REGENERON
Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN
VERSION: 2.0

Clinical Study Protocol Title:

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

Compound:	Pozelimab (REGN3918)
	Cemdisiran (ALN-CC5)
Protocol Number:	R3918-PNH-2092
Clinical Phase:	Phase 2
Sponsor:	Regeneron Pharmaceuticals, Inc.
Study Biostatistician:	[redacted]
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
AH50	Alternative pathway hemolytic activity assay
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the curve
C	Complement component (e.g., C3, C5)
CH50	Total complement hemolysis activity assay
COA	Clinical outcome assessment
CRF	Case report form (electronic or paper)
CRP	C-reactive protein
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer: Quality-of-Life Questionnaire core 30 items
EOT	End of treatment
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue score
FAS	Full analysis set
FBR	Future biomedical research
FDA	Food and Drug Administration
GHS	Global health status
ICF	Informed consent form
ICH	International Council for Harmonisation
IV	Intravenous
LDH	Lactate dehydrogenase
MAVE	Major adverse vascular events
MI	Multiple Imputation
OLEP	Open-label extension period (an optional period)
OLTP	Open-label treatment period (main study period)

PD	Pharmacodynamics
PF	Physical function
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetic
PNH	Paroxysmal nocturnal hemoglobinuria
PT	Preferred term
Q2W	Every 2 weeks
Q4W	Every 4 weeks
QoL	Quality of life
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous
SOC	System organ class
TEAE	Treatment-emergent adverse event
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Woman of childbearing potential

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of study results. The SAP is intended to be a comprehensive and detailed description of the strategy and statistical methods to be used in the analysis of data for this study.

1.1. Background/Rationale for Study Design

Background information on paroxysmal nocturnal hemoglobinuria (PNH), pozelimab (REGN3918) and cemdisiran (ALN-CC5) may be found in the protocol. This trial is designed as a randomized, open-label, 28-week treatment study to assess the safety, efficacy, and PD effects of 2 dose regimens of pozelimab and cemdisiran combination in patients with PNH who have been treated with pozelimab monotherapy for at least 26 weeks.

Patients will be randomized in 1:1 ratio to receive pozelimab 400 mg SC Q4W and cemdisiran 200 mg SC Q4W (arm 1) or pozelimab 400 mg SC Q2W and cemdisiran 200 mg SC Q4W (arm 2).

In addition to safety, the study includes secondary efficacy endpoints to assess the effect of the combination treatment on control of intravascular hemolysis, as measured by LDH.

The long-term safety and efficacy of the combination treatment will be assessed by providing the patients who complete the main 28-week open-label treatment period (OLTP) on combination treatment an opportunity to participate in an optional long-term open-label extension period (OLEP), in which patients shall continue to receive study treatment for an additional 52 weeks. During the OLTP, a patient meeting breakthrough hemolysis criteria and inadequate LDH response will qualify for intensified treatment, which consists of an initial IV loading dose of pozelimab and intensified pozelimab regimen to be administered Q2W along with cemdisiran at Q4W, for a period of 32 weeks. Patients who opt not to participate in the OLEP (or those who stop treatment for any reason) will be followed for 52 weeks after the last dose of study treatment, to monitor for safety as the study drugs are gradually eliminated from the body. Patients who complete the OLEP and stop study treatment will also be followed for 52 weeks after their last dose of study treatment.

1.2. Study Objectives

1.2.1. Primary Objective

The primary objective of the study is to evaluate the safety and tolerability of 2 dosing regimens of pozelimab and cemdisiran combination therapy during the OLTP.

1.2.2. Secondary and Exploratory Objectives

The secondary objectives of the study are:

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

The exploratory objectives of the study are:

- To explore the effect of the combination treatment on clinical thrombosis events
- To explore the effect of the combination treatment on renal function and renal injury biomarkers
- To explore the effect of the combination treatment on complement activation and intravascular hemolysis relevant to PNH and other related diseases
- To explore the effect of the combination treatment on PNH clone size
- To evaluate the effect of the combination treatment on treatment satisfaction
- To explore the effect of the combination treatment on a novel COA measuring PNH-specific symptoms
- To study the combination treatment mechanism of action (including relationship to safety and efficacy), complement pathway biology, PNH and related complement-mediated diseases
- To explore the effect of the combination treatment on PNH symptoms
- To explore potential differences in genotype and gene expression that may influence efficacy and safety of the combination treatment for further understanding of C5, PNH, or other conditions associated with complement-mediated injury (for patients who consent to participate in a genomics sub-study)
- To explore safety and efficacy after dose intensification with pozelimab and cemdisiran
- To explore the long-term effects of the combination treatment on clinical and PD assessments in an optional OLEP

1.2.3. Modifications from the Statistical Section in the Final Protocol

This SAP is based on protocol amendment 1.

1.2.4. Revision History for SAP Amendments

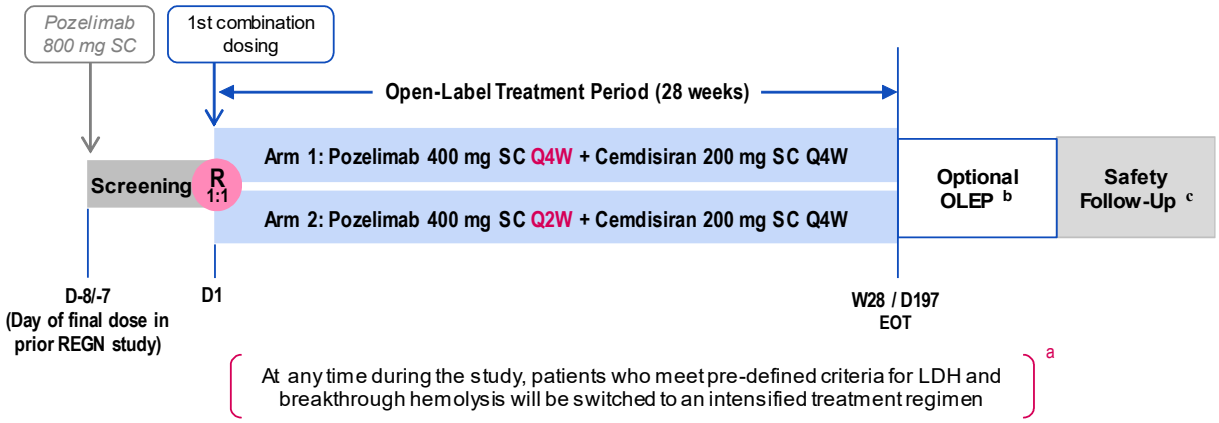
Summary of Changes from SAP Version 1 to Version 2 Due to Protocol Amendment 1	
Changes	**Sections changed**
Updated information about post-trial treatment access for patients who complete the optional OLEP	Figure 1 footnote
Removed several rows from the List of Abbreviations, due to their not being included in this document	List of Abbreviations and Definition of Terms
Revised the descriptions of several secondary endpoints, to match the revisions in the protocol. This applies to OLTP and OLEP endpoints.	Section 4.4.2
Added new secondary endpoint: the proportion of patients with adequate control of hemolysis at each visit	Section 4.4.2
Added analysis window tables	Section 6.4
Updated SOE tables	Section 10.1
Clarifications and corrections	Throughout the document

2. INVESTIGATION PLAN

2.1. Study Design

This is a randomized, open-label, 2-arm, 28-week study to evaluate the safety, efficacy, and PD effects of 2 dose regimens of pozelimab and cemdisiran combination treatment in patients with PNH who had been receiving treatment with pozelimab monotherapy in a Regeneron-sponsored clinical study (R3918-PNH-1868). A schematic of the study design is shown in Figure 1. Eligible patients will be randomized 1:1 to 1 of 2 combination regimens of pozelimab and cemdisiran.

Figure 1: Study Flow Diagram



In lieu of the safety follow-up period, patients who complete the optional OLEP may be able to continue study treatment in a post-trial access program.

2.2. Sample Size Considerations

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

2.3. Study Plan

The study event tables are presented in Appendix 10.1.

3. ANALYSIS POPULATIONS

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. The Full Analysis Sets (FAS)

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

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

3.2. The Safety Analysis Sets (SAF)

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

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

3.3. The Pharmacokinetic (PK) Analysis Sets

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

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

3.4. The Immunogenicity Analysis Sets

The ADA analysis sets (AAS) are defined for each study drug separately and include all treated patients who received any amount of that study drug (SAF) and had at least 1 non-missing ADA result following the first on-study dose of the respective study drug. The definition of the ADA analysis set for each study drug is based on the actual treatment received. Patients' baseline immunogenicity status for pozelimab will be determined from the initial treatment study.

The OLEP AASs are defined for each study drug separately and include all patients who participated in the OLEP who received any amount of study drug in the OLEP and had at least 1 non-missing ADA result following the first OLEP dose of respective study drug. The ADA analysis set for each study drug is based on the actual treatment received. Patients' baseline immunogenicity status for pozelimab will be determined from the initial treatment study.

3.5. The Exploratory Biomarkers Endpoint Analysis Set

The exploratory biomarker endpoint (pharmacodynamic) analysis set includes all patients who received any amount of study drug and who had at least 1 non-missing analyte measurement following the first dose of combination treatment.

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

The following demographic and baseline variables will be summarized:

- Age at screening (years)
- Sex (Male, Female)
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White and Other)
- Ethnicity (Hispanic/Latino)
- Baseline Weight
- Baseline Height
- Baseline Body mass index (BMI) calculated from weight and height
- PNH signs and symptoms at baseline
- Baseline hemoglobin
- Baseline eGFR
- Baseline creatinine
- Baseline total C5
- Baseline PNH clone size
- Baseline LDH
- Baseline total bilirubin
- Baseline CH50
- RBC/whole blood transfusions in last year
- Breakthrough hemolysis in last year

4.2. Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA®). In addition, history in the previous year of RBC/whole blood transfusions and breakthrough hemolyses will be summarized.

4.3. Prior/Concomitant Medication and Procedures

Medications will be recorded from the day of informed consent (ICF) until their final study visit. Medications will be coded using WHO Drug Dictionary (WHODD).

Prior medications are medications taken prior to receiving any study drug following randomization. Concomitant medications are medications taken between the first dose of combination treatment and the end of the safety follow-up period.

Prior/concomitant procedures will be recorded. Prior procedures are procedures performed prior to administration of the first dose of combination treatment. Concomitant procedures are procedures performed between the first dose of combination treatment and the end of the safety follow-up period.

In addition, use of erythropoietin, immunosuppressive drugs, corticosteroids, anti-thrombotic agents, anticoagulants, iron supplements, and folic acid will be recorded.

4.4. Efficacy Variables

4.4.1. Primary Efficacy Variables

Not Applicable

4.4.2. Secondary Efficacy Variables

The secondary efficacy endpoints for the OLTP are:

- Percent change of LDH from pre-treatment (defined as mean of LDH values at day -7 and day 1 [prior to combination dosing]) to end-of-treatment period (defined as mean of LDH values at week 24 through week 28)
- Maintenance of adequate control of hemolysis, defined as LDH $\leq 1.5 \times$ ULN after baseline through week 28, inclusive
- Maintenance of adequate control of hemolysis, defined as LDH $\leq 1.5 \times$ ULN from week 4 through Week 28, inclusive
- Adequate control of hemolysis (defined as LDH $\leq 1.5 \times$ ULN) at each visit from baseline through week 28, inclusive
- Normalization of LDH (defined as LDH $\leq 1.0 \times$ ULN) at each visit from baseline through week 28, inclusive
- Area under the curve (AUC) of LDH over time from baseline through week 28, inclusive
- Area under the curve (AUC) of LDH over time from week 4 through week 28, inclusive
- Breakthrough hemolysis (as defined in the protocol) from baseline through week 28
- Hemoglobin stabilization (defined as patients who do not receive RBC transfusion and have no decrease in hemoglobin levels of ≥ 2 g/dL) from baseline through week 28
- Change in hemoglobin levels from baseline to week 28

- Transfusion avoidance (defined as not requiring an RBC transfusion as per protocol algorithm) from baseline to week 28
- Rate (defined as number of events per patient-years) and number of units of RBCs transfused from baseline to week 28
- Change in CH50 from baseline to week 28
- Change in fatigue as measured by Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale from baseline to week 28
- Change from baseline to week 28 in global health status/quality of life scale (GHS/QoL) and physical function (PF) scores on the European Organization for Research and Treatment of Cancer: Quality-of-Life Questionnaire core 30 items (EORTC QLQ-C30)
- Concentrations of total pozelimab in serum and cemdisiran in plasma, assessed throughout the study
- Change from baseline in concentration of total C5 assessed throughout the study
- Assessment of immunogenicity to pozelimab and cemdisiran as determined by the incidence, titer, and clinical impact of treatment-emergent anti-drug antibody (ADA) responses over time

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

The secondary endpoints for the optional OLEP are:

- Change and percent change of LDH from day 1e to week 24e of the OLEP
- Change and percent change of LDH from day 1e to week 52e of the OLEP
- Maintenance of adequate control of hemolysis, defined as LDH ≤1.5 × ULN from day 1e of the OLEP through week 24e
- Maintenance of adequate control of hemolysis, defined as LDH ≤1.5 × ULN from day 1e of the OLEP through week 52e
- Adequate control of hemolysis (defined as LDH ≤1.5 × ULN) at each visit from day 1e of the OLEP through week 52e
- Normalization of LDH (defined as LDH ≤1.0 × ULN) at each visit, from day 1e of the OLEP through week 52e
- Area under the curve (AUC) of LDH over time between day 1e of the OLEP through week 52e
- Breakthrough hemolysis from day 1e of the OLEP through week 24e
- Breakthrough hemolysis from day 1e of the OLEP through week 52e
- Hemoglobin stabilization (defined as patients who do not receive RBC transfusion and have no decrease in hemoglobin levels of ≥2 g/dL) from day 1e to week 24e and week 52e of the OLEP

- Change in hemoglobin levels from day 1e to week 24e of the OLEP
- Change in hemoglobin levels from day 1e to week 52e of the OLEP
- Transfusion avoidance (defined as not requiring an RBC transfusion as per protocol algorithm) from day 1e to week 24e and week 52e of the OLEP
- Rate and number of units of RBCs transfused from day 1e to week 24e of the OLEP
- Rate and number of units of RBCs transfused from day 1e to week 52e of the OLEP
- Change and percent change in CH50 from day 1e to week 16e of the OLEP
- Change and percent change in CH50 from day 1e to week 24e of the OLEP
- Change and percent change in CH50 from day 1e to week 52e of the OLEP
- Change in fatigue as measured by FACIT-Fatigue scale from day 1e to week 52e of the OLEP
- Change in global health status/quality of life scale (GHS/QoL) and physical function (PF) scores on the European Organization for Research and Treatment of Cancer: Quality-of-Life Questionnaire core 30 items (EORTC QLQ-C30) from day 1e to week 52e of the OLEP
- Concentrations of total pozelimab in serum and total C5 and cemdisiran in plasma, assessed over time during the OLEP
- Assessment of immunogenicity to pozelimab and cemdisiran as determined by the incidence, titer, and clinical impact of treatment-emergent anti-drug antibody (ADA) responses over time during the OLEP

The following table summarizes the OLTP and OLEP secondary endpoints:

OLTP and OLEP			
Measurement	**Metric**	**Time Period in OLTP**	**Time Period in OLEP**
LDH	Change	Not Applicable	Day 1e (BL of the OLEP) to week 24e
	Change	Not Applicable	Day 1e (BL of the OLEP) to week 52e
LDH	Percent change	From pre-treatment (defined as mean of LDH values at day -7 and day 1 [prior to combination dosing]) to EOT period (as defined by the mean of LDH values at Week 24 through Week 28 in the OLTP)	Day 1e (BL of the OLEP) to week 24e
		Not Applicable	Day 1e (BL of the OLEP) to week 52e
Patients who are transfusion-avoidant	Proportion	BL through Week 28	Day 1e through week 24e
		Not Applicable	Day 1e through week 52e
Units of RBC's transfused	Rate and Number	BL through Week 28	Day 1e through week 24e
		Not Applicable	Day 1e through week 52e
Breakthrough hemolysis	Proportion	BL through Week 28	Day 1e through week 24e
		Not Applicable	Day 1e through week 52e
LDH	Proportion of patients maintaining adequate control of hemolysis (defined as $LDH \leq 1.5 * ULN$ at all times at which LDH is measured)	BL through Week 28	Day 1e through week 24e
		Week 4 through Week 28	Day 1e through week 52e

OLTP and OLEP			
Measurement	**Metric**	**Time Period in OLTP**	**Time Period in OLEP**
LDH	Proportion of patients with adequate control of hemolysis (defined as $LDH \leq 1.5 * ULN$ at each visit)	BL through Week 28	Day 1e through week 52e
LDH	Proportion of patients with normalization of LDH (defined as $LDH \leq 1.0 * ULN$ at each visit)	BL through Week 28	Day 1e through week 52e
		Week 4 through Week 28	Not Applicable
LDH	AUC over time	BL through Week 28	Day 1e through week 52e
		Week 4 through Week 28	Not Applicable
Hemoglobin stabilization	Proportion of patients who do not receive a per-protocol RBC transfusion and have no decrease in hemoglobin level of ≥ 2 g/dL)	BL through Week 28	Day 1e through week 24e
		Not Applicable	Day 1e through week 52e
Hemoglobin	Change	BL through Week 28	Day 1e through week 24e
		Not Applicable	Day 1e through week 52e
Fatigue	Change in FACIT-Fatigue Scale	BL to Week 28	Day 1e to week 52e
Global health status	Change in GHS in EORTC QLQ-C30	BL to Week 28	Day 1e to week 52e
Physical Function	Change in PF in EORTC QLQ-C30	BL to Week 28	Day 1e to week 52e
Total CH50	Change	BL to Week 28	Day 1e to week 16e
		Not Applicable	Day 1e to week 24e
		Not Applicable	Day 1e to week 52e
Total CH50	Percent Change	Not Applicable	Day 1e to week 16e
		Not Applicable	Day 1e to week 24e
		Not Applicable	Day 1e to week 52e

OLTP and OLEP			
Measurement	**Metric**	**Time Period in OLTP**	**Time Period in OLEP**
Total Pozelimab in serum	Concentrations	Whole OLTP	Whole OLEP
Total Cemdisiran in plasma	Concentrations	Whole OLTP	Whole OLEP
Concentration of total C5	Change	Whole OLTP	Whole OLEP
Immunogenicity to pozelimab and cemdisiran	Incidence, titer, and clinical impact of treatment-emergent ADA responses over time	Whole OLTP	Whole OLEP

4.4.3. Exploratory Efficacy Variables

The exploratory endpoints for the OLTP are:

- Treatment intensification throughout the study
- Incidence of MAVE (defined in Section 10.1.3 of the protocol) from baseline to week 28
- Change in renal function as measured by estimated glomerular filtration rate (eGFR) from baseline to week 28
- Percent change in free hemoglobin from baseline to week 28
- Change in bilirubin from baseline to week 28
- Change in reticulocyte count from baseline to week 28
- Change and percent change in the alternative pathway hemolytic activity assay (AH50) from baseline to week 28
- Change of PNH erythrocytes and granulocytes from baseline to week 28
- Change from baseline to week 28 in functional scale scores (Role functioning, Emotional Functioning, Cognitive Functioning and Social Functioning) and symptom scale scores (Fatigue, Nausea and vomiting, Pain, Dyspnoea, Insomnia, Appetite loss, Constipation, Diarrhoea) of the EORTC QLQ-C30
- Stability in global health status, functioning and symptoms as measured by the EORTC QLQ-C30 from baseline to week 28
- Change in Treatment satisfaction (as assessed by the Treatment Satisfaction Questionnaire for Medication [TSQM]) from baseline to week 28

The following table summarizes the OLTP and OLEP exploratory endpoints:

Measurement	Metric	Time Period in OLTP	Time Period in OLEP
Treatment Intensification	Proportion	Whole OLTP	Not applicable
MAVE	Incidence	BL to Week 28	Day 1e to week 52e
Renal functions	Change measured by eGFR	BL to Week 28	Day 1e to week 52e
Free hemoglobin	Percent change	BL to Week 28	Day 1e to week 52e
Bilirubin	Change	BL to Week 28	Day 1e to week 52e
Reticulocyte count	Change	BL to Week 28	Day 1e to week 52e
AH50	Change	BL to Week 28	Day 1e to week 52e
	Percent change	BL to Week 28	Day 1e to week 52e
PNH erythrocytes	Change	BL to Week 28	Day 1e to week 52e
PNH granulocytes	Change	BL to Week 28	Day 1e to week 52e
Role Functioning	Change in Functional Scale Scores: EORTC QLQ-C30	BL to Week 28	Day 1e to week 52e
Emotional Functioning	Change in Functional Scale: EORTC QLQ-C30	BL to Week 28	Day 1e to week 52e
Cognitive Functioning	Change in Functional Scale: EORTC QLQ-C30	BL to Week 28	Day 1e to week 52e
Social Functioning	Change in Functional Scale: EORTC QLQ-C30	BL to Week 28	Day 1e to week 52e
Fatigue	Change in Symptom Scale: EORTC QLQ-C30	BL to Week 28	Day 1e to week 52e
Nausea and Vomiting	Change in Symptom Scale: EORTC QLQ-C30	BL to Week 28	Day 1e to week 52e
Pain	Change in Symptom Scale: EORTC QLQ-C30	BL to Week 28	Day 1e to week 52e
Dyspnea	Change in Symptom Scale: EORTC QLQ-C30	BL to Week 28	Day 1e to week 52e
Insomnia	Change in Symptom Scale: EORTC QLQ-C30	BL to Week 28	Day 1e to week 52e
Appetite Loss	Change in Symptom Scale: EORTC QLQ-C30	BL to Week 28	Day 1e to week 52e

Measurement	Metric	Time Period in OLTP	Time Period in OLEP
Constipation	Change in Symptom Scale: EORTC QLQ-C30	BL to Week 28	Day 1e to week 52e
Diarrhea	Change in Symptom Scale: EORTC QLQ-C30	BL to Week 28	Day 1e to week 52e
Stability in global health status	Proportion with stability based on accepted MIDs for the EORTC QLQ-C30	BL to Week 28	Day 1e to week 52e
Stability in functioning, and symptoms	Proportion with stability based on accepted MIDs for the EORTC QLQ-C30	BL to Week 28	Day 1e to week 52e
Stability in symptoms	Proportion with stability based on accepted MIDs for the EORTC QLQ-C30	BL to Week 28	Day 1e to week 52e
Treatment satisfaction	Comparison between two therapies as assessed by TSQM	BL to Week 28	Not applicable
Change in PNH symptoms	De novo PNH Symptom-Specific Questionnaire	BL to Week 28	Not applicable

4.5. Safety Variables

The safety variables are

- TEAEs
- Body weight
- Vital signs
- Electrocardiogram (ECG)
- Physical examination
- Routine safety laboratory tests (hematology, chemistry, urinalysis, and pregnancy testing [for WOCBP only])

4.5.1. Adverse Events and Serious Adverse Events

An Adverse Event is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

For safety variables, there are four observation periods:

- The pre-treatment period is defined as the time from signing the ICF to before the first dose of the combination treatment
- The OLTP on-treatment period is defined as the time of first dose of the combination treatment in the OLTP to:
  - For Arm 1, the last dose of study drug (Q4W) in the OLTP + 4 weeks but before first dose of OLEP
  - For Arm 2, the last dose of pozelimab (Q2W) in the OLTP + 2 weeks, or the last dose of cemdisiran (Q4W) in the OLTP + 4 weeks, whichever is later , but before first dose of OLEP
- The OLEP on-treatment period is defined as the time of first dose of the combination treatment in the OLEP to:
  - For Arm 1, the last dose of study drug (Q4W) in the OLEP + 4 weeks
  - For Arm 2, the last dose of pozelimab (Q2W) in the OLEP + 2 weeks, or the last dose of cemdisiran (Q4W) in the OLEP + 4 weeks, whichever is later
- The post-treatment period is defined as the time after the end of the OLTP on-treatment period or OLEP on-treatment period, whichever is later.

Pre-treatment AEs are defined as AEs that developed or worsened during the pre-treatment period.

Treatment-emergent AEs (TEAEs) are defined as AEs that developed or worsened after the first dose of combination treatment and during treatment.

A Serious Adverse Event is an adverse event (AE) that is classified as serious according to the criteria specified in the protocol.

The severity of AEs and of infusion reaction AEs are graded according to the criteria given in the protocol.

Pregnancy and symptomatic overdose of study drug events require expedited reporting to the sponsor, and they will be described.

4.5.2. Adverse Events of Special Interest

Adverse events of special interest (AESIs) are AEs (serious or non-serious) required to be monitored, documented, and managed in a pre-specified manner as described in the protocol sections 10.1.3 and 10.1.4.

4.5.3. Laboratory Safety Variables

The clinical laboratory data consists of serum chemistry, hematology, urinalysis, and other.

Clinical laboratory values will be grouped by function in summary tables. Laboratory tests are categorized in the protocol as follows:

- Hematology
- Coagulation panel
- Chemistry, including LDH
- Urinalysis
- Other tests

4.5.4. Vital Signs

Temperature, pulse, systolic and diastolic blood pressure will be collected.

4.5.5. 12-Lead Electrocardiography (ECG)

Heart rate will be recorded from the ventricular rate, and the PR, QRS, and QT, and QTcF will also be recorded.

4.6. Pharmacokinetic Variables

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

4.7. Immunogenicity Variables

The immunogenicity variables include ADA status and titer at nominal sampling time/visit. Serum samples for ADA will be collected at the clinic visits specified in Appendix 10.1. For each study drug, samples positive in the ADA assay will be further characterized for ADA titers.

4.8. Pharmacodynamic Variables

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

- CH50 (an assay assessing the activity of the classical pathway of complement) will be used to measure C5 activity. This is the principle PD marker for the study and is also an efficacy variable in this study (Section 5.2.1 of the protocol).
- Parameters of intravascular hemolysis: i.e., haptoglobin, reticulocyte count, and bilirubin
- Free hemoglobin
- Alternative pathway hemolytic activity, as measured by AH50
- Complement activation markers: i.e., sC5b-9
- PNH clone size: i.e., PNH erythrocytes and granulocytes

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

4.9. Clinical Outcome Assessments (COAs)

COAs include the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue), the EORTC-QLQ-C30, the Treatment Satisfaction Questionnaire for Medication (TSQM), and the PNH Symptom-Specific Questionnaire.

5. STATISTICAL METHODS

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

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

5.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group, and for all patients combined. Baseline is defined as the last available value prior to study drug administration unless otherwise specified.

5.2. Medical History

Medical history will be descriptively summarized by treatment group and overall for the study in the safety analysis set.

All reported patient medical history will be presented by primary SOC and PT. The tables will be presented by SOC sorted alphabetically and decreasing patient frequency of PT. In addition, all medical history of specific interest will be summarized by patient incidence and percentage.

5.3. Prior/concomitant Medications

All prior medications will be descriptively summarized by treatment group and overall for the study, for patients in the safety set. Summaries will present patient counts (and percentages) for all prior medications, by decreasing frequency of the overall incidence of ATC followed by therapeutic class. In the case of equal frequency across anatomic or therapeutic categories, alphabetical order will be used. Patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication but may be counted again for a different category if the same medication falls under multiple categories.

All concomitant medications will be descriptively summarized for patients in the safety set, separately for the OLTP and OLEP on-treatment periods, as defined in Section 4.5.1. In the case of equal frequency across anatomic or therapeutic categories, alphabetical order will be used. Patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication, and hence may be counted again for a different category if the same medication falls under multiple categories.

For the post-treatment period, medications will be listed.

5.4. Prohibited Medications

A listing of prohibited medications will be provided for the patients in the safety analysis set for the treatment period.

5.5. Patient Disposition

The following displays will be provided:

- The total number of screened patients: signed the main ICF
- The total number of randomized patients
- The total number of patients who discontinued the study, and the reasons for discontinuation
- The total number of patients who discontinued from the study treatment, and the reasons for discontinuation
- A listing of patients prematurely discontinued from treatment, along with reasons discontinuation
- Total number of patients who received treatment intensification
- Total number of patients who continued into the OLEP

5.6. Extent of Study Treatment Exposure and Compliance

5.6.1. Measurement of Compliance

Compliance with each protocol-defined investigational product will be calculated for each study period as follows:

> Treatment Compliance = (Number of investigational product doses taken during the study period)/(Number of investigational product doses prescribed to be taken during the study period) x 100%.

Separate summaries will be provided for pozelimab and cemdisiran by treatment group.

5.6.2. Exposure to Investigational Product

Treatment exposure will be presented separately for pozelimab and cemdisiran by treatment group.

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

> (Date of last administration of study drug – date of the first administration of study drug for the study period) + 28 days (for Q4W dosing), and
>
> (Date of last administration of study drug – date of the first administration of study drug for the study period) + 14 days (for Q2W dosing)

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

The total number of complete and incomplete study drug administrations will be summarized.

In addition, the number of patients exposed to the investigational product will be presented by specific time period. The time periods of interest are as follows:

For the OLTP:

- ≥ Day 29 (Week 4)
- ≥ Day 57 (Week 8)
- ≥ Day 85 (Week 12)
- ≥ Day 113 (Week 16)
- ≥ Day 141 (Week 20)
- ≥ Day 197 (Week 28)

For OLEP:

- ≥ Day 57 (Week 8)
- ≥ Day 113 (Week 16)
- ≥ Day 169 (Week 24)
- ≥ Day 225 (Week 32)
- ≥ Day 281 (Week 40)
- ≥ Day 365 (Week 52)

Few patients are expected to be in the intensified OLTP; their exposure information will be listed.

5.7. Analyses of Efficacy Variables

There are no primary efficacy variables in this study. The analysis is determined by type of efficacy variable (i.e., continuous or binary). Secondary efficacy analysis for the optional OLEP will be performed using the same approach described for corresponding analyses in the OLTP, described in sections 5.7.1 and 5.7.2 . Analyses will be performed on the FAS. Levels of LDH in serum will be analyzed by a central laboratory. Efficacy analysis of LDH will be based on central laboratory data. In an attempt to exclude hemolyzed samples, LDH values will be excluded from the analysis if the LDH was ≥ 2 x ULN and potassium was ≥ 6 mmol/L, in the absence of an event of breakthrough hemolysis. LDH values will be included in the analysis if there is an associated breakthrough hemolysis.

5.7.1. Analysis of Continuous Secondary Efficacy Variables

Percent change from pre-treatment mean LDH to the mean of LDH at weeks 24 and 28 will be analyzed using multiple imputation (MI) with an Analysis of Covariance (ANCOVA) model based on the FAS. Missing data for the mean of LDH at weeks 24 and 28 will be imputed 30 times to generate 30 complete data sets by using the SAS procedure MI as follows:

- Step 1: A monotone missing pattern for each treatment arm separately is induced by the Markov Chain Monte Carlo (MCMC) method in the MI procedure using seed number 39182092.
- Step 2: The missing data at subsequent visits will be imputed using the regression method with seed number 39182092 adjusting for treatment group, pre-treatment mean LDH, and all values at preceding visits. The mean of LDH at weeks 24 and 28 will be calculated based on the imputed complete data.

The percent change from pre-treatment mean LDH to the mean of LDH at weeks 24 and 28 of each of the 30 complete datasets will be analyzed using an Analysis of Covariance (ANCOVA) with treatment group and pre-baseline mean LDH included in the model, and the SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results from the 30 analyses using Rubin's formula (Rubin 1987). As an additional analysis, the ANCOVA model will be fitted using only available data.

All other secondary efficacy variables involving change or percent change from baseline to week 28 will be analyzed using multiple imputation (MI) with an Analysis of Covariance (ANCOVA) model based on the FAS. Imputation and modeling will be done as described above; the same seed will be used.

The AUC (based on the trapezoidal rule) of LDH over time from baseline through week 28, and from week 4 through week 28 will be calculated based on observed data and will be analyzed using an ANCOVA model comparing treatments, with baseline LDH as a covariate.

For rate and number of units of transfusion with RBCs from baseline through week 28, the analysis set will consist of all treated patients up to the time they intensified treatment, if applicable. The rate of units of transfusion for a patient will be calculated based on the duration of treatment exposure of the patient and will be analyzed with negative binomial model with treatment group as a term. The number of transfusions will be summarized descriptively by treatment group.

5.7.2. Analysis of Categorical Secondary Efficacy Variables

Proportions and 95% confidence intervals by the Clopper Pearson exact method for the endpoints will be reported by treatment group and overall. A Fisher's exact test will be performed to assess the difference between groups. Patients with missing data will be considered as failures or non-responders.

For the secondary variable of breakthrough hemolysis through week 28, defined as the measurement of LDH $\geq$ 2 x ULN at any time subsequent to an initial achievement of disease control (i.e., LDH $\leq$ 1.5 x ULN) concomitant with associated signs or symptoms, the proportion of patients achieving normalization of their intravascular hemolysis will be calculated, along with a 95% confidence interval by the exact Clopper Pearson method. Signs and symptoms will be tabulated, as will number of breakthrough hemolyses per patient.

For the secondary variable of the proportion of patients achieving adequate control of their LDH (defined as LDH ≤ 1.5 x ULN at every scheduled time point between week 4 through week 28, inclusive), patients who have one or more of the following will be considered as not achieving adequate control of their intravascular hemolysis:

- Have at least one measurement of LDH > 1.5 x ULN
- Discontinue from study treatment early
- Have 2 consecutive missing values of the scheduled LDH measurements
- Have 25% or more missing values of the scheduled LDH measurements
- Having received intensified treatment

Patients who complete study treatment, have no more than 2 consecutive missing values of the scheduled LDH measurements between week 4 and week 28, have fewer than 25% missing values of the scheduled LDH measurements between week 4 and week 28 and have no breakthrough hemolysis will be evaluated based on their non-missing LDH measurements. The analysis will be based on scheduled central laboratory data. The proportion of patients achieving adequate control of their intravascular hemolysis will be calculated, along with a 95% confidence interval, by the exact Clopper Pearson method for each treatment group separately. In addition, proportion of patients with LDH ≤1.50 x ULN at each scheduled assessment timepoint will be summarized. A similar summary will be presented for patients with normalization of LDH.

For the endpoints of adequate control of hemolysis at each visit and normalization of LDH at each visit, proportions of response will be tabulated by visit.

For the secondary variable of the rate of transfusion of RBCs through week 28, the 28-week total for each patient will be used. A mean and 95% confidence interval will be calculated for each treatment group and for the treatment difference, based on the assumption of a negative binomial distribution of the rate of transfusions with RBCs.

5.7.3. Analysis of Exploratory Variables

For the incidence of MAVE through week 28, the proportion of patients with at least one MAVE will be presented along with 95% confidence interval using exact Clopper-Pearson for each treatment group separately. A Fisher's exact test will be performed to assess the difference between groups.

For change-from-baseline exploratory variables, descriptive statistics will be presented for baseline, week 28 and the change from baseline, for each treatment group, along with the treatment difference.

Results of exploratory endpoint analyses may be reported separately from the CSR.

5.8. Analysis of Safety Data

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

Thresholds for Potential Clinically Significant Values (PCSV) in laboratory variables, vital signs and ECG are defined in Appendix 10.2.

The summary of safety results will be presented by treatment group and overall, separately for OLTP and OLEP.

For patients who enter the OLEP, safety data will be summarized in a similar manner.

For patients who received intensified treatment, safety data after intensified treatment will be listed.

5.8.1. Adverse Events

Summaries that include frequencies and proportions of patients reporting AEs will include the PTs and the SOCs. Summaries will be presented for the OLTP on-treatment period, the OLEP on-treatment period, and the post-treatment period.

Summaries of all TEAEs will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and PT
- TEAEs by severity presented by SOC and PT
- Study drug related TEAEs presented by SOC and PT
- Treatment-emergent AESIs (defined by experiencing a prespecified PT or prespecified grouping of PTs, or by being put in a grouping specified in the CRF)
- Non-serious TEAEs by SOC and PT

Deaths and other SAEs will be listed and summarized.

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

5.8.2. Analysis of Vital Signs

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

Listings will be provided with flags indicating treatment-emergent PCSVs.

5.8.3. Analysis of Laboratory Tests

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

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

For samples with LDH ≥ 2 x ULN and potassium ≥ 6 mmol/L, the potassium, ALT, AST, magnesium, and phosphorous will not be used in the analysis due to hemolysis possibly caused by sample mishandling.

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.

5.8.4. Analysis of 12-Lead ECG

ECG parameters (PR interval, QT interval, QTcF interval, QRS interval, and heart rate [from ventricular rate]) will be summarized by treatment group and overall for baseline and change from baseline to each scheduled and collected assessment time. Listings will be provided with flags indicating PCSVs.

5.9. Analysis of Pharmacokinetic and Immunogenicity Data

5.9.1. Analysis of Pharmacokinetic Data

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

No formal statistical analysis will be performed.

5.9.2. Analysis of Immunogenicity Data

5.9.2.1. Analysis of ADA Data

Analyses will be performed separately for ADA against cemdisiran and ADA against pozelimab in all study cohorts unless otherwise specified. The immunogenicity variables described in Section 4.7 will be summarized using descriptive statistics.

Immunogenicity will be characterized by ADA status, ADA category and maximum titer observed in patients in the ADA analysis set.

The ADA status of each patient 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 4-fold (for anti-cemdisiran) 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 patient 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-cemdisiran) or ≥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. Patients 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 a 16-week post baseline period [based on nominal sampling time], with no ADA-negative results in-between, regardless of any missing samples
  - Transient - Not persistent or indeterminate, 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

The maximum titer category of each patient is classified as:

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

The following listings will be provided:

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

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

5.9.3. Association of Immunogenicity with Exposure, Safety and Efficacy

5.9.3.1. Immunogenicity and Exposure

Association between immunogenicity and systemic exposure to pozelimab will be analyzed. Plots of pozelimab concentration may be provided to examine the potential impact of ADA category and maximum titer on these profiles.

5.9.3.2. Immunogenicity and Safety and Efficacy

Association between immunogenicity variables and safety may be explored with a primary focus on the following safety events during the TEAE period:

- Injection site reaction (serious or severe and lasting 24 hours or longer)
- Hypersensitivity (SMQ: Hypersensitivity [Narrow])
- Anaphylaxis (SMQ: Anaphylaxis [Narrow])

Association between immunogenicity variables and efficacy endpoints may be explored (e.g. scatter plot or spaghetti plot).

The above-mentioned safety and efficacy analyses will be conducted using the following categories:

- ADA Positive
- Treatment-emergent
- Treatment-boosted
- Maximum post-baseline titer category

5.10. Analysis of Pharmacodynamic and Biomarker Data

Pharmacodynamic and biomarker variable listed in Section 4.8 may be analyzed and summarized. For each biomarker variable, time profile and percent of change from baseline at each time point will be summarized through 28 weeks.

6. DATA CONVENTIONS

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

6.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the Baseline assessment for all measurements will be the latest available valid measurement taken prior to the administration of investigational product. If the scheduled baseline day 1 measurements are not available, screening assessments may be used; when scores are used, this rule applies to scores, not individual variables.

6.2. Data Handling Convention for Missing Data

Rules for handling missing data for secondary efficacy variables are described in Section 5.7.

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. This section includes the methods for missing data imputation for some summary analyses, if necessary.

6.2.1. Adverse events

If the severity of a TEAE is missing, it will be classified as “severe” in the frequency tables by severity of TEAE. If the measurement of relationship of a TEAE to the investigational product is missing, it will be classified as “related” in the frequency tables by relation to the investigational product.

Adverse event start date

AE start date will be used for AE classification and analysis. If AE start date is not complete, then the character variable will keep the original incomplete date, the numerical date variable will be imputed, and an imputation flag will indicate which date component is missing.

If AE start day is missing, and AE start month and year are not missing: If AE start year is the same as first dose year and the AE start month is the same as the first dose month then impute AE start day using the day of first dose. If this leads to a date after the AE end date, use AE end date instead. Otherwise impute the AE start day using the first day of the month. If this leads to a date before informed consent, the informed consent date will be used. Imputation flag is ‘D’.

If AE start month is missing, and AE start year is not missing: If AE start year is less than the first dose year, use the informed consent day and month. If AE start year is equal to the first dose year, use the first dose day and month. If this leads to a date after the AE end date, use AE end date instead. If AE start year is after the first dose year, use 01 January. Imputation flag is ‘M’.

If AE start year is missing: Impute AE start date using the day of first dose. If this leads to a date after the AE end date, use AE end date instead. Imputation flag is ‘Y’.

Adverse event end date

The general recommendation is not to impute AE end date. However, since AE end date will be used for AE starting date imputation, in order to carry through the logic for programming, the following intermediate step will be used. Afterwards, only the original character/numeric date recorded in CRF will be kept in the final analysis dataset.

If AE end day is missing, and AE end month and year are not missing: Impute AE end date using the last day of the month. If this leads to a date after end of study follow up date, use the last study visit date instead.

If AE end month is missing, and AE end year is not missing: Impute AE end date using 31 December as the day and month. If this leads to a date after end of study follow up date, use the last study visit date instead.

If AE end year is missing: Impute AE end date using the end of follow up date.

Medication start and end date missing

To determine whether a medication is pre-treatment (described in Section 5.8) medication or concomitant medication or both, the missing medication start date is estimated as early as possible, and the missing medication end date is estimated as late as possible. If the medication start date is missing, the onset day will not be calculated in medication listings.

Prior medication start date

If start day is missing, and start month and year are not missing: Impute the start day using the first day of the month. Imputation flag is 'D';

If start month is missing, and start year is not missing: Impute the day and month using 01 January. Imputation flag is 'M'.

If start year is missing: Impute start date using 2 years before informed consent date. Imputation flag is 'Y'.

A special note: for start date with year missing, the general principle is not to impute. However, in order to simplify the programming flow, the imputation is proposed to align with the protocol which specifies to collect up to 2 years prior medication. Since the start date of prior medication will not be used in any analysis, the rule will not impact the analysis result.

Prior medication end date

If end day is missing, and end month and year are not missing: Impute end date using the last day of the month. If this leads to a date on or after first dose intake date, use first dose intake date -1 instead. Imputation flag is 'D'.

If end month is missing, and end year is not missing: Impute end date using 31 December as the day and month. If this leads to a date on or after first dose intake date, use first dose intake date -1 instead. Imputation flag is 'M'

If end year is missing: Impute end date using the first dose intake date –1. Imputation flag is 'Y'.

Concomitant medication start date

The imputation rule for concomitant medication start date is the same as AE start date.

Concomitant medication end date

If end day is missing, and end month and year are not missing: Impute end date using the last day of the month. If this leads to a date after end of study follow up date, use the last visit study date instead. Imputation flag is 'D'.

If end month is missing, and end year is not missing: Impute end date using 31 December as the day and month. If this leads to a date after end of study follow up date, use the last study visit date instead. Imputation flag is 'M'.

If end year is missing: Impute date using the end of last study visit date. Imputation flag is 'Y'.

Medication coding

Medications whose ATC level 4 cannot be coded will be summarized by setting ATC4=ATC2 in the table programs. However, these uncoded ATC level 4 records still need to be confirmed with study DM and study MD.

No imputations for missing laboratory data, ECG data, vital sign data, or physical examination data will be made.

6.2.2. PCSV

Patients who had post-baseline PCSV, but missing baseline value will be regarded as having treatment emergent PCSV.

6.2.3. Date of first / last study drug administration

Date of first study drug administration is the first non-missing start date of dosing filled in the CRF "Investigational Product" module.

If a patient's date of the last dose is totally missing or unknown, his/her last visit date will be substituted.

6.3. Analysis Windows

Data analyzed by visit (including efficacy, laboratory data, vital signs, ECG) will be summarized by the study scheduled visits described Appendix 10.1 (Schedule of Time and Events). The analysis visit windows will be exhaustive so that all available values obtained from unscheduled visits, early termination visit (ETV) and end of treatment (EOT)/end of study (EOS) have the potential to be summarized. No analysis visit windows will be applied to the study scheduled visits. The visit windows are constructed using ranges applied to the number of days in study (study days) when the measure is collected. Day 1 is defined as the first date of study treatment. Analysis windows are given in Tables 1 and 2.

Table 1: Efficacy Analysis Windows

Visit	Targeted Study Day	Analysis Windows			
		Haptoglobin	PNH Eryth, PNH Gran	CH50, AH50, sC5b-9	FACIT-Fatigue, EORTC-QLQ-C30, TSQM
Screening		Scr 1	Scr 1	Scr 1	
Week 0	1	1		1	1
Week 1	8			[2, 12]	
Week 2	15			[13, 25]	[2, 25]
Week 4	29	[2, 81]		[26, 53]	[26, 53]
Week 6	43				
Week 8	57		[2,133]	[54, 81]	[54, 81]
Week 10	71				
Week 12	85	[82, 189]		[82, 105]	[82, 105]
Week 16	113			[106, 133]	[106, 133]
Week 20	141		[134, 189]	[134, 161]	[134, 161]
Week 24	169			[162, 189]	[162, 189]
Week 28	197	[190, 204]	[190, 204]	[190, 204]	[190, 204]
OLEP-1 (Week 0e)	1e	1e	1e	1e	1e
OLEP-2 (Week 8e)	57e				
OLEP-3 (Week 16e)	113e			[2e, 217e]	
OLEP-4 (Week 24e)	169e		[2e, 357e]		[2e, 357e]
OLEP-5 (Week 32e)	225e			[218e, 357e]	
OLEP-6 (Week 40e)	281e				
OLEP-7 (Week 52e)	365e	[2e, 368e]	[358e, 368e]	[358e, 368e]	[358e, 368e]

Table 2: Safety Analysis Windows

Visit	Targeted Study Day	Analysis Windows				
		Blood Chem (Including LDH), Coagulation	Hematology (Including Hemoglobin), Urinalysis	Vital Signs	ECG	Body Weight
Screening				Scr 1		Scr 1
Week 0	1	1	1		1	
Week 1	8	[2, 12]	[2, 12]			
Week 2	15	[13, 25]	[13, 25]	[2, 25]		
Week 4	29	[26, 39]	[26, 53]	[26, 53]		[2, 53]
Week 6	43	[40, 53]				
Week 8	57	[54, 67]	[54, 81]	[54, 81]		[54, 81]
Week 10	71	[68, 81]				
Week 12	85	[82, 105]	[82, 105]	[82, 105]		[82, 105]
Week 16	113	[106, 133]	[106, 133]	[106, 133]		[106, 133]
Week 20	141	[134, 161]	[134, 161]	[134, 161]		[134, 161]
Week 24	169	[162, 189]	[162, 189]	[162, 189]		[162, 217]
Week 28	197	[190, 204]	[190, 204]	[190, 204]	[2, 204]	[190, 204]
OLEP-1 (Week 0e)	1e	1e	1e	1e	1e	1e
OLEP-2 (Week 8e)	57e	[2e, 105e]	[2e, 105e]	[2e, 105e]		[2e, 105e]
OLEP-3 (Week 16e)	113e	[106e, 161e]	[106e, 161e]	[106e, 161e]		[106e, 161e]
OLEP-4 (Week 24e)	169e	[162e, 217e]	[162e, 217e]	[162e, 217e]		[162e, 217e]
OLEP-5 (Week 32e)	225e	[218e, 273e]	[218e, 273e]	[218e, 273e]		[218e, 273e]
OLEP-6 (Week 40e)	281e	[274e, 357e]	[274e, 357e]	[274e, 357e]		[274e, 357e]
OLEP-7 (Week 52e)	365e	[358e, 368e]	[358e, 368e]	[358e, 368e]	[2e, 368e]	[358e, 368e]

6.4. Unscheduled Assessments

The determination of baselines and values at the end of treatment for both efficacy and safety variables will be based on scheduled available assessments and unscheduled available assessments.

Extra assessments (laboratory data or vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing adverse events) will be included in listings, but not summaries except for the endpoint determination. If more than one laboratory value is available for a given visit, the first observation will be used in summaries and all observations will be presented in listings.

7. INTERIM ANALYSIS

An interim analysis may be conducted after 6 patients have completed at least 16 weeks of the OLTP. Additional/other interim analyses may be performed to support regulatory interactions. No alpha adjustment will be applied for the interim analysis since all analyses are descriptive.

8. SOFTWARE

All analyses will be done using SAS Version 9.4 or higher, or using R.

9. REFERENCES

1. ICH. (1998, February 5). ICH Harmonized tripartite guideline: Statistical principles for clinical trials (E9). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

10. APPENDIX

10.1. Schedule of Time and Events

Footnotes for Tables 3 through 6 can be found immediately after Table 6.

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

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

	Screening Period	Open-Label Treatment Period [3]											
Study Procedure (Visit) [1,2]	**Screening V1**	**V2**[4]	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**EOT**[5] **V13**
Week	**Up to -1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**28**
Day	**Up to -8**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**113**	**141**	**169**	**197**
Window (day)	**--**	**--**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-7/+3**	**-7/+3**	**-7/+3**	**-7/+3**
Clinical Outcome Assessments:													
FACIT-Fatigue		x		x	x		x		x	x	x	x	x
EORTC-QLQ-C30		x		x	x		x		x	x	x	x	x
TSQM		x		x	x		x		x	x	x	x	x
PNH symptom-specific questionnaire (daily) [17]	<----------x---------->												
PGIS		x			x				x		x		x
PGIC					x				x		x		x
Safety and Anthropometric:													
Body weight	x				x		x		x	x	x	x	x
Vital signs	x			x	x		x		x	x	x	x	x
Physical examination	x				x				x				x
Electrocardiogram	x												x
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x
Breakthrough hemolysis assessment [18]	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant meds/treatments	x	x	x	x	x	x	x	x	x	x	x	x	x
Transfusion record update	x	x	x	x	x	x	x	x	x	x	x	x	x
Laboratory Testing [19] **:**													
Titers to measure *N. meningitidis* (only if required per parent study)	x												
Coagulation panel	x	x	x	x	x	x	x	x	x	x	x	x	x
Chemistry (long panel) including LDH [20]	x	x	x	x	x	x	x	x	x	x	x	x	x
Hematology [21]	x	x	x	x	x		x		x	x	x	x	x
Immunoglobulin G		x			x				x				
Pregnancy test (WOCBP only): serum (S) or urine (U)	s	u			u		u		u	u	u	u	u
Urinalysis	x	x	x	x	x		x		x	x	x	x	x
Pharmacokinetics and Immunogenicity Sampling:													
Pozelimab conc. sample [22]	x	x	x	x	x		x		x	x	x	x	x
Cemdisiran and its metabolite conc. sample [22]		x			x				x			x	
Pozelimab immunogenicity sample [24]	x								x				x
Cemdisiran immunogenicity sample [24]		x							x				x

	Screening Period	Open-Label Treatment Period [3]											
Study Procedure (Visit) [1,2]	**Screening V1**	**V2**[4]	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**EOT**[5] **V13**
Week	**Up to -1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**28**
Day	**Up to -8**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**113**	**141**	**169**	**197**
Window (day)	**--**	**--**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-7/+3**	**-7/+3**	**-7/+3**	**-7/+3**
Total C5 (plasma) [22]	x	x	x	x	x		x		x	x	x	x	x
Biomarkers:													
Free hemoglobin	x	x			x		x		x	x	x	x	x
Haptoglobin	x	x			x				x				x
Complement hemolytic assay (serum CH50) [25]	x	x	x	x	x		x		x	x	x	x	x
Complement hemolytic assay (serum AH50) [25]	x	x	x	x	x		x		x	x	x	x	x
sC5b-9 (plasma)	x	x	x	x	x		x		x	x	x	x	x
PNH erythrocyte cells	x						x				x		x
PNH granulocyte cells	x						x				x		x
Optional research:													
Serum and plasma for FBR (optional)	x				x				x				x
Whole blood sample for DNA isolation for genomics research (optional) [26]		x											
Whole blood RNA sample for genomics research (optional)		x	x										x

Table 4: Schedule of Events for Patients on Intensified Treatment in the OLTP

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

Study Procedure (Visit) [1,2]	Intensified Treatment Period in the OLTP [3]											
	RV1	RV2	RV3	RV4	RV5	RV6	RV7	RV8	RV9	RV10	RV11	EOT RV12
Week	**0r**	**1r**	**2r**	**4r**	**6r**	**8r**	**10r**	**12r**	**16r [5]**	**20r [5]**	**24r [5]**	**28r [6]**
Day	**1r**	**8r**	**15r**	**29r**	**43r**	**57r**	**71r**	**85r**	**113r**	**141r**	**169r**	**197r**
Window (day)	**--**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-7/+3**	**-7/+3**	**-7/+3**	**-7/+3**
Laboratory Testing [14.] :												
Coagulation panel	x	x	x	x	x	x	x	x	x	x	x	x
Chemistry (long panel) including LDH [15]	x	x	x	x	x	x	x	x	x	x	x	x
Hematology [16]	x	x	x	x		x		x	x	x	x	x
Immunoglobulin G	x			x				x				
Pregnancy test (WOCBP only) [17]	u			u		u		u	u	u	u	u
Urinalysis	x	x	x	x		x		x	x	x	x	x
Pharmacokinetics and Immunogenicity Sampling:												
Pozelimab drug conc. sample [18]	x	x	x	x		x		x	x	x	x	x
Cemdisiran and its metabolite conc. sample [19]	x			x				x			x	
Pozelimab immunogenicity sample [20]	x							x				x
Cemdisiran immunogenicity sample [20]	x							x				x
Total C5 (plasma) [18]	x	x	x	x		x		x	x	x	x	x
Biomarkers:												
Free hemoglobin	x			x		x		x	x	x	x	x
Haptoglobin	x			x				x				x
Complement hemolytic assay (serum CH50) [21]	x	x	x	x		x		x	x	x	x	x
Complement hemolytic assay (serum AH50) [21]	x	x	x	x		x		x	x	x	x	x
sC5b-9 (plasma)	x	x	x	x		x		x	x	x	x	x
PNH erythrocyte cells	x					x				x		x
PNH granulocyte cells	x					x				x		x

Table 5: Schedule of Events (Optional Open-Label Extension Period)

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

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

Table 6: Schedule of Events (Post-Treatment Safety Follow-Up Period)

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

Footnotes for Table 3 Schedule of Events (Treatment Period)

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

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

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

    Care must be taken to coordinate dosing for visits where a post-dose sample is collected to measure the concentration of cemdisiran and its metabolites. The final SC dosing of the combination (pozelimab and cemdisiran) during the OLTP is at week 24 for arm 1 and the final SC dosing of cemdisiran is at week 24 with pozelimab at week 26 for arm 2.

12. Patients should be monitored for at least 30 minutes after completing the first cemdisiran injection. A 30 minute monitoring period is not needed after the pozelimab injection.

13. Injection training will be provided to patients who desire self-injection or injection by a designated person. Site should observe patient self-injection or injection by a designated person and confirm adequacy. Patient instruction materials will be provided. SC injections may either be performed by the site personnel or another healthcare professional at the patient's home or preferred location or be administered by the patient or a designated person who has successfully completed the injection training.

14. If study treatment is given by the patient or by a designated person, the patient will complete a diary for recording compliance with study treatment administration. If patient diary is provided to the patient, then it should be reviewed at each clinic visit and data collected into the case report forms (CRFs). On the final visit, the diary should be collected by the site.

15. At the screening visit, patient diary should be reviewed for the R3918-PNH-1868 (parent) study.

16. Daily oral antibiotic prophylaxis against *Neisseria meningitidis* is recommended starting on the first day of dosing with study treatment and continuing until 52 weeks after discontinuation of study treatment.

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

Footnotes for Table 4 Schedule of Events (for Patients on Intensified Treatment)

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

7. On day1r, pozelimab IV will be given first, with a 30-minute observation period before administration of SC doses. Subsequent pozelimab SC dose will be administered Q2W and cemdisiran SC dose will be administered Q4W. The SC injections may either be performed by the site personnel or another healthcare professional at patient's home or preferred location or be administered by the patient or by a designated person who has successfully completed the injection training.
8. Injection training will be provided to patients who desire self-injection or injection by a designated person. Site should observe patient self-injection or injection by a designated person and confirm adequacy. Patient instruction materials will be provided.
9. If study treatment is given by the patient or by a designated person, the patient will complete a diary for recording compliance with study treatment administration. If patient diary is provided to the patient, then it should be reviewed at each clinic visit and data collected into the CRFs. On the final visit, the diary should be collected by the site.
10. Daily oral antibiotic prophylaxis against *Neisseria meningitidis* is recommended until 52 weeks after discontinuation of study treatment.
11. Patients should try to complete the PNH Symptom-Specific Questionnaire at the same time each day whenever possible.
12. Patient safety card: Site should review the instructions on the safety card with the patient at each visit. Replacement cards may be given to the patient as needed.
13. Breakthrough hemolysis assessment: If a patient is suspected of having a breakthrough hemolysis event, then in addition to the required laboratory collection, additional samples for drug concentrations of pozelimab will be collected unless already noted in the schedule of events for that visit. If the suspected event does not occur at a scheduled visit then an unscheduled visit should occur with an evaluation of the patient and collection of coagulation, chemistry, and drug concentrations of pozelimab.
14. Clinical lab samples will be collected prior to any study drug administration (pre-dose) unless otherwise specified. During lab collection, handling and processing, the same methodology will be applied across study visits, as best as possible, to preserve the quality of sample and avoid hemolysis. The coagulation blood sample (tube) must always be collected first, followed by the blood chemistry sample (tube).
15. Serum LDH, CRP, and bilirubin (total and direct) will be assessed as part of the blood chemistry analysis. Blood chemistry sample should be collected before study treatment administration (pre-dose). During lab collection, handling and processing, the same methodology will be applied across study visits, as best as possible, to preserve the quality of sample and avoid hemolysis during sample processing. If the investigator or sponsor suspects that the lab result is not an accurate reflection of the patient's condition, the lab sample should be repeated.
16. Hematology sample should be collected before study treatment administration (pre-dose).
17. Pregnancy test for WOCBP: A urine test will be done at all visits indicated. Any positive urine pregnancy test should be confirmed with a serum pregnancy test.

18. On day 1r, obtain blood sample for pozelimab concentration and total C5 prior to IV administration of pozelimab and also within 15 minutes after the end of the IV infusion. At subsequent timepoints, blood samples for pozelimab drug concentration analysis and total C5 analysis will be obtained prior to any study treatment administration (pre-dose).
19. Blood samples for cemdisiran drug concentration analysis and concentrations of its metabolites will be collected on the specified days prior to any study treatment administration (pre-dose) and 2 to 6 hours post cemdisiran administration. The post-dose sample should be carefully coordinated with the dosing of cemdisiran and may be collected at the clinic or by a visiting health care professional.
20. Blood samples for immunogenicity will be collected on the specified days prior to any study treatment administration (pre-dose). At the visits where immunogenicity samples are to be taken, the sample should be collected with the sample for drug concentration. In the event of suspected treatment-related SAEs, such as anaphylaxis or hypersensitivity, additional samples for drug concentration and immunogenicity may be collected at or near the onset and the resolution of the event.
21. Blood samples for CH50 (efficacy endpoint) and AH50 will be obtained prior to any study treatment administration (pre-dose).

Footnotes for Table 5 Schedule of Events (for Open-Label Extension Period)

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

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

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

    Care must be taken to coordinate dosing for visits where a post-dose sample is collected to measure concentration of cemdisiran and its metabolites. For patients whose treatment is not intensified during the OLEP, the last doses of cemdisiran and pozelimab are administered at week 52e. For patients whose treatment was intensified during the OLEP, the last doses of study treatment will be determined based on the time of treatment intensification.
6. Injection training will be provided to patients who desire self-injection or injection by a designated person. Site should observe patient self-injection or injection by a designated person and confirm adequacy. Patient instruction materials will be provided.
7. If study treatment is given by the patient or by a designated person, the patient will complete a diary for recording compliance with study treatment administration. If patient diary is provided to the patient, then it should be reviewed at each clinic visit and data collected into the CRFs. On the final visit, the diary should be collected by the site.
8. Daily oral antibiotic prophylaxis against *Neisseria meningitidis* is recommended until 52 weeks after discontinuation of study treatment.
9. Patient safety card: Site should review the instructions on the safety card with the patient at each visit. Replacement cards may be given to the patient as needed.
10. Breakthrough hemolysis assessment: If a patient is suspected of having a breakthrough hemolysis event, then in addition to the required laboratory collection, additional samples for drug concentrations of pozelimab will be collected unless already noted in the schedule of events for that visit. If the suspected event does not occur at a scheduled visit then an unscheduled visit should occur with an evaluation of the patient and collection of coagulation, chemistry, and drug concentration of pozelimab.

11. Clinical lab samples will be collected prior to any study drug administration (pre-dose) unless otherwise specified. During lab collection, handling and processing, the same methodology will be applied across study visits, as best as possible, to preserve the quality of sample and avoid hemolysis. The coagulation blood sample (tube) must always be collected first, followed by the blood chemistry sample (tube).
12. Serum LDH, CRP, and bilirubin (total and direct) will be assessed as part of the blood chemistry analysis. Blood chemistry sample should be collected before study treatment administration (pre-dose). During lab collection, handling and processing, the same methodology will be applied across study visits, as best as possible, to preserve the quality of sample and avoid hemolysis during sample processing. If the investigator or sponsor suspects that the lab result is not an accurate reflection of the patient's condition, the lab sample should be repeated.
13. Hematology sample should be collected before study treatment administration (pre-dose).
14. Pregnancy test for WOCBP: A urine test will be done at all visits indicated. Any positive urine pregnancy test should be confirmed with a serum pregnancy test.
15. Blood samples for pozelimab concentration analysis and total C5 analysis will be obtained on the specified days prior to any study treatment administration (pre-dose).
16. Blood samples for cemdisiran concentration analysis and concentrations of its metabolites will be collected on the specified days prior to any study treatment administration (pre-dose) and 2 to 6 hours post cemdisiran administration. The post-dose sample should be carefully coordinated with the dosing of cemdisiran and may be collected at the clinic or by a visiting health care professional.
17. Blood samples for immunogenicity will be collected on the specified days prior to any study treatment administration (pre-dose). At the visits where immunogenicity samples are to be taken, the sample should be collected with the drug concentration sample. In the event of suspected treatment-related SAEs, such as anaphylaxis or hypersensitivity, additional drug concentration and immunogenicity samples may be collected at or near the onset and the resolution of the event.
18. Blood samples for CH50 (efficacy endpoint) and AH50 will be obtained prior to any study treatment administration (pre-dose).

Footnotes for Table 6 Schedule of Events (Post-Treatment Safety Follow-Up Period)

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

10.2. Criteria for Potentially Clinically Significant Values (PCSV)

Parameter	PCSV	Comments
Clinical chemistry		
ALT	By distribution analysis: > 3 ULN > 5 ULN > 10 ULN > 20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007 Internal DILI WG Oct 2008 Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
AST	By distribution analysis: > 3 ULN > 5 ULN > 10 ULN > 20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007 Internal DILI WG Oct 2008 Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
Alkaline Phosphatase	> 1.5 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008
Total Bilirubin	> 1.5 ULN > 2 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Concept paper on DILI – FDA draft Guidance Oct 2008 Internal DILI WG Oct 2008 Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
Conjugated bilirubin	> 35% total bilirubin (when total bilirubin >1.5 ULN)	Conjugated bilirubin dosed on a case-by-case basis
ALT and Total Bilirubin	ALT > 3 ULN and Total Bilirubin > 2 ULN	Concept paper on DILI – FDA draft Guidance Oct 2007 Internal DILI WG Oct 2008 To be counted within the same treatment phase, whatever the interval between measurement

Parameter	PCSV	Comments
CPK	> 3 ULN >10 ULN	FDA Feb 2005 Am J Cardiol April 2006 Categories are cumulative First row is mandatory. Rows following one mentioning zero can be deleted.
Creatinine	≥ 150 µmol/L (adults) ≥ 90 µmol/L (6-12 year-old) ≥ 30% from baseline ≥ 100% from baseline	Benichou C., 1994
eGFR (Chronic Kidney Disease – Epidemiology Collaboration Equation 2009)	< 30 ml/min (severe renal impairment) ≥ 30 - < 59 ml/min (moderate renal impairment) ≥60 - <89 ml/min (mild renal impairment) ≥ 90 ml/min (no renal impairment)	
Uric Acid Hyperuricemia: Hypouricemia:	 >408 µmol/L <120 µmol/L	Harrison- Principles of internal Medicine 17th Ed. 2008
Sodium	≤129 mmol/L ≥ 160 mmol/L	
Potassium	< 3 mmol/L ≥ 5.5 mmol/L	FDA Feb 2005
Total Cholesterol	≥ 7.74 mmol/L (3 g/L)	Threshold for therapeutic intervention
Triglycerides	≥ 4.6 mmol/L (4 g/L)	Threshold for therapeutic intervention
Glucose Hypoglycaemia Hyperglycaemia	 ≤ 3.9 mmol/L and < LLN ≥ 7 mmol/L (fasted); ≥ 11.1 mmol/L (unfasted)	 ADA May 2005 ADA Jan 2008
CRP	> 2 ULN or >10 mg/L, if ULN not provided	FDA Sept 2005

Parameter	PCSV	Comments
Hematology		
WBC	< 3.0 Giga/L (3000/mm3) < 2.0 Giga/L (2000/mm3) (Black)	Increase-in WBC: not relevant To be interpreted only if no differential count available.
Neutrophils	< 1.5 Giga/L (1500/mm3) < 1.0 Giga/L (1000/mm3) Black	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria
Eosinophils	> 0.5 Giga/L (500/mm^3) or > ULN if ULN ≥ 0.5 Giga/L	Gallin 1989, Harrisson 13th Ed, 1994.
Hemoglobin	At least 20 g/L (1.24 mmol/L) decrease versus baseline	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥ 30 g/L, ≥ 40 g/L, ≥ 50 g/L)
Platelets	< 100 Giga/L (100 000/mm^3)	International Consensus meeting on drug-induced blood cytopenias, 1991.
Vital signs		
HR	≤ 40 bpm and decrease from baseline ≥ 20 bpm ≥ 100 bpm and increase from baseline ≥ 20 bpm	Proposed change: To be are applied for all positions (including missing) except STANDING
SBP	≤ 95 mmHg and decrease from baseline ≥ 20 mmHg ≥ 140 mmHg and increase from baseline ≥ 20 mmHg	Proposed change: To be are applied for all positions (including missing) except STANDING
DBP	Young and elderly subjects ≤ 45 mmHg and decrease from baseline ≥ 10 mmHg ≥ 90 mmHg and increase from baseline ≥ 10 mmHg	Proposed change: To be are applied for all positions (including missing) except STANDING
Orthostatic Hypotension	SBP St – Su ≤ - 20 mmHg DBP St – Su ≤ - 10 mmHg	
Weight	≥ 5 % increase versus baseline ≥5% decrease versus baseline	FDA Feb 2007

Parameter	PCSV	Comments
ECG parameters		CPMP 1997 guideline
HR	≤ 40 bpm and decrease from baseline ≥ 20 bpm ≥ 100 bpm and increase from baseline ≥ 20 bpm	
PR	≥ 220 ms	
QRS	≥ 120 ms	
QTc Borderline Prolonged* Additional	<u>Absolute values (ms)</u> Males Females Borderline 431-450 ms 451-470 ms Prolonged* > 450 ms > 470 ms QTc ≥500 ms ≥ 500 ms <u>Increase versus baseline</u> (Males and Females) Borderline Δ 30-60 ms Prolonged * Δ > 60 ms	To be applied to any kind of QT correction formula *QTc prolonged and ΔQTc > 60 ms are the PCSA to be identified in individual subjects/patients listings.

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