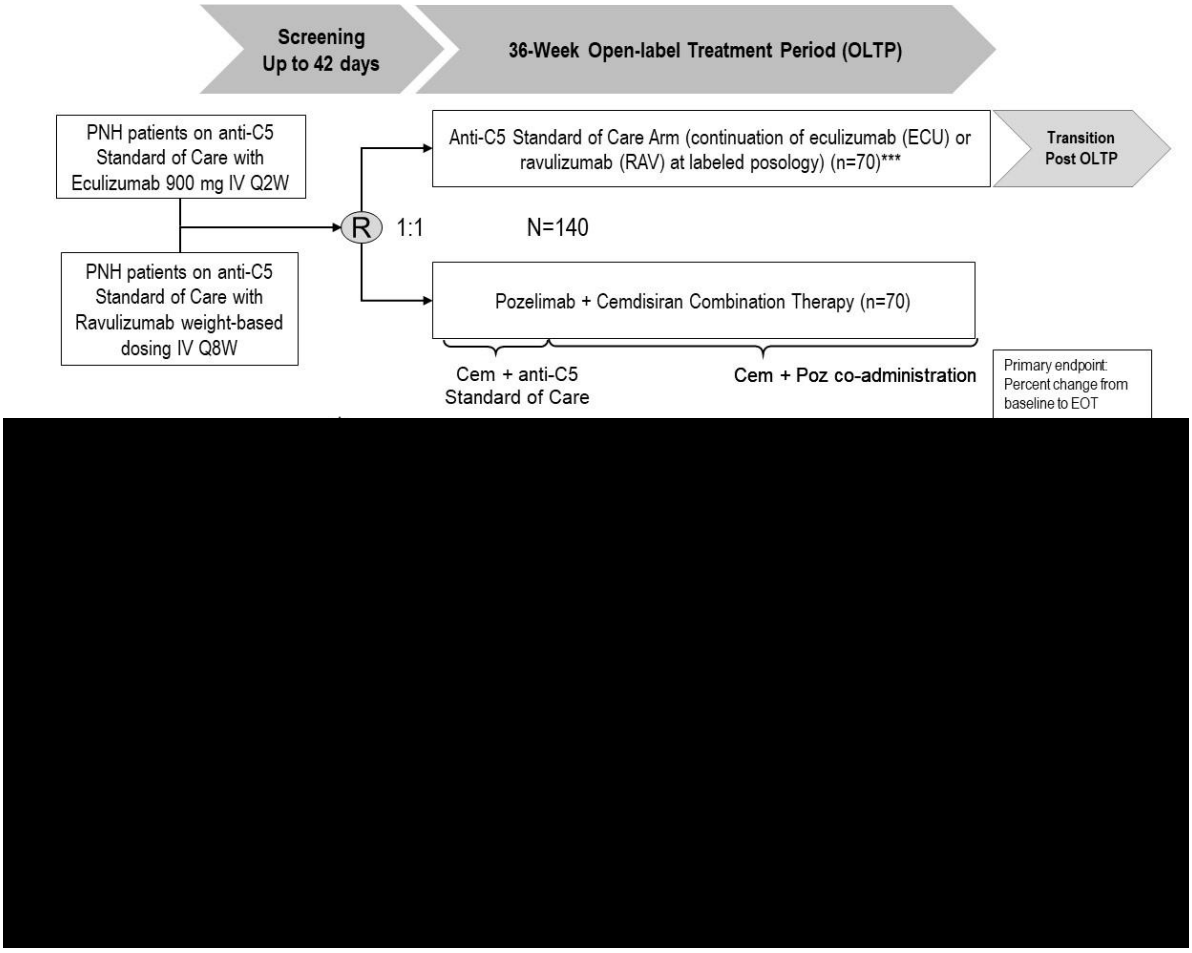
[redacted]	[redacted]

Randomization was stratified based on the following factors:

1. The screening visit LDH value used for randomization (≤ 1.5 × ULN, > 1.5 × ULN)
2. RBC/whole blood transfusion within the past 1 year prior to day 1 (yes, no)
3. Anti-C5 standard-of-care therapy taken at screening (eculizumab, ravulizumab)

Presented below in Figure 1 is the study flow diagram depicting the different periods of the study with the scheduled visits and treatment administrations.

Figure 1: Study Flow Diagram



3. ANALYSIS SETS

In accordance with guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (ICH, 1998), the following populations will be used for statistical analysis:

3.1. Full Analysis Set

The full analysis set (FAS) is comprised of all patients who were randomized who received at least one dose of any investigational study drug (pozelimab, cemdisiran, eculizumab or ravulizumab). For analyses utilizing the FAS, the treatment assignments are defined to be those assigned via the randomization (as-randomized).

3.2. Safety Analysis Set

The safety analysis set (SAF) includes all randomized participants who received any investigational study drug (pozelimab, cemdisiran, eculizumab or ravulizumab). It is based on the treatment received (as-treated).

3.3. Pharmacokinetic Analysis Sets

The PK analysis population includes all patients who received any investigational study drug (pozelimab, cemdisiran, eculizumab, and ravulizumab) and who had at least 1 non-missing result following the first dose of study drug.

3.4. Immunogenicity Analysis Sets

The ADA analysis sets are defined for each study drug separately (pozelimab or cemdisiran) includes all patients who received any study drug and had at least one non-missing ADA result following the first dose of the respective study drug. The ADA analysis set is based on the actual treatment received (as treated) rather than as randomized.

4. GENERAL STATISTICAL ANALYSIS CONSIDERATIONS

As the scope of the analysis is limited to listings, the data displayed will simply be a reiteration of the data captured in the study databases.

5. PATIENT DISPOSITION

Due to early termination of the study, a total of 3 patients were enrolled. A patient disposition listing and listing of screen-failed patients will be provided.

6. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

6.1. Demographics

The following demographic variables were recorded in the study and presented in a listing:

- 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) (kg/m2)

6.2. Baseline Disease Characteristics

The following baseline disease characteristcs were recorded in the study:

- 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 day 1 (yes or 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 or ravulizumab)
- Number of RBC/whole blood transfusion within the past year prior to day 1 (0, 1 to 14; >14)
- Number of units of RBC transfused within the past year prior to day 1 (0, 1 to 14, >14)
- Baseline LDH level
- Baseline renal function (ie, Creatinine and eGFR)
- PNH clone size
- History of venous thromboembolism
- Baseline hemoglobin level
- History of aplastic anemia

- History of breakthrough hemolysis

Listings will be generated for baseline disease characteristics of interest.

6.3. Medical History

Patient medical history were recorded and coded to a Preferred Term (PT) and associated primary System Organ Class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA®). All reported patient medical history will be presented in a listing.

7. EFFICACY

Due to early termination, efficacy variables will not be analyzed. Listings of important efficacy variables will be provided.

7.1. Description of Efficacy Data

7.1.1. Primary Efficacy Data

LDH (Lactate Dehydrogenase)

LDH (serum) is a lab-based measure ascertained from analysis of patients' blood samples that is a measure of intravascular hemolysis. Blood samples from patients will be drawn at the first screening visit (V1) and all visits post-randomization (V3 – V15). These samples will be sent to a lab for analysis to determine the amount of LDH in the serum (LDH value).

Transfusion Record

Transfusions with RBCs during the study (including the screening period) may proceed according to the following predefined criteria that will trigger a transfusion (referred subsequently as the protocol algorithm), 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

LDH assessments were collected per the Schedule of Events in Section 13.1. Listings that contain relevant information pertaining to all LDH and Blood Transfusions will be provided.

7.1.2. Secondary Efficacy Data

The following are secondary efficacy measures that were captured in the study:

- Hemoglobin
- FACIT-Fatigue Scale
- EORTC-QLQ-C30

The assessments were collected per the Schedule of Events in Section 13.1. Detailed description of these measurements can be found in section 9.2.3 of the study protocol.

Listings will be provided for the assessments listed above.

8. SUMMARY OF EXPOSURE DATA

8.1. Investigational Study Drug Exposure

Listings will be provided for IV infusions [redacted] and the number of SC injections during the OLTP for each investigational study drug.

8.2. Duration of Follow-up

Not Applicable

8.3. Prior and Concomitant Medications

Medications usage, dictionary coded by WHODD, will be classified according to the time of usage. Prior medications are medications taken prior to the date of randomization with a stop date prior to the date of randomization. Concomitant medications are medications taken between the date of randomization and the EOS visit (inclusive for both dates). This includes medications with a start date before administration of study drug. Listings will be provided.

8.4. Prior and Concurrent Procedures

Procedures undergone by the patient, dictionary coded by MedDRA, will be classified according to the time of occurrence. Prior procedures are procedures performed prior to the date of randomization. Concomitant procedures are procedures performed between the date of randomization and the EOS visit (inclusive for both dates). Listings will be provided.

9. ANALYSIS OF SAFETY DATA

9.1. Adverse Events

All AEs will be reported and coded using Medical Dictionary for Regulatory Activities (MedDRA®). A listing of all AEs will be included.

9.2. Laboratory Parameters

The clinical laboratory data consists of blood chemistry, hematology, urinalysis, coagulation, pregnancy test and other tests and will be collected according to the Schedule Events in Section 13.1.

Listings will be provided for lab tests of interest. Abnormal lab values will be noted.

9.3. Vital Signs

Body weight and vital signs (temperature, pulse, and sitting blood pressure) were collected at scheduled visits according to the schedule of events in Section 13.1.

Body weight, BMI and vital signs values will be included in a listing.

9.4. Electrocardiogram (ECG)

The following standard 12-lead ECG parameters were recorded and analyzed according to the Schedule Events in Section 13.1:

- Ventricular rate
- Heart rate
- QRS interval
- QT corrected for heart using Fridericia's formula (QTcF) defined as

  $QTcF\ (ms) = QT/RR^{1/3}$

  where QT is the uncorrected QT interval measured in ms, and RR is 60/HR with HR being the heart rate in beats per minutes.
- Overall ECG status along with findings.

Listings of ECG parameters (PR interval, QT interval, QTcF interval, QRS interval, and heart rate [from ventricular rate]) will be provided.

9.5. Other Safety Data

Not applicable

9.6. Immunogenicity Data

9.6.1. Immunogenicity Variables

The Immunogenicity variables include ADA status and titer at nominal sampling time/visit. Serum samples for ADA were collected at the clinic visits specified in Section 13.1. For each study drug, samples positive in the ADA assay will be further characterized for ADA titers.

9.6.2. Analysis of Immunogenicity Data

9.6.2.1. Analysis of ADA Data

The immunogenicity variables described in Section 9.6.1 will be summarized using descriptive statistics. Immunogenicity will be characterized per study drug by ADA status, ADA category and maximum titer observed in participants in the ADA analysis sets. For samples confirmed as drug specific ADA positive, but found negative at the lowest titer dilution, the lowest dilution in the titer assay is imputed.

The ADA status of each participant may be classified as one of the following:

- Positive
- Pre-existing - If the baseline sample is positive and all post baseline ADA titers are reported as less than 4-fold (for anti-cemsiran) and 9-fold (for anti-pozelimab) over the baseline titer value
- Negative - If all samples are found to be negative in the ADA assay.

The ADA category of each positive participant is classified as:

- Treatment-boosted - A positive result at baseline in the ADA assay with at least one post baseline titer result ≥4-fold (for anti-cemsiran) and 9-fold (for anti-pozelimab) over the baseline titer value
- Treatment-emergent - A negative result or missing result at baseline with at least one positive post baseline result in the ADA assay. Participants that are treatment-emergent will be further categorized as follows:

Treatment-emergent is further sub-categorized as:

- Persistent - A positive result in the ADA assay detected in at least 2 consecutive post baseline samples separated by at least a16-week post baseline period [based on nominal sampling time], with no ADA-negative results in-between, regardless of any missing samples
- Indeterminate - A positive result in the ADA assay at the last collection time point only, regardless of any missing samples
- Transient - Not persistent or indeterminate, regardless of any missing samples

The maximum titer category of each participant is classified as:

- Low (titer <1,000)

- Moderate (1,000 ≤ titer ≤ 10,000)
- High (titer >10,000)

The following will be summarized by treatment group and ADA titer level:

- Number (n) and percent (%) of ADA-negative participants
- Number (n) and percent (%) of pre-existing participants
- Number (n) and percent (%) of treatment-emergent ADA positive participants
  - Number (n) and percent (%) of persistent treatment-emergent ADA positive subjects/patients
  - Number (n) and percent (%) of indeterminate treatment-emergent ADA positive subjects/patients
  - Number (n) and percent (%) of transient treatment-emergent ADA positive subjects/patients
- Number (n) and percent (%) of treatment-boosted ADA positive participants

Listing of all ADA titer levels will be provided for participants with pre-existing, treatment-emergent and treatment-boosted ADA response.

9.7. Pharmacokinetic Data

Listings of relevant parameters will be provided .

10. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

10.1. Definition of Baseline for Efficacy/Safety Variables

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/safety variables, baseline is the last value of assessment immediately preceding randomization. When scores are used, this rule applies to scores, not individual variables.

10.2. Data Handling Conventions

In the event there are multiple assessments for the same endpoint within an analysis window, the assessment occurring on the day of the corresponding study visit will be utilized in the efficacy analysis. In the event there is no assessment on the day of the study visit, the assessment closest in temporal proximity to the day of study visit will be utilized in the efficacy analysis, and will prioritize measurements taken pre-dose if applicable. If there are two assessments that are equidistant from the day of study visit (one assessment prior and one assessment after the day of study visit), the prior assessment will be utilized in the efficacy analysis.

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

Missing data will not be imputed in listings.

10.3. Missing Data Conventions for Non-Efficacy Endpoints

Not Applicable

10.4. Assignment of Data to Visit Windows and Unscheduled Assessments

Not Applicable

10.5. Pooling of Categorical Variables for Statistical Analyses

Not Applicable

11. TECHNICAL DETAILS PERTAINING TO INTERIM ANALYSIS

Not applicable

12. REFERENCES

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13. APPENDIX

13.1. Schedule of Time and Events

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

Schedule of Events for the Open-Label Treatment Period

Study Procedure (Visit)[1]	Screening Period[2]		Open Label Treatment Period (OLTP)												
															EOLTP / EOS
Visit #	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Week	Up to -6	-2	0	2	4	6	8	10	12	16	20	24	28	32	36
Day	Up to -42	-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:															
eCOA device dispensation		X													
Inclusion/Exclusion	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														
Patient safety card for *Neisseria meningitidis*[10]			X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization			X												
Treatment:															
IVRS/IWRS	X		X	X	X	X	X	X	X	X	X	X	X	X	X

Study Procedure (Visit)[1]	Screening Period[2]		Open Label Treatment Period (OLTP)												
															EOLTP / EOS
Visit #	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Week	Up to -6	-2	0	2	4	6	8	10	12	16	20	24	28	32	36
Day	Up to -42	-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
Pozelimab and cemdisiran arm	[redacted]														
Anti-C5 standard-of-care arm: Eculizumab															
Anti-C5 standard-of-care arm: Ravulizumab															
Concomitant meds and treatment	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
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:															
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

Study Procedure (Visit)[1]	Screening Period[2]		Open Label Treatment Period (OLTP)												
															EOLTP / EOS
Visit #	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Week	Up to -6	-2	0	2	4	6	8	10	12	16	20	24	28	32	36
Day	Up to -42	-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
Adverse events	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
Laboratory Testing[24]:															
Titers to measure *N. meningitidis* (only if required per local practice/regulations)	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
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]:															
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 conc. of eculizumab			X	X	X				X			X			X
Blood samples for conc. of ravulizumab			X	X	X				X			X			X
Blood samples for conc. of total C5			X	X	X		X		X	X	X	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
Biomarkers:															
[redacted]															

Study Procedure (Visit)[1]	Screening Period[2]		Open Label Treatment Period (OLTP)												
															EOLTP / EOS
Visit #	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Week	Up to -6	-2	0	2	4	6	8	10	12	16	20	24	28	32	36
Day	Up to -42	-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
Optional pharmacogenomics (DNA AND RNA):															
Whole blood for DNA isolation (optional genomics sub-study)[33]			X												
Whole blood for RNA isolation (optional genomics sub-study)			X						X						X

1. 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. Assessments common to both studies (screening visit of R3918 PNH-2022 and V1t of the R3918-PNH-2021) will not be duplicated.

2. Additional screening visits may be needed such as to obtain LDH one day before or on the day of eculizumab or ravulizumab administration, repeat blood collection, vaccination, etc.

3. For patients taking ravulizumab, the randomization visit should occur 4 weeks 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 with a known C5 mutation (ie, C5 variants R885H/C) or those 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 who have not previously had testing for a C5 mutation may be asked for a mutation analysis to be conducted locally as part of the study, if the patient consents 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 or any other visit when needed. Site should review the instructions on the safety card with the patient at each visit.

11. [redacted]

12. Pozelimab administration: administer study treatment to patients previously taking eculizumab or ravulizumab and randomized to pozelimab/cemdisiran arm.

13. Cemdisiran administration: administer study treatment to patients randomized to pozelimab/cemdisiran arm.

14. [redacted]

[redacted]

15. [redacted]

16. [redacted]

17. Intentionally left blank

18. Intentionally left blank

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, chemistry, reticulocyte count, total C5, CH50, drug concentrations of pozelimab/cemdisiran/eculizumab/ravulizumab (depending on the patient's randomization/enrollment), 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, chemistry, reticulocyte count, total C5, CH50 and drug concentrations of pozelimab/cemdisiran/eculizumab/ravulizumab, 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, the lab sample should be repeated. 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 screening, 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.

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 1-4 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 ADA and PK samples may be collected at or near the onset of the event.

32. [redacted]

33. Whole blood samples for DNA extraction (optional) should be collected on day 1 (pre dose) but can be collected at a later study visit.

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Approval/eSignature	[redacted] 20-Jul-2023 20:06:40 GMT+0000
Approval/eSignature	[redacted] 20-Jul-2023 22:40:09 GMT+0000
Approval/eSignature	[redacted] 21-Jul-2023 10:33:12 GMT+0000

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