REGENERON
Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN
VERSION: 2.0

Clinical Study Protocol Title:	**A SINGLE ARM, OPEN-LABEL STUDY TO ASSESS THE SAFETY, EFFICACY, AND PHARMACODYNAMIC EFFECTS OF POZELIMAB AND CEMDISIRAN COMBINATION THERAPY IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA WHO SWITCH FROM ECULIZUMAB THERAPY**
Compound:	Pozelimab (REGN3918) Cemdisiran (ALN-CC5)
Protocol Number:	R3918-PNH-20105
Clinical Phase:	Phase 2
Sponsor:	Regeneron Pharmaceuticals, Inc.
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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
AH50	Alternative pathway hemolytic activity assay
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
C	Complement component (e.g., C3, C5)
CH50	Total Complement hemolytic activity assay
CI	Confidence interval
COA	Clinical outcome assessment
CRF	Case report form (electronic or paper)
CRP	C-reactive protein
CSR	Clinical Study Report
dL	Deciliter
DTD	Drug-target-drug
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EORTC-QLQ-30	European Organisation for Research and Treatment of Cancer Quality of Life of Cancer Patients Questionnaire-30
EOT	End of treatment
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full analysis set
FBR	Future biomedical research
FDA	Food and Drug Administration
g	Grams
GHS	Global health status
HRQoL	Health-related quality of life
ICF	Informed consent form
ICH	International Council for Harmonisation
INR	International normalized ratio
IV	Intravenous

kg	Kilogram
LDH	Lactate dehydrogenase
MAVE	Major adverse vascular event
mg	Milligram
µg	Microgram
mL	Milliliter
OLEP	Open-label extension period (an optional period)
OLTP	Open-label treatment period (main study period)
PD	Pharmacodynamic
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
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SC	Subcutaneous
SOC	System organ class
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Women of childbearing potential

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the 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 is a single-arm study and thus patients and the investigator will be aware of treatment allocation.

The long-term safety and efficacy of the combination treatment will be assessed by providing the patients who complete the main 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. Patients who opt not to participate in the optional 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.

1.2. Study Objectives

1.2.1. Primary Objective

The primary objective of the study is to evaluate the safety and tolerability of pozelimab and cemdisiran (ALN-CC5) combination therapy in patients with PNH who switch from eculizumab therapy.

1.2.2. Secondary and Exploratory Objectives

The secondary objectives of the study are:

- To assess the effect of the combination treatment on the following parameters of intravascular hemolysis: lactate dehydrogenase (LDH) control, breakthrough hemolysis, and inhibition of complement hemolysis activity (CH50)
- To assess the stability of LDH during the transition period from eculizumab monotherapy to combination with pozelimab and cemdisiran
- To assess the effect of the combination treatment on red blood cell (RBC) transfusion requirements
- To assess the effect of the combination treatment on hemoglobin levels
- To assess the effect of the combination treatment on clinical outcome assessments (COAs) measuring fatigue and health-related quality of life (HRQoL)
- To assess the concentrations of total pozelimab and eculizumab in serum, and total cemdisiran and C5 protein in plasma
- To assess the immunogenicity of pozelimab and cemdisiran
- To assess safety after dose intensification

- To assess the long-term safety and efficacy of the combination treatment in an optional open-label extension period (OLEP)

The exploratory objectives of the study are:

- To assess the need for intensified treatment
- To assess the effect of the combination treatment on clinical thrombosis events
- To assess the effect of the combination treatment on renal function and renal injury biomarkers
- To assess the effect of the combination treatment on complement activation and intravascular hemolysis relevant to PNH and other related diseases
- To assess the effect of the combination treatment on PNH clone size
- To assess the effect of the combination treatment on a COA measuring treatment satisfaction (TSQM)
- To assess the effect of the combination treatment on a novel COA measuring PNH-specific symptoms
- To assess the effect of the combination treatment on PNH symptoms
- To assess 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)
    - DNA and RNA collected from patients who agree to participate in the optional genomics sub-study will be analyzed. Separate analysis plan(s) and report(s) will be written. Results will not be included in the CSR.
- To assess pozelimab and cemdisiran mechanism of action (related to efficacy and/or safety), complement pathway biology, PNH, and related complement-mediated diseases
- To assess efficacy after dose intensification with pozelimab and cemdisiran
- To assess 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 3.

1.2.4. Revision History for SAP Amendments

Summary of Changes from SAP Version 1 to Version 2 Due to Protocol Amendment 3	
Changes	**Sections changed**
Revised and clarified the following secondary endpoints: • Proportion of patients who maintain adequate control of hemolysis, defined as lactate dehydrogenase (LDH) ≤1.5 x upper limit of normal (ULN) from post-baseline (on day 1) through day 225 and from day 57 through day 225, inclusive • Proportion of patients with normalization of LDH at each visit, defined as LDH ≤1.0 x ULN from post-baseline (on day 1) through day 225, inclusive Corresponding changes were made to secondary endpoints for the optional open-label extension period (OLEP)	Section 4.5.2
Added new secondary endpoint on the proportion of patients with adequate control of hemolysis at each visit	Section 4.5.2
Added immunogenicity sample (anti-pozelimab antibodies) and D-dimer as part of laboratory analyses in the event of suspected breakthrough hemolysis	Table 3 Table 4 Table 5
Revised sample size language to “up to 12 patients”	Section 2.1 Section 2.2
Updated information about post-trial treatment access for patients who complete the optional OLEP	Figure 3 footnote
Removed eculizumab concentration from open-label extension period (OLEP) analysis	Section 4.5.2
Added baseline LDH, time since PNH diagnosis and Prior eculizumab dosing regime to baseline characteristics	Section 4.1
Moved PNH signs and symptoms from baseline to medical history	Sections 4.1 and 4.2
Clarified on-treatment period definition	Section 4.6.1
Added analysis window tables (Tables 1 and 2)	Section 6.4
Removed several rows from the List of Abbreviations, due to their not being included in this document	List of Abbreviations and Definition of Terms
Clarifications and corrections	Throughout the document

2. INVESTIGATION PLAN

2.1. Study Design

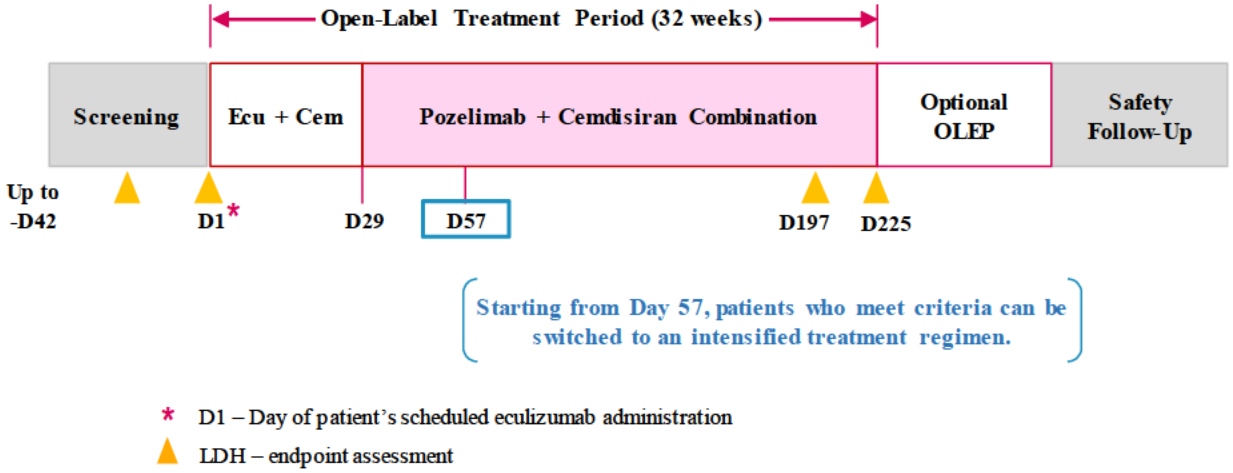
The study is a single-arm, open-label study whereby up to 12 patients with PNH who are currently receiving eculizumab will be switched to pozelimab and cemdisiran combination therapy. The study will include patients who are currently receiving eculizumab at the labeled dosing regimen (900 mg intravenously [IV] every 2 weeks [Q2W]) or patients who are currently receiving eculizumab at a dose higher than the labeled dose (>900 mg IV) or more frequently than labeled.

The study consists of 4 periods:

- A screening period of up to 42 days
- A 32-week open-label treatment period (OLTP, longer for patients who are switched to treatment intensification)
- An optional 52-week OLEP
- A 52-week post-treatment safety follow-up period

The fourth period begins when a patient completes or permanently discontinues study treatment (e.g., at the time of premature study drug discontinuation, at the completion of study treatment in the OLTP for patients who decline the optional OLEP, or at the completion of study treatment in the optional OLEP for patients who do not continue treatment in a post-trial access setting).

Figure 1: Study Flow Diagram



Cem, cemdisiran; Ecu, eculizumab; LDH, lactate dehydrogenase; optional OLEP, open-label extension period.
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

A total of up to 12 patients with PNH who are currently receiving eculizumab will switch to pozelimab and cemdisiran combination therapy. Patients will be switched from eculizumab administration at the labeled dosing regimen or at a dose higher than labeled and/or administered more frequently than labeled.

2.3. Study Plan

The study event table is presented in Section 10.

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 Set (FAS)

The full analysis set (FAS) includes all enrolled patients (i.e., patients for whom the CRF's subject enrollment field was entered as 'Yes') who received any study drug and have at least 1 post-baseline efficacy assessment. 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 Set (SAF)

The safety analysis set (SAF) includes all enrolled patients who received any amount of study drug. 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 Analysis Set

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

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 result following the first dose of study drug in the OLEP.

3.4. The Immunogenicity Analysis Sets

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

The OLEP ADA analysis set includes all patients 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.

3.5. The Exploratory Biomarker 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 study drug.

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

The following demographic and baseline characteristic 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
- Baseline hemoglobin
- Baseline eGFR
- Baseline creatinine
- Baseline total C5
- Baseline PNH clone size
- Baseline LDH
- Time since diagnosis of PNH
- Prior eculizumab dosing regimen (900 mg Q2W vs. >900 mg Q2W)

4.2. Medical History

Medical history will be coded to a Preferred Term (PT) and associated primary System Organ Class (SOC) according to the latest available version of Medical Dictionary for Regulatory Activities (MedDRA®).

In addition, the following historical data will be summarized:

- History in the past 12 months of the following:
  - Transfusions
  - Breakthrough hemolysis (numbers of patients and events)
- All available laboratory parameters for measurement of hemolysis at baseline:
  - LDH
  - Bilirubin
  - Haptoglobin
  - Reticulocyte count
  - Hemoglobin
- Prior history of thrombosis at any time
- Prior history of *Neisseria* infections at any time
- PNH signs or symptoms in the past 3 months
- Tuberculosis history
- Aplastic anemia history

4.3. Prior/Concomitant Medication and Procedures

Prior medications include detailed eculizumab administration history (past 26 weeks) and *N. meningitidis* vaccination (past 5 years); all other prior medications 12 weeks prior to screening.

Medications will be recorded by patients from the day of informed consent until their final study visit. Medications will be coded to the ATC level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the latest available version of WHO Drug Dictionary (WHODD). Patients will be counted once in all ATC categories linked to the medication.

Prior medications are medications taken prior to administration of the first dose of study drug. Concomitant medications are medications taken between the first dose of study drug to the end of the safety follow-up period.

Prior/concomitant medications will include Meningococcal vaccinations and oral antibiotic prophylaxes.

Prior/concomitant procedures will be recorded. Prior procedures are procedures performed prior to administration of the first dose of study drug. Concomitant procedures are procedures performed between the first dose of study drug and the EOS visit.

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

4.4. Prohibited Medication During Study if Applicable

The use of the following concomitant medications is not permitted:

- The use of any other complement inhibitor is prohibited while the patient is taking study treatments, with the exception of eculizumab as ongoing background therapy during the transition to the combination treatment
- Other investigational treatments during the course of the study

4.5. Efficacy Variables

4.5.1. Primary Efficacy Variables

Not Applicable

4.5.2. Secondary Efficacy Variables

The secondary efficacy endpoints for the OLTP are:

- The percent change in LDH from pre-treatment (as defined by the mean of the LDH values at the screening visit [obtained no more than one day before administration with eculizumab] and baseline (day 1 visit, prior to administration of cemdisiran and eculizumab) to end-of-treatment period (as defined by the mean of the LDH values at days 197 and 225 in the OLTP)
- The percent change in LDH from pre-treatment to day 29
- The proportion of patients who are transfusion-free (defined as not requiring an RBC transfusion as per protocol algorithm) from baseline through day 225
- The proportion of patients who are transfusion-free (defined as not requiring an RBC transfusion as per protocol algorithm) from day 29 through day 225
- The rate and number of units of RBCs transfused from baseline through day 225, inclusive
- The rate and number of units of RBCs transfused from day 29 through day 225, inclusive
- The proportion of patients with breakthrough hemolysis from baseline through day 225, inclusive
- The proportion of patients with breakthrough hemolysis from day 29 through day 225, inclusive
- The proportion of patients who maintain adequate control of hemolysis, defined as LDH $\leq$1.5 x ULN from post-baseline (on day 1) through day 225, inclusive
- The proportion of patients who maintain adequate control of hemolysis, defined as LDH $\leq$1.5 x ULN from day 57 through day 225, inclusive

- The proportion of patients with adequate control of hemolysis at each visit from post-baseline (on day 1) through day 225, inclusive
- The proportion of patients with normalization of their LDH at each visit, defined as LDH ≤1.0 x ULN , from post baseline (on day 1) through day 225, inclusive
- The area under the curve (AUC) of LDH over time between baseline through day 225, inclusive
- The area under the curve (AUC) of LDH over time between day 57 through day 225, inclusive
- The proportion of patients with hemoglobin stabilization (defined as patients who do not receive an RBC transfusion and have no decrease in hemoglobin level of ≥2 g/dL) from baseline through day 225, inclusive
- The proportion of patients with hemoglobin stabilization (defined as patients who do not receive an RBC transfusion and have no decrease in hemoglobin level of ≥2 g/dL) from day 29 through day 225, inclusive
- Change in hemoglobin levels from baseline to day 225, inclusive
- Change in fatigue as measured by the FACIT-Fatigue Scale from baseline to day 225, inclusive
- Change from baseline to day 225 in global health status/QoL scale (GHS) and physical function (PF) scores on the European Organization for Research and Treatment of Cancer: Quality-of-Life Questionnaire core-30 items (EORTC QLQ-C30)
- Change in CH50 from baseline to day 225, inclusive
- Concentrations of total pozelimab and eculizumab in serum, and total 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

The secondary efficacy endpoints for the optional OLEP are:

- Change and percent change of LDH from day 1e (baseline of the OLEP) to week 24e and week 52e (the suffix "e" denoting extension)
- The proportion of patients who are transfusion-free (defined as not requiring an RBC transfusion as per protocol algorithm) from day 1e through week 24e and week 52e (i.e., transfusion avoidance)
- The rate and number of units of RBCs transfused from day 1e through week 24e and week 52e.
- The proportion of patients with breakthrough hemolysis from day 1e through week 24e and week 52e
- The proportion of patients who maintain adequate control of their hemolysis, defined as LDH ≤1.5 x ULN between day 1e through week 24e and week 52e, inclusive
- The proportion of patients with adequate control of hemolysis at each visit from day 1e through week 24e and week 52e, inclusive
- The proportion of patients with normalization of their LDH, defined as LDH ≤1.0 x ULN at each visit from day 1e through week 24e and week 52e, inclusive
- The AUC of LDH over time between day 1e through week 24e and week 52e, inclusive
- The proportion of patients with hemoglobin stabilization (defined as patients who do not receive an RBC transfusion and have no decrease in hemoglobin level of ≥2 g/dL) from day 1e through week 24e and week 52e
- Change in hemoglobin levels from day 1e to week 24e and week 52e of the OLEP
- Change in fatigue as measured by the FACIT-Fatigue Scale from day 1e to week 52e of the OLEP
- Change from day 1e to week 52e of the OLEP in GHS/QoL scale PF scores on the EORTC QLQ-C30
- Change in CH50 from day 1e to week 16e, week 24e, and 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 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	BL through D225	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 (as defined by the mean of the LDH values at the screening visit [obtained no more than one day before administration with eculizumab] to EOT period (as defined by the mean of LDH values at D197 and D225 in the OLTP)	Day 1e (BL of the OLEP) to week 24e
		Pre-treatment to D29	Not Applicable
Patients who are transfusion-free	Proportion	BL through D225	Day 1e through week 24e
		D29 through D225	Day 1e through week 52e
Units of RBC's transfused	Rate and Number	BL through D225	Day 1e through week 24e
		D29 through D225	Day 1e through week 52e
Breakthrough hemolysis	Proportion	BL through D225	Day 1e through week 24e
		D29 through D225	Day 1e through week 52e
LDH	Proportion who maintain adequate control of hemolysis (defined as $LDH \leq 1.5 * ULN$)	D1 through D225	Day 1e through week 24e
		D57 through D225	Day 1e through week 52e

OLTP and OLEP			
Measurement	**Metric**	**Time Period in OLTP**	**Time Period in OLEP**
LDH	Proportion with adequate control of hemolysis at each visit	D1 through D225	Day 1e through week 24e
			Day 1e through week 52e
LDH	Proportion with normalization of LDH (defined as $LDH \leq 1.0 * ULN$)	D1 through D225	Day 1e through week 24e
			Day 1e through week 52e
LDH	AUC over time	BL through D225	Day 1e through week 24e
		D57 through D225	Day 1e through week 52e
Hemoglobin stabilization	Proportion of patients who do not receive an RBC transfusion and have no decrease in hemoglobin level of ≥ 2 g/dL)	BL through D225	Day 1e through week 24e
		D29 through D225	Not Applicable
Hemoglobin	Change	BL through D225	Day 1e through week 24e
		D29 through D225	Day 1e through week 52e
Fatigue	Change in FACIT-Fatigue Scale	BL to D225	Day 1e to week 52e
Global health status	Change in GHS in EORTC QLQ-C30	BL to D225	Day 1e to week 52e
Physical Function	Change in PF in EORTC QLQ-C30	BL to D225	Day 1e to week 52e
CH50	Change	BL to D225	Day 1e to week 16e
		Not Applicable	Day 1e to week 24e
		Not Applicable	Day 1e to week 52e
Total Pozelimab in serum	Concentrations	Whole OLTP	Whole OLEP

OLTP and OLEP			
Measurement	**Metric**	**Time Period in OLTP**	**Time Period in OLEP**
Total Eculizumab in serum	Concentrations	Whole OLTP	Not applicable
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

4.5.3. Exploratory Efficacy Variables

The exploratory endpoints for the OLTP are:

- Proportion of patients who require treatment intensification throughout the study
- Incidence of MAVE from baseline through day 225
- Change in renal function as measured by estimated glomerular filtration rate (eGFR) from baseline to day 225
- Percent change in free hemoglobin from baseline to day 225
- Change in bilirubin from baseline to day 225
- Change in reticulocyte count from baseline to day 225
- Change and percent change in AH50 from baseline to day 225
- Proportion of PNH erythrocytes and granulocytes from baseline to day 225
- Change from baseline to day 225 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
- Proportion of patients with stability in global health status, functioning, and symptoms as measured by the EORTC QLQ-C30 from baseline to day 225
- Comparison of treatment satisfaction (as assessed by the TSQM) at baseline (with eculizumab) versus treatment at day 225 (with pozelimab/cemdisiran)

Note: The exploratory variables PGIC, PGIS and the PNH Symptom Specific Questionnaire will not be analyzed for the CSR.

Exploratory endpoints will be assessed in the OLEP in the same way as in the OLTP. 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	Whole OLEP
MAVE	Proportion	BL to D225	Day 1e to week 52e
Renal functions	Change measured by eGFR	BL to D225	Day 1e to week 52e
Free hemoglobin	Percent change	BL to D225	Day 1e to week 52e
Bilirubin	Change	BL to D225	Day 1e to week 52e
Reticulocyte count	Change	BL to D225	Day 1e to week 52e
AH50	Change	BL to D225	Day 1e to week 52e
	Percent change	BL to D225	Day 1e to week 52e
PNH erythrocytes	Change	BL to D225	Day 1e to week 52e
PNH granulocytes	Change	BL to D225	Day 1e to week 52e
Role Functioning	Change in Functional Scale Scores: EORTC QLQ-C30	BL to D225	Day 1e to week 52e
Emotional Functioning	Change in Functional Scale: EORTC QLQ-C30	BL to D225	Day 1e to week 52e
Cognitive Functioning	Change in Functional Scale: EORTC QLQ-C30	BL to D225	Day 1e to week 52e
Social Functioning	Change in Functional Scale: EORTC QLQ-C30	BL to D225	Day 1e to week 52e
Fatigue	Change in Symptom Scale: EORTC QLQ-C30	BL to D225	Day 1e to week 52e
Nausea	Change in Symptom Scale: EORTC QLQ-C30	BL to D225	Day 1e to week 52e
Vomiting	Change in Symptom Scale: EORTC QLQ-C30	BL to D225	Day 1e to week 52e
Pain	Change in Symptom Scale: EORTC QLQ-C30	BL to D225	Day 1e to week 52e
Dyspnea	Change in Symptom Scale: EORTC QLQ-C30	BL to D225	Day 1e to week 52e
Insomnia	Change in Symptom Scale: EORTC QLQ-C30	BL to D225	Day 1e to week 52e
Appetite Loss	Change in Symptom Scale: EORTC QLQ-C30	BL to D225	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 D225	Day 1e to week 52e
Diarrhea	Change in Symptom Scale: EORTC QLQ-C30	BL to D225	Day 1e to week 52e
Stability in global health status	Proportion with stability as measured by EORTC QLQ-C30	BL to D225	Day 1e to week 52e
Stability in functioning, and symptoms	Proportion with stability as measured by EORTC QLQ-C30	BL to D225	Day 1e to week 52e
Stability in symptoms	Proportion with stability as measured by EORTC QLQ-C30	BL to D225	Day 1e to week 52e
Treatment satisfaction	Comparison between two therapies as assessed by TSQM	BL to D225	Not applicable

4.6. Safety Variables

The safety variables are

- TEAEs
- Body weight
- Vital signs
- Electrocardiogram (ECG)
- Physical examination
- Routine safety laboratory tests (hematology, chemistry, urinalysis)

4.6.1. Adverse Events and Serious Adverse Events

Adverse events and serious adverse events will be collected from the time of informed consent signature and then at each visit until the end of the study. All adverse events are to be coded to a "Preferred Term (PT)" and associated primary "System Organ Class (SOC)" according to the Medical Dictionary for Regulatory Activities (MedDRA, the most current available version).

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 three observation periods:

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

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 during the on-treatment period.

Post-treatment AEs are AEs that developed or worsened during the post-treatment period.

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

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

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Important medical event

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

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

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

4.6.2. 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. In this study, AESIs are listed below (as provided in the protocol):

- Suspected Neisseria infection
- Moderate or severe infusion reactions
- Major adverse vascular events (MAVE)
- Moderate or severe hypersensitivity reactions potentially related to study treatment
- Adverse events potentially due to suspected large DTD immune complexes
- Liver transaminase elevations as evidenced by one or more of the following:
  - ALT or AST>8 × ULN, or
  - ALT or AST>5 × ULN for more than 2 weeks, or
  - ALT or AST>3 × ULN and total bilirubin >2 × ULN (or international normalized ratio [INR] > 1.5) not related to PNH

The following events are also AESIs but do not require expedited safety reporting to the sponsor:

- Mild infusion reactions to study treatment
- Mild hypersensivity reactions to study treatment
- Injection site reactions due to study treatment

4.6.3. 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. Conventional units may be provided. Laboratory tests are categorized in the protocol as follows:

- Titers to measure *N. Meningitidis* (only if required per local practice/regulations)
- Hematology
- Coagulation panel
- Chemistry, including LDH
- Hepatitis B and C testing
- Pregnancy test (for applicable patients)
- Urinalysis

4.6.4. Vital Signs

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

4.6.5. 12-Lead Electrocardiography (ECG)

Heart rate will be recorded from the ventricular rate and the PR, QRS, and QT, QTcF, and ECG status (normal, abnormal not clinically significant or abnormal clinical significant) will also be recorded.

4.7. Pharmacokinetic Variables

The PK endpoints are concentrations of total pozelimab, cemdisiran and eculizumab. Target engagement will be assessed by the concentration of total C5. The sampling time points are specified in Section 10.

4.8. Immunogenicity Variables

The immunogenicity variables are ADA status and titer at nominal sampling time point/visit. Samples in this study will be collected at the clinic visits specified in Section 10.

4.9. Pharmacodynamic Variables

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

- Serum CH50, an assay assessing the activity of the classical pathway of complement, will be used to measure C5 activity. It is the principal PD marker for the study and is also an efficacy variable in this study
- Free hemoglobin
- Parameters of intravascular hemolysis: i.e., haptoglobin, reticulocyte count, and bilirubin
- AH50 (serum)
- 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.

4.10. 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 de novo 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 subgroup (switched from eculizumab administration at the labeled dosing regimen or switched from eculizumab at a dose higher than labeled and/or more frequently than labeled), and for all patients combined for the FAS. 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 overall for the study in 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, dictionary coded by WHODD, will be descriptively summarized 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 during the treatment period, dictionary coded by WHODD, will be descriptively summarized for patients in the safety set. 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.

5.4. Prohibited Medications

A listing of prohibited medications, found in Section 4.4, 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 who signed the ICF
- The total number of enrolled patients
- The total number of patients who discontinued the study, and the reasons for discontinuation, by study period
- The total number of patients who discontinued from the study treatment, and the reasons for discontinuation, by study period
- A listing of patients prematurely discontinued from treatment, along with reasons discontinuation
- Total number of patients who received treatment intensification, by study period
- Total number of patients who continued into the OLEP and who completed the OLEP

5.6. Extent of Study Treatment Exposure and Compliance

5.6.1. Measurement of Compliance

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

> Treatment Compliance = (Number of investigational product doses or background eculizumab taken during study period)/(Number of investigational product or background eculizumab doses prescribed to be taken during period) x 100%,

where temporary dose discontinuation is ignored. Separate summaries will be provided for pozelimab and cemdisiran.

5.6.2. Exposure to Investigational Product

Treatment exposure will be presented separately for pozelimab and cemdisiran.

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 OLTP:

- ≥ Day 29 (Week 4)
- ≥ Day 57 (Week 8)
- ≥ Day 85 (Week 12)
- ≥ Day 113 (Week 16)
- ≥ Day 141 (Week 20)
- ≥ Day 169 (Week 24)
- ≥ Day 197 (Week 28)
- ≥ Day 225 (Week 32)

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

The analysis of secondary and exploratory efficacy variables is determined by type of 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 but using OLEP data. 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. 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

For visit-oriented, continuous secondary efficacy variables in Section 4.5.2, descriptive statistics for change from baseline and/or percent change from baseline to each time point will be presented by patient subgroup (switched from eculizumab administration at the labeled dosing regimen or switched from eculizumab at a dose higher than labeled and/or more frequently than labeled) and overall, and visit.

In addition, for LDH, hemoglobin and CH50, spaghetti plots will be provided for patients who did not have intensified treatment, patients who received intensified treatment, patients who discontinued treatment due to lack of efficacy, and patients who stopped treatment for other reasons, if numbers permit.

For the AUC of LDH over time from baseline through day 225, from day 57 through day 225 during OLTP, and from day 225 and onward during OLEP, inclusive, the analysis set will include all treated patients. The AUC will be computed using available LDH values using the trapezoidal rule. The mean AUC, 95% CI, and other summary statistics will be provided.

For the rate and number of units of RBCs transfused from baseline through day 225, and from day 29 through day 225, the analysis set will consist of all treated patients who never received the intensified regimen during treatment. For the rate of transfusion (number of transfusions of RBCs through day 225), the rate and 95% confidence interval will be calculated, based on an assumption of a negative binomial distribution, adjusted for time on study. The number of units of transfusion for a patient will be calculated based on the duration of treatment exposure of the patient. Descriptive statistics will be reported for all patients and for the 2 patient subgroups, if sample size allows. A transfusion will be counted only if it follows the pre-defined transfusion algorithm.

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 for all patients and for the 2 patient subgroups separately.

For the secondary variable of the rate of breakthrough hemolysis through day 225, defined as the measurement of LDH $\geq$ 2 x ULN concomitant with associated signs or symptoms at any time subsequent to an initial achievement of disease control (i.e., LDH $\leq$ 1.5 x ULN), the proportion of patients with breakthrough 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 who maintain adequate control of hemolysis (defined as LDH $\leq$1.5 x ULN from post-baseline (on day 1) through day 225, and from day 57 through day 225, inclusive), patients who have one or more of the following will be considered as not maintaining adequate control of their intravascular hemolysis:

- Having at least one measurement of LDH > 1.5 x ULN
- Discontinuing from study treatment early
- Having 2 consecutive missing values of the scheduled LDH measurements
- Having 3 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 day 57 and day 225, have fewer than 3 missing values of the scheduled LDH measurements between day 57 and day 225 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. If the LDH value at the scheduled central lab assessment is missing, the LDH value from the unscheduled central lab within the analysis visit window (see Section 6.4) that is the closest to the visit date will be used. The proportion of patients maintaining adequate control of their intravascular hemolysis will be calculated, along with a 95% confidence interval, by the exact Clopper Pearson method. In addition, proportion of patients with LDH ≤1.50 x ULN at each scheduled assessment timepoint will be summarized.

Percentages of patients with LDH ≤ 1.5 x ULN and LDH ≤ 1.0 x ULN will be tabulated and plotted at each visit.

5.7.3. Analysis of Exploratory Variables

For categorical exploratory variables, such as "Incidence of MAVE through week 32" the proportion of patients with at least one MAVE will be presented along with 95% confidence interval using the exact Clopper-Pearson method.

For continuous, visit-oriented exploratory variables, the change and/or percent change from baseline will be assessed in the same way as the secondary variables of this type.

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

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

5.8. Analysis of Safety Data

The primary endpoint in this study is the incidence and severity of TEAEs through day 225 of the OLTP. Safety analysis will be conducted when all patients (including patients on treatment intensification) complete the 32-week treatment period or prematurely discontinue study.

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®).

The analysis of safety data will be performed on the SAF, as defined in Section 3.2.

The safety analysis will be based on the reported AEs and other safety information (clinical laboratory evaluations, vital signs, and 12-lead ECG).

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

The summary of safety results will be presented overall.

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

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

5.8.1. Adverse Events

Summaries of frequencies and proportions of patients reporting AEs will include the PTs and the SOCs. Summaries will be presented for the OLTP (overall and separately for the eculizumab + cemdisiran and pozelimab + cemdisiran treatment periods) and for the OLEP.

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 (according to the grading scale outlined in Section 4.6.1), 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 and leading to study discontinuation will be listed and summarized.

5.8.2. Analysis of Vital Signs

Vital signs (temperature, pulse, blood pressure) will be summarized by 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 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 $\geq$ 2 x ULN and potassium $\geq$ 6 mmol/L in the absence of an event of breakthrough hemolysis, 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 visit 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, eculizumab 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 pozelimab and total C5 will be presented over time (linear and log scales). When the scale is linear, concentrations below the lower limit of quantification (LLOQ) will be set to zero. In the log-scaled figures, concentrations below the LLOQ will be imputed as LLOQ/2. Summary statistics of concentrations of total pozelimab and total C5 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.

Descriptive concentration-response (AH50, CH50 and total C5) analysis will be performed as appropriate.

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 this study unless otherwise specified. The immunogenicity variables described in Section 4.8 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) and ≥9-fold (for anti-pozelimab) over the baseline titer value .
- Treatment-emergent - A negative result or missing result at baseline with at least one positive post baseline result in the ADA assay. 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 in ADA positive patients

5.10. Analysis of Pharmacodynamic and Biomarker Data

Pharmacodynamic and biomarker variable listed in Section 4.9 may be analyzed and summarized. For each biomarker variable, time profile and percent of change from baseline at each time point will be summarized over time.

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 Efficacy Variables

6.3. 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.

6.3.1. 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

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

6.3.2. PCSV

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

6.3.3. 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.

6.4. Analysis Windows

Data analyzed by visit (including efficacy, laboratory data, vital signs, ECG) will be summarized by the study scheduled visits described in Appendix 10.1 (Schedule of Time and Events). Analysis visit windows will be constructed using ranges applied to the number of days in study (study days) when the measure is collected, according to the analysis windowing described in the tables below. 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.

Table 1: Efficacy Analysis Windows

Visit	Targeted Study Day	Haptoglobin	PNH Eryth, PNH Gran	CH50, AH50, sC5b-9	FACIT-Fatigue, EORTC-QLQ-C30, TSQM
Screening 1			Scr 1		
Screening 2					
Day 1	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		[2,217]	[54, 81]	[54, 81]
Week 10	71				
Week 12	85	[82, 217]		[82, 105]	[82, 105]
Week 16	113			[106, 133]	[106, 133]
Week 20	141			[134, 161]	[134, 161]
Week 24	169			[162, 189]	[162, 189]
Week 28	197			[190, 217]	[190, 217]
Week 32	225	[218, 232]	[218, 232]	[218, 232]	[218, 232]
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	Blood Chem (Including LDH), Coagulation	Hematology (Including Hemoglobin)	Urinalysis	Vital Signs	ECG	Body Weight
Screening 1					Scr 1		Scr 1
Screening 2							
Day 1	1	1	1	1		1	
Week 1	8	[2, 12]	[2, 12]	[2, 12]			
Week 2	15	[13, 25]	[13, 25]	[13, 25]	[2, 25]		
Week 4	29	[26, 39]	[26, 53]	[26, 53]	[26, 53]		[2, 53]
Week 6	43	[40, 53]					

Visit	Targeted Study Day	Blood Chem (Including LDH), Coagulation	Hematology (Including Hemoglobin)	Urinalysis	Vital Signs	ECG	Body Weight
Week 8	57	[54, 67]	[54, 81]	[54, 81]	[54, 81]		[54, 81]
Week 10	71	[68, 81]					
Week 12	85	[82, 105]	[82, 105]	[82, 105]	[82, 105]		[82, 105]
Week 16	113	[106, 133]	[106, 133]	[106, 133]	[106, 133]		[106, 133]
Week 20	141	[134, 161]	[134, 161]	[134, 161]	[134, 161]		[134, 161]
Week 24	169	[162, 189]	[162, 189]	[162, 217]	[162, 217]	[2, 217]	[162, 217]
Week 28	197	[190, 217]	[190, 217]				
Week 32	225	[218, 232]	[218, 232]	[218, 232]	[218, 232]	[218, 232]	[218, 232]
OLEP-1 (Week 0e)	1e	1e	1e	1e	1e	1e	1e
OLEP-2 (Week 8e)	57e	[2e, 105e]	[2e, 105e]	[2e, 105e]	[2e, 105e]		[2e, 105e]
OLEP-3 (Week 16e)	113e	[106e, 161e]	[106e, 161e]	[106e, 161e]	[106e, 161e]		[106e, 161e]
OLEP-4 (Week 24e)	169e	[162e, 217e]	[162e, 217e]	[162e, 217e]	[162e, 217e]		[162e, 217e]
OLEP-5 (Week 32e)	225e	[218e, 273e]	[218e, 273e]	[218e, 273e]	[218e, 273e]		[218e, 273e]
OLEP-6 (Week 40e)	281e	[274e, 357e]	[274e, 357e]	[274e, 357e]	[274e, 357e]		[274e, 357e]
OLEP-7 (Week 52e)	365e	[358e, 368e]	[358e, 368e]	[358e, 368e]	[358e, 368e]	[2e, 368e]	[358e, 368e]

6.5. 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 unscheduled laboratory value is available for a given visit, the observation closest to the target visit date 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.

8. SOFTWARE

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

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

Table 3: Schedule of Events for Open-Label Treatment Period

Study Procedure[1]	Screening Period		Open-Label Treatment Period												
Visit #	V1a	V1b[2]	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	EOT V14
Week	Up to -6		0	1	2[12]	4	6	8	10	12	16	20	24	28	32
Day	Up to -42		1	8	15	29	43	57	71	85	113	141	169	197	225
Window (day)				±2	±2	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7
Screening/Baseline:															
Inclusion/exclusion criteria	X	X	X												
Informed consent	X														
Informed consent for OLEP	X														
Informed consent for FBR (optional)	X														
Informed consent for genomic testing (optional)	X														
Medical history[3]	X														
Prior medications[4]	X	X													
Demographics	X														
Height	X														
Vaccination/re-vaccinate for *Neisseria meningitidis*[5]	X														
Vaccination against *Streptococcus pneumoniae* and *Haemophilus influenza* type B (if needed)	X														
Tuberculosis history and assessment[6]	X														
Risk assessment for *Neisseria gonorrhea*[7]	X														
Patient safety card for *Neisseria meningitidis*[8]			X	X	X	X	X	X	X	X	X	X	X	X	X
Enrollment			X												
Treatment:															
Administer Cemdisiran 200 mg SC Q4W[9,11]			X			X		X		X	X	X	X	X	
Administer Pozelimab IV 60 mg/kg[10]						X									
Administer Pozelimab 400 mg SC Q4W[11]						X		X		X	X	X	X	X	

Study Procedure[1]	Screening Period		Open-Label Treatment Period												
Visit #	**V1a**	**V1b[2]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**EOT V14**
Week	Up to -6		0	1	2[12]	4	6	8	10	12	16	20	24	28	32
Day	Up to -42		1	8	15	29	43	57	71	85	113	141	169	197	225
Window (day)				±2	±2	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7
Administer eculizumab[12]			X		X										
Injection Training/patient instructions, if needed[13]						X	X	X	X	X	X	X	X	X	
Patient diary[14]								X	X	X	X	X	X	X	X
Concomitant meds and procedure			<----------X---------->												
Transfusion record update	<----------X---------->														
Antibiotics prophylaxis (recommended)[15]			<----------X---------->												
Revaccination against meningococcal infection *(if needed)*	<----------X---------->														
Clinical Outcome Assessments:															
FACIT-Fatigue			X		X	X		X		X	X	X	X	X	X
EORTC-QLQ-30			X		X	X		X		X	X	X	X	X	X
TSQM			X		X	X		X		X	X	X	X	X	X
PNH symptom-specific questionnaire (daily)[16]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
PGIS			X			X				X		X	X		X
PGIC						X				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		X
Physical examination	X		X			X				X					X
Electrocardiogram	X												X		X
Adverse events	<----------X---------->														
Breakthrough hemolysis assessment[17]	<----------X---------->														
Laboratory Testing[18]:															
Titers to measure *N. Meningitidis (*only if required per local practice/regulations)	X														
Hematology	X	X[2]	X	X	X	X		X		X	X	X	X	X	X

Study Procedure[1]	Screening Period		Open-Label Treatment Period												
Visit #	**V1a**	**V1b[2]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**EOT V14**
Week	Up to -6		0	1	2[12]	4	6	8	10	12	16	20	24	28	32
Day	Up to -42		1	8	15	29	43	57	71	85	113	141	169	197	225
Window (day)				±2	±2	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7
Coagulation panel	X	X[2]	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry, including LDH[19]	X	X[2]	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatitis B and C testing	X														
Pregnancy test (applicable patients)[20]	X		X			X		X		X	X	X	X	X	X
Urinalysis	X		X	X	X	X		X		X	X	X	X		X
Pharmacokinetics, total C5, and Immunogenicity Sampling:															
Blood samples for conc. of pozelimab[21]						X		X		X	X	X	X	X	X
Blood samples for conc. of cemdisiran and metabolites[22]			X							X				X	
Blood samples for conc. of eculizumab[21]			X		X	X		X		X	X	X	X		X
Blood samples for conc. of total C5[21]			X	X	X	X		X		X	X	X	X	X	X
Blood samples for immunogenicity of pozelimab[23]			X								X				X
Blood samples for immunogenicity of cemdisiran[23]			X							X				X	
Biomarkers:															
Free hemoglobin			X			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	X
Complement hemolytic assay (serum AH50)[21]			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
PNH granulocyte cells	X							X							X
Optional pharmacogenomics and future biomedical research:															
Future research serum and plasma (optional)[24]			X		X	X		X			X				X
Whole blood sample for DNA isolation (optional)[25]			X												
Whole blood RNA sample (optional)			X												X

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

Study Procedure[1]	Intensified Treatment Period in the OLTP												
Visit #	**RV1**	**RV2**	**RV3**	**RV4**	**RV5**	**RV6**	**RV7**	**RV8**	**RV9**	**RV10**	**RV11**	**RV12**	**EOT RV13**
Week	0r	1r	2r	4r	6r	8r	10r	12r	16r	20r	24r	28r	32r
Day	1r	8r	15r	29r	43r	57r	71r	85r	113r	141r	169r	197r	225r
Window (day)		±2	±2	±3	±3	±3	±3	±3	-7/+3	-7/+3	-7/+3	-7/+3	-7/+3
Treatment:[2]													
Administer Pozelimab IV 30 mg/kg	X												
Administer Pozelimab 400 mg SC Q2W[3]	X		X	X	X	X	X	X	X	X	X	X[3]	
Administer Cemdisiran 200 mg SC Q4W[3]	X			X		X		X	X	X	X	X	
Injection Training/patient instructions, if needed[4]	X	X	X	X	X	X	X	X	X	X	X	X	
Patient diary[5]	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant meds and procedures	<-----							X					----->
Transfusion record update	<-----							X					----->
Antibiotics prophylaxis (recommended)[6]	<-----							X					----->
Re-vaccination against meningococcal infection *(if needed)*	<-----							X					----->
Clinical Outcome Assessments:													
FACIT-Fatigue	X		X	X		X		X	X	X	X	X	X
EORTC-QLQ-30	X		X	X		X		X	X	X	X	X	X
TSQM	X		X	X		X		X	X	X	X	X	X
PNH symptom-specific questionnaire (daily)[7]	X	X	X	X	X	X	X	X	X	X	X	X	X
PGIS	X			X				X		X	X		X
PGIC				X				X		X	X		X
Safety and Anthropometric:													
Patient safety card for *Neisseria meningitidis*[8]	<-----							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

Study Procedure[1]	Intensified Treatment Period in the OLTP												
Visit #	**RV1**	**RV2**	**RV3**	**RV4**	**RV5**	**RV6**	**RV7**	**RV8**	**RV9**	**RV10**	**RV11**	**RV12**	**EOT RV13**
Week	0r	1r	2r	4r	6r	8r	10r	12r	16r	20r	24r	28r	32r
Day	1r	8r	15r	29r	43r	57r	71r	85r	113r	141r	169r	197r	225r
Window (day)		±2	±2	±3	±3	±3	±3	±3	-7/+3	-7/+3	-7/+3	-7/+3	-7/+3
Electrocardiogram											X		X
Adverse events	<----------X---------->												
Breakthrough hemolysis assessment[9]	<----------X---------->												
Laboratory Testing[10]:													
Titers to measure *N. Meningitidis (*only if required per local practice/regulations)	X												
Hematology	X	X	X	X		X		X	X	X	X	X	X
Coagulation panel	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry including LDH[11]	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (applicable patients)[12]	X			X		X		X	X	X	X	X	X
Urinalysis	X	X	X	X		X		X	X	X	X		X
Pharmacokinetics, total C5, and Immunogenicity Sampling:													
Blood samples for conc. of pozelimab[13]	X		X	X		X		X	X	X	X	X	X
Blood samples for conc. of cemdisiran and metabolites[14]	X							X				X	
Blood samples for conc. of total C5[13]	X	X	X	X		X		X	X	X	X	X	X
Blood samples for immunogenicity of pozelimab[15]	X								X				X
Blood samples for immunogenicity of cemdisiran[15]	X							X				X	
Biomarkers:													
Free hemoglobin	X			X		X		X	X	X	X	X	X
Haptoglobin	X			X				X					X
Complement hemolytic assay (serum CH50)[13]	X	X	X	X		X		X	X	X	X	X	X
Complement hemolytic assay (serum AH50)[13]	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
PNH granulocyte cells	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	OLEP-3	OLEP-4	OLEP-5	OLEP-6	OLEP-7
Week	**0e**	**8e**	**16e**	**24e**	**32e**	**40e**	**52e**
Day	**1e**	**57e**	**113e**	**169e**	**225e**	**281e**	**365e**
Window (day)[4]	--	-7/+3	-7/+3	-7/+3	-7/+3	-7/+3	-7/+3
Treatment[5]:							
Re-vaccination against meningococcal infection (if needed)	<----------X---------->						
Pozelimab 400 mg SC Q2W or Q4W[6]	X	X	X	X	X	X	X
Cemdisiran 200 mg SC Q4W[6]	X	X	X	X	X	X	X
Injection training/patient instructions (as needed)[7]	<----------X---------->						
Patient diary[8]	X	X	X	X	X	X	X
Antibiotics prophylaxis (recommended)[9]	<----------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*[10]	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[11]	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

Study Procedure (Visit)[1,2]	Optional Open-Label Extension Period						
	OLEP-1[3]	OLEP-2	OLEP-3	OLEP-4	OLEP-5	OLEP-6	OLEP-7
Week	**0e**	**8e**	**16e**	**24e**	**32e**	**40e**	**52e**
Day	**1e**	**57e**	**113e**	**169e**	**225e**	**281e**	**365e**
Window (day)[4]	--	**-7/+3**	**-7/+3**	**-7/+3**	**-7/+3**	**-7/+3**	**-7/+3**
Laboratory Testing[12] :							
Titers to measure *N. Meningitidis (*only if required per local practice/regulations)	X						
Coagulation panel	X	X	X	X	X	X	X
Chemistry (long panel) including LDH[13]	X	X	X	X	X	X	X
Hematology[14]	X	X	X	X	X	X	X
Pregnancy test (WOCBP only)[15]	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X
Pharmacokinetics, total C5, and Immunogenicity:							
Blood samples for conc. of pozelimab[16]	X			X			X
Blood samples for conc. of cemdisiran and metabolites[17]	X			X			X
Blood samples for conc. of total C5[16]	X			X			X
Blood samples for immunogenicity of pozelimab[18]	X			X			X
Blood samples for immunogenicity of cemdisiran[18]	X			X			X
Biomarkers:							
Free hemoglobin	X						X
Haptoglobin	X						X
Complement hemolytic assay (serum CH50)[19]	X		X		X		X
Complement hemolytic assay (serum AH50)[19]	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:							
Future research serum and plasma (optional)	X						X
Whole blood RNA sample (optional)	X						X

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

Study Procedure	52-Week Post-Treatment Safety Follow-Up Period					
Visit # [1]	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	253	281	309	379	463	561
Window (day)	±10	±10	±10	±10	±10	±10
Safety Assessments:						
Patient safety card for *Neisseria meningitidis*[2]	<----------X---------->					
Antibiotics prophylaxis (recommended)[3]	<----------X---------->					
Vital signs	X	X	X	X		
Physical examination		X		X		
Concomitant meds and procedures	X	X	X	X	X	X
Adverse events	<----------X---------->					
Pregnancy reporting	<----------X---------->					
Laboratory Testing:						
Hematology	X	X	X	X		
Chemistry	X	X	X	X		

10.1. Footnotes for the Schedule of Events Tables

10.1.1. Footnotes for Table 3 Schedule of Events (Open-Label Treatment Period)

1. Study procedures: when multiple procedures are performed on the same day, the sequence of procedures is as follows: COA assessments, ECG and/or vital signs, blood collection, study treatment administration, and any pre-specified post-dose sample collection.
2. Screening visit 1b can be combined with visit 1a, if LDH can be obtained one day before or on the day of eculizumab administration. Visit 1b and additional interim visits may also be needed for repeat blood collection, vaccination, etc.
3. Medical history: 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 1 year, if possible. Prior history at any time of thrombosis and *Neisseria* infections will be collected if feasible. Ongoing PNH symptoms and signs will also be collected.
4. Prior medications: including detailed eculizumab administration history (past 26 weeks) and *N. meningitidis* vaccination (past 5 years); all other prior medications 12 weeks prior to screening
5. Patients will require administration with meningococcal vaccination unless documentation is provided of prior immunization in the past 5 years prior to screening, or less than 5 years if required according to national vaccination guidelines for vaccination use with complement inhibitors or local practice. For patients who require administration with meningococcal vaccination(s) during the screening period, administration should occur preferably at least 2 weeks prior to day 1, or at another time point according to local practice or national guidelines.
6. Tuberculosis history and assessment. Screening by tuberculin skin test or T-cell interferon-gamma release assay may be performed according to local practice or guidelines at the discretion of the investigator.
7. A risk factor assessment for *N. gonorrhea* is recommended, and counseling is advised for at-risk patients.
8. Patient safety card: provide the patient safety card for *N. meningitidis* infection to the patient on day 1 or any other visit when needed. Site should review the instructions on the safety card with the patient at each visit.
9. Cemdisiran administration: the first day of dosing of cemdisiran will take place at the patient's usual schedule of administration for eculizumab.

10. Pozelimab IV administration: administration at day 29 should precede SC administration. After completion of IV administration, the patient should be observed for at least 30 minutes and if no clinical concern, then SC administration of the combination should proceed. Patients should be monitored for at least another 30 minutes after the first SC dosing.

11. The SC doses of pozelimab and cemdisiran should be given Q4W (every 28 days) starting at day 29 (week 4). From day 57 (week 8) onward, cemdisiran and pozelimab SC administration may either be continued by the site personnel or another healthcare professional at the patient's home, or administration by the patient or designated person at the patient's preferred location after adequate training. The final SC dosing of the combination during the OLTP is at week 28.

    During the Q4W dose administration interval starting at day 57, 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 7 days before or up to 7 days after the planned dosing date, provided that the dosing takes place after the corresponding study visit has been completed. For example, the day 57 (week 8) visit can take place from day 54 to day 60 given the visit window. The corresponding dose of pozelimab and cemdisiran can be given from day 54 to day 64, but only after the week 8 visit assessments have been performed. Similarly, the day 113 (week 16) visit can take place from day 106 to day 120 given the visit window. The corresponding dose of pozelimab and cemdisiran can be given from day 106 to day 120, but only after the week 16 visit assessments have been performed. Pozelimab and cemdisiran should be administered on the same day whenever possible. 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.

12. Eculizumab administration: continue patient's eculizumab administration at the usual dose and dosing interval. Administration of eculizumab at day 1 (when first dose of cemdisiran is administered) may occur up to 2 days later.

    NOTE: the week 2 visit should be scheduled relative to the patient's typical dosing frequency. For patients taking eculizumab with a frequency of:

    - Every 12 days
      - The visit should be scheduled on day 13 (±2 days).
    - Every 13 days
      - The visit should be scheduled on day 14 (±2 days).
    - Every 14 days
      - The visit should be scheduled on day 15 (±2 days).

The dose of eculizumab should be administered according to the usual dose frequency and must be dosed on or after the visit and corresponding assessments have been performed.

13. Injection training will be provided to patients who desire self-injection or injection by a designated person. Site staff should observe patient's self-injection or injection by a designated person and confirm adequacy. Patient instruction materials will be provided.
14. If needed, based on patient self-administration/administration by a designated person, the patient will complete a diary for recording data on study treatment administration starting at the day 57 visit or a subsequent visit. If patient diary is provided to the patient, then it should be reviewed at each clinic visit and data collected into the case report forms (CRFs). On the final visit, the diary should be collected by the site.
15. Daily oral antibiotic prophylaxis against *N. meningitidis* is recommended starting on the first day of dosing with study treatment and continuing until 52 weeks after discontinuation of pozelimab/cemdisiran. If vaccination for *N. meningitidis* occurs less than 2 weeks prior to day 1, then antibiotic prophylaxis must be administered for at least 2 weeks from the time of vaccination.
16. Patients will complete the PNH Symptom-Specific Questionnaire on a daily basis for at least 14 days prior to the day 1 visit. Patients should try to complete the PNH Symptom-Specific Questionnaire at the same time each day whenever possible.
17. 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 coagulation parameters, chemistry, hematology, reticulocyte count, D-dimer, total C5, CH50, ADA (against pozelimab), and drug concentrations of pozelimab and eculizumab 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 parameters, chemistry, hematology, reticulocyte count, total C5, CH50 and drug concentrations of pozelimab and eculizumab.
18. 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). 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.
19. Serum LDH, CRP, and bilirubin will be assessed as part of the blood chemistry analysis. The coagulation blood sample (tube) must always be collected first, followed by the blood chemistry sample (tube). During screening, obtain chemistry including LDH prior to eculizumab administration on the day of (or if not possible, one day before) eculizumab administration. On day 1 and all subsequent visits, obtain chemistry including LDH prior to any study treatment administration.

20. Pregnancy test for WOCBP: a serum test will be done at the screening visit and a urine test will be done at all other visits indicated. Any positive urine test should be confirmed with a serum pregnancy test.
21. Blood sample collection for concentrations of pozelimab, eculizumab, total C5, CH50 (efficacy endpoint), and AH50: obtain samples prior to any study drug administration (pre-dose). On day 29, obtain blood samples prior to IV administration of pozelimab and also within 15 minutes after the end of the IV infusion.
22. Blood samples for concentrations of cemdisiran and its metabolites will be collected prior to any study treatment administration (pre-dose) and at 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 healthcare professional.
23. Blood samples for immunogenicity will be collected before the administration of any study drug (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 SAEs, such as anaphylaxis or hypersensitivity, additional samples for drug concentration and immunogenicity may be collected at or near the event.
24. Future research serum and plasma (optional): samples should be collected, as permitted by patient consent and local regulatory policies. They may be stored for up to 15 years or as permitted by local regulatory policies, whichever is shorter, for future biomedical research.
25. Whole blood samples (optional) for DNA extraction should be collected on day 1 (pre-dose) but can be collected at a later study visit.

10.1.2. Footnotes for Table 4 Schedule of Events (Open-Label Treatment Period for Patients on Intensified Therapy)

1. Study procedures: When multiple procedures are performed on the same day, the sequence of procedures is as follows: COA assessments, ECG and/or vital signs, blood collection, study treatment administration, and any pre-specified post-dose sample collection.
2. Patients should be monitored for at least 30 minutes after completion of pozelimab 30 mg/kg IV. Subsequent SC doses will be administered Q2W (pozelimab) and Q4W (cemdisiran) and may either be performed by the site personnel or another healthcare professional at the patient's home, or administered by the patient or by a designated person. For patients on intensified treatment in the OLTP, the final SC dose of cemdisiran is at day 197r, week 28r, and the final SC dose of pozelimab is at day 211r (week 30r).
3. Pozelimab and cemdisiran SC administration: the dose of pozelimab SC should be given Q2W (every 14 days) and cemdisiran should be given Q4W (every 28 days) and on the day of the corresponding study visit whenever possible and as applicable. Study treatment administration should always be the last procedure after all blood sample collection and study assessments have been completed unless otherwise specified. If administration of pozelimab or cemdisiran cannot be administered on the day of the corresponding study visit, the dose may be administered up to 3 days before or up to 3 days after the planned dosing date as long as 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. 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. 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. Whenever possible, the dose of cemdisiran should be administered on the same day as the Q4W dose of pozelimab.-The final dose of cemdisiran is at week 28r and the final dose of pozelimab is at week 30r.
4. Injection training will be provided to patients who desire self-injection or injection by a designated person. The site should observe patient self-injection or injection by a designated person and confirm adequacy. Patient instruction materials will be provided.
5. If needed, based on patient self-administration/administration by a designated person, the patient will complete a diary for recording data on study treatment administration. If the 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.
6. Daily oral antibiotic prophylaxis against *N. meningitidis* is recommended until 52 weeks after discontinuation of pozelimab/cemdisiran.
7. Patients should try to complete the PNH Symptom-Specific Questionnaire at the same time each day whenever possible.

8. Patient safety card: the site should review the instructions on the safety card with the patient at each visit.
9. 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 coagulation parameters, chemistry, hematology, reticulocyte count, D-dimer, total C5, CH50, ADA (against pozelimab) and 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 parameters, chemistry, hematology, reticulocyte count, total C5, CH50 and drug concentrations of pozelimab.
10. During lab collection, handling, and processing, the same methodology will be applied across study visits, as best as possible, to preserve the quality of the sample and avoid hemolysis. The coagulation blood sample (tube) must always be collected first, followed by the blood chemistry sample (tube).
11. Serum LDH, CRP, and bilirubin will be assessed as part of the blood chemistry analysis.
12. Pregnancy test for WOCBP: a urine test will be done at all visits indicated.
13. Blood sample collection for concentrations of pozelimab, total C5, CH50 (efficacy endpoint), and AH50: obtain samples prior to any study drug administration (pre-dose). On day 1, 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.
14. Blood samples for concentrations of cemdisiran and its metabolites will be collected prior to any study treatment administration (pre-dose) and at 2 to 6 hours post-cemdisiran dosing. The post-dose sample should be carefully coordinated with the dosing of cemdisiran and may be collected at the clinic or by a visiting healthcare professional.
15. Blood samples for immunogenicity will be collected before the administration of any study drug (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 SAEs, such as anaphylaxis or hypersensitivity, additional samples for drug concentration and immunogenicity may be collected at or near the event.

10.1.3. Footnotes for Table 5 Schedule of Events (for Optional 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 the availability of a 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. Study procedures (visits): when multiple procedures are performed on the same day, the sequence of procedures is as follows: COA assessments, ECG and/or vital signs, blood collection, study treatment administration, and any pre-specified post-dose sample collection.
3. Day 1e of OLEP should be scheduled on the same day as week 32 (or week 32r for patients on intensified treatment) of the OLTP, and any common assessments will be performed once for both the OLTP and OLEP visits.
4. 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 for patients in an intensified treatment regimen (pozelimab Q2W dosing) or up to 7 days before or 7 days after the planned dosing date for patients on a maintenance treatment regimen (pozelimab Q4W dosing), provided that the dosing takes place after the corresponding study visit has been completed. Care must be taken to coordinate dosing for visits where a post-dose sample is collected to measure concentration of cemdisiran and its metabolites.
5. *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 will continue their visit schedule at the next OLEP visit.
6. Study treatment administration should always be the last procedure after all blood sample collection and study assessments have been completed unless otherwise specified. 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.
7. Injection training will be provided to patients who desire self-injection or injection by a designated person. The site should observe patient self-injection or injection by a designated person and confirm adequacy. Patient instruction materials will be provided.

8. 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 the 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.
9. Daily oral antibiotic prophylaxis against *N. meningitidis* is recommended until 52 weeks after discontinuation of study treatment.
10. Patient safety card: the site should review the instructions on the safety card with the patient at each visit.
11. 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 coagulation parameters, chemistry, hematology, reticulocyte count, D-dimer, total C5, CH50, ADA (against pozelimab) and 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 parameters, chemistry, hematology, reticulocyte count, total C5, CH50 and drug concentrations of pozelimab.
12. Clinical lab samples will be collected prior to any study drug administration (pre-dose) unless otherwise specified. The coagulation blood sample (tube) must always be collected first, followed by the blood chemistry sample (tube). During lab collection, handling, and processing, the same methodology will be applied across study visits, as best as possible, to preserve the quality of the sample and avoid hemolysis.
13. Serum LDH, CRP, and bilirubin will be assessed as part of the blood chemistry analysis. The blood chemistry sample should be collected before study treatment administration (pre-dose). 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.
14. Hemoglobin and free hemoglobin will be assessed as part of the hematology analysis. A separate sample for hemoglobin and free hemoglobin is not required if a hematology sample is collected on the same day. The hematology sample should be collected before study treatment administration (pre-dose).
15. 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.
16. 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). If the patient receives treatment intensification during the open-label extension period, a PK sample should be obtained prior to IV pozelimab administration and 15 minutes post-dose.
17. 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 healthcare professional.

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

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

Patients who discontinue study treatment in either the OLTP or the intensified OLTP will be asked to remain in the study until week 32 EOT (or week 32r EOT) and follow the original Schedule of Events as applicable. After the week 32 or week 32r EOT visit, the entry point into the safety follow-up schedule will depend on the number of weeks that have elapsed since patient's last dose (e.g., a patient who is 20 weeks after his/her 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 32r in the OLTP who choose not to continue treatment in the OLEP, patients who complete the optional OLEP but do not continue study treatment in a post-trial access program, and patients who permanently discontinue treatment during the OLEP will enter into the safety follow-up period at FU-1.

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
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
Hematology		

Parameter	PCSV	Comments
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 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 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 applied for all positions (including missing) except STANDING
Weight	≥ 5 % increase versus baseline ≥5% decrease versus baseline	FDA Feb 2007
ECG parameters		CPMP 1997 guideline

Parameter	PCSV	Comments
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	Absolute values (ms) Males Females Borderline 431-450 ms 451-470 ms Prolonged* > 450 ms > 470 ms QTc ≥500 ms ≥ 500 ms Increase versus baseline (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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