NCT04888507
EudraCT: 2020-005006-25
IRAS: 295375

Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

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)
Clinical Phase:	2
Protocol Number:	R3918-PNH-20105
Protocol Version:	R3918-PNH-20105 Amendment 3
Date of Issue:	*See appended electronic signature page*
Amendment 2 Date of Issue:	02 Aug 2021
Amendment 1 Date of Issue:	17 Mar 2021
Original Date of Issue:	23 Dec 2020
Medical/Study Director:	[redacted] Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591

AMENDMENT HISTORY

Amendment 3

The main purpose for this amendment is to modify the timing of the interim analysis.

Description of Change	Brief Rationale	Section # and Name
Modified the description of the interim analysis to allow for an analysis of the data at an earlier time point (week 16)	The interim analysis timing and scope is revised to allow for an earlier analysis and for the preliminary results to be shared externally (for example, upon request by regulatory authorities).	Clinical Study Protocol Synopsis: Statistical Plan Section 6.2 Planned Interim Analysis Section 11.5 Interim Analysis
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)	This change clarifies how these analyses will be performed. "At all time points at which LDH is measured" is deleted to better reflect the analyses that will be performed	Clinical Study Protocol Synopsis: Secondary Endpoints Section 4.1.2 Secondary Endpoints Section 4.1.2.1 Secondary Endpoints for the Optional Open-Label Extension Period Section 11.4.3.1 Secondary Efficacy Analysis
Added new secondary endpoint on the proportion of patients with adequate control of hemolysis at each visit	This new endpoint assesses control of hemolysis using an additional methodology	Clinical Study Protocol Synopsis: Secondary Endpoints Section 4.1.2 Secondary Endpoints Section 4.1.2.1 Secondary Endpoints for the Optional Open-Label Extension Period Section 11.4.3.1 Secondary Efficacy Analysis

Description of Change	Brief Rationale	Section # and Name
Updated information about post-trial treatment access for patients who complete the optional OLEP	This change provides information on post-trial access to study drugs for those with a favorable benefit-risk profile for continued treatment	Clinical Study Protocol Synopsis: Study Design, Study Duration Section 6.1 Study Description and Duration Figure 1: Study Flow Diagram Section 6.1.1.3 Optional Open-Label Extension Period Section 6.1.1.4 Post-Treatment Safety Follow-Up Section 6.1.1.5 End of Study Definition Section 8.9 Post-Trial Access to Study Treatment Section 9.1.1.4 Footnotes for Table 4 Schedule of Events (Post-Treatment Safety Follow-Up Period for All Patients), footnote #1
Changed baseline sample collection for PNH clones from day 1 to screening visit V1a	This change is made to facilitate study conduct	Table 1 Schedule of Events for Open-Label Treatment Period
Clarified that free hemoglobin is collected as a separate sample at visits OLEP-1 and OLEP-7 only	This change clarifies details regarding sample collection	Table 3: Schedule of Events (Optional Open-Label Extension Period) Section 9.1.1.3 Footnotes for Table 3 Schedule of Events (for Optional Open-Label Extension Period), footnote #14
For patients requiring intensified treatment, clarified that samples for pozelimab concentration and total C5 will be collected on day 1r pre-dose and post-infusion	This change clarifies details regarding sample collection	Section 9.1.1.2 Footnotes for Table 2 Schedule of Events (Open-Label Treatment Period for Patients on Intensified Therapy), footnote #13
Added immunogenicity sample (anti-pozelimab antibodies) and D-dimer as part of laboratory analyses in the event of suspected breakthrough hemolysis	This change includes additional sample collection in the event of suspected breakthrough hemolysis to aid analysis	Section 9.1.1.1 Footnotes for Table 1 Schedule of Events (Open-Label Treatment Period), footnote #17 Section 9.1.1.2 Footnotes for Table 2 Schedule of Events (Open-Label Treatment Period for Patients on Intensified Therapy), footnote #9 Section 9.1.1.3 Footnotes for Table 3 Schedule of Events (for Optional Open-Label Extension Period), footnote #11 Section 9.2.3.5 Laboratory Testing (Safety and Other)

Description of Change	Brief Rationale	Section # and Name
Included daily antibiotic prophylaxis and review of patient safety card in the safety follow-up period	This is a correction. These procedures are intended to be performed throughout the study for risk mitigation	Table 4 Schedule of Events for Open-Label Treatment Period Section 9.1.1.4 Footnotes for Table 4 Schedule of Events (Post-Treatment Safety Follow-Up Period for All Patients), footnotes #2 and #3 (new)
Removed fasting requirement for blood chemistry sample	This change reduces study complexity as the results of the endpoints should not be impacted in a meaningful way by fasting status	Section 9.2.3.5 Laboratory Testing (Safety and Other), Blood Chemistry
Added language to ask that patients refrain from strenuous exercise within 24 hours prior to a blood draw	This change is added to minimize the effect of vigorous exercise on blood analyses	Section 8.8.1 Prohibited Medications and Procedures
Revised sample size language to "up to 12 patients"	This change allows more flexibility regarding enrollment. Because the analysis is descriptive only and not based on any formal sample size calculation, this change has no impact on the analysis	Clinical Study Protocol Synopsis: Study Design, Population, Statistical Plan Section 6.1 Study Description and Duration Section 7.1 Number of Patients Planned Section 11.2 Justification of Sample Size
Removed eculizumab concentration from open-label extension period (OLEP) analysis	This is a correction: eculizumab concentration is not measured during the optional open-label extension period	Section 4.1.2.1 Secondary Endpoints for the Optional Open-Label Extension Period
Revised description of Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue) to a 5-point Likert scale. A higher score indicates a higher quality of life	This is a correction	Section 9.2.2.2.1 Functional Assessment of Chronic Illness Therapy – Fatigue
Clarifications and corrections	These are minor editorial changes to improve clarity	Throughout the document

Amendment 2

The main purpose for this amendment is to ensure that pozelimab concentrations will be assessed pre-dose and 15 minutes post-dose on the day of treatment intensification (day 1r) in patients requiring dose intensification. In addition, the number of patients enrolled who are taking eculizumab at the labeled dose vs those taking eculizumab at a dose higher or more frequently than labeled, was removed, to allow patients to enroll regardless of whether they are on the labeled dose of eculizumab or on a higher or more frequently than labeled dose.

Description of Change	Brief Rationale	Section # and Name
The specific number of patients enrolled who are currently receiving eculizumab at the labeled dose or patients receiving eculizumab at a dose higher than labeled or more frequently than labeled has been removed.	To allow any proportion of patients to be enrolled whether on the labeled dose or on a dose higher than labeled/more frequently then labeled up to a total of approximately 12 patients. This will allow enrollment of these patient subgroups to facilitate recruitment.	Clinical Study Protocol Synopsis, (Study Design; Justification of Sample Size) Section 6.1 Study Description and Duration Section 11.2 Justification of Sample Size
The criterion for provision of an additional IV pozelimab dose in the event of an acute complement-activating condition was modified.	To allow for patients to receive an additional IV pozelimab dose in the event they have an elevated LDH ≥2 x ULN resulting from an acute complement-activating condition even if not meeting the protocol definition of breakthrough hemolysis.	Clinical Study Protocol Synopsis (Treatment(s) Study Drug Dose/Route/Schedule) Section 6.1.3 Treatment Intensification Section 8.3.2 Treatment Intensification
Timing of statistical analysis updated to include the timing of the analysis for the intensified OLTP.	To clarify that the primary analysis will be performed at the completion of the main OLTP and prior to the end of the intensified open label treatment period.	Clinical Study Protocol Synopsis (Statistical Plan)
Language on study drug administration in patients who require treatment intensification and the corresponding intensified treatment visit schedule clarified	Clarifying language has been added to ensure proper understanding of the timing of study visits and study drug administration for patients who require treatment intensification.	Section 6.1.1.3 Optional Open-Label Extension Period Section 6.1.3 Treatment Intensification
Assessment of body weight added prior to any administration of IV pozelimab.	Weight added in order to assist in the calculation of dose to be administered for IV pozelimab in patients who require treatment intensification or additional pozelimab administration in the event of a complement-activating condition.	Section 6.1.3 Treatment Intensification Section 8.3.2 Treatment Intensification

Description of Change	Brief Rationale	Section # and Name
Revised exclusion criterion regarding positive infection with hepatitis B or C.	To harmonize the criteria with other studies in the program and to more closely align with standard practice with regards to screening for hepatitis B	Section 7.2.2 Exclusion Criteria, #11
Clarified exclusion criterion pertaining to *Haemophilus influenza* serotype b and *Streptococcus pneumoniae* vaccinations	To align the criterion with the updated cemdisiran investigators brochure and to harmonize with the other phase 2 study of pozelimab and cemdisiran combination treatment.	Section 7.2.2 Exclusion Criteria, #30
Removed 30-minute observation period after subcutaneous injection on the day of treatment intensification.	Corrected as patients only require 30-minute on-site observation after intravenous pozelimab and the first cemdisiran and pozelimab subcutaneous injections	Section 8.3.2 Treatment Intensification Section 9.1.1.2 Footnotes for Table 2 Schedule of Events (Open-Label Treatment Period for Patients on Intensified Therapy) – Footnote #2.
Removal of the requirement for mandatory discontinuation of study drug in the event of treatment for a meningococcal infection	To allow investigators to use clinical discretion with regards to continuing complement inhibition during a serious meningococcal infection. Withdrawal of complement inhibition in the face of an ongoing complement activating condition may have serious clinical consequences	Section 8.3.3.1 Reasons for Permanent Discontinuation of Study Drug
Blood samples for the concentration of pozelimab are to be taken prior to IV pozelimab administration and 15 minutes post-dose on day 1r and the day of intensification for patients receiving treatment intensification in the open label extension. A pre-dose PK sample was also included on D15r.	Corrected as patients who receive intensified treatment will receive an IV loading dose of pozelimab on the first day of the intensified open label treatment period (day 1r) requiring earlier assessment of drug concentrations in the intensified OLTP. A pre- and 15-minute post-dose PK assessment also shall be performed in the open label extension period the day of intensification for patients who receive an unplanned treatment intensification. A pre-dose PK sample was added at day 15r.	Table 2 Schedule of Events for Treatment Period (for Patients on Intensified Treatment in the OLTP) Section 9.1.1.3 Footnotes for Table 3 Schedule of Events (for Optional Open-Label Extension Period) – Footnote 16
Blood samples for eculizumab concentrations removed from the intensified OLTP SOE.	Corrected as patients will not receive eculizumab during the intensified OLTP.	Table 2 Schedule of Events for Treatment Period (for Patients on Intensified Treatment in the OLTP)

Description of Change	Brief Rationale	Section # and Name
Clarification that patients who discontinue study treatment in the intensified OLTP will also be asked to remain in study until week 32r EOT).	Clarified that the request to remain in the study off-treatment pertains to both the main and the intensified OLTP.	Section 8.3.3 Study Drug Discontinuation Section 9.1.1.4 Footnotes for Table 4 Schedule of Events (Post-Treatment Safety Follow-Up Period for All Patients) – Footnote 1
Criteria for urine culture updated.	To allow urine culture to be performed per the Investigator judgment in the event of clinical suspicion of infection.	Section 9.2.3.5 Laboratory Testing (Safety and Other)
Unscheduled blood collection for suspected breakthrough hemolysis events was updated.	Additional list of blood collections for suspected breakthrough hemolysis were included.	Section 9.1.1.1 Footnotes for Table 1 Schedule of Events (Open-Label Treatment Period) Section 9.1.1.2 Footnotes for Table 2 Schedule of Events (Open-Label Treatment Period for Patients on Intensified Therapy) Section 9.1.1.3 Footnotes for Table 3 Schedule of Events (for Optional Open-Label Extension Period) Section 9.2.3.5 Laboratory Testing (Safety and Other)
List of assessments for drug hypersensitivity events revised to remove the additional assessments in the event of suspected breakthrough hemolysis.	Correction as additional list of assessments was intended for drug hypersensitivity events only.	Section 9.2.3.5 Laboratory Testing (Safety and Other)
List of AESIs updated to replace 'any thrombotic or embolic event' with 'Major Adverse Vascular Events'	To provide more specific instructions on the type of events qualifying as an AESI and harmonize the AESI across the program.	Section 10.1.3 Events that Require Expedited Reporting to Sponsor.
Total number of screened patients revised to include all patients who signed the ICF.	To consider a patient as screened if signing the main ICF even if inclusion criterion is not met.	Section 11.4.1 Patient Disposition
Statistical analysis for secondary endpoints revised to remove multiple imputation and subgroup analysis.	Updated given that patient numbers in each subgroup of patients may be too small to allow for multiple imputation. Subgroup analyses will be specified in the SAP.	Clinical Study Protocol Synopsis (Secondary Endpoints,) Section 11.4.3.1 Secondary Efficacy Analysis

Description of Change	Brief Rationale	Section # and Name
Language added to allow for unused/left over samples to be used for exploratory research.	Exploratory research can be conducted in all patients using leftover/unused blood samples.	Section 9.2.6 Pharmacodynamic and Exploratory Biomarker Procedures
Editorial changes and clarifications	For consistency within the protocol, clarity, administrative updates, and correction of typographical errors.	Title Page List of Abbreviations and Definitions of Terms Clinical Study Protocol Synopsis (Secondary Endpoints,) Section 4.1.2 Secondary Endpoints Section 5.6 Pharmacodynamic and Other Biomarker Variables Table 1: Schedule of Events for Open-Label Treatment Period Table 2: Schedule of Events for Treatment Period (for Patients on Intensified Treatment in the OLTP) Table 3: Schedule of Events (Optional Open-Label Extension Period) Section 9.1.1.2 Footnotes for Table 2 Schedule of Events (Open-Label Treatment Period for Patients on Intensified Therapy) Section 6.1.2 Breakthrough Hemolysis Section 9.2.3.5 Laboratory Testing (Safety and Other) Section 9.2.5 Immunogenicity Measurements and Samples Section 9.2.6 Pharmacodynamic and Exploratory Biomarker Procedures Section 11.4.3.1 Secondary Efficacy Analysis

Amendment 1

The main purpose for this amendment is to address feedback from a health authority.

Description of Change	Brief Rationale	Section # and Name
Added exclusion criterion for patients with severe allergies and/or patients who has had anaphylactic reaction to prescription or non-prescription drugs.	[redacted]	Section 7.2.2 Exclusion Criteria, #29 (new)
Added exclusion criterion for patients who cannot or will not receive vaccinations against *Streptococcus pneumoniae* and *Haemophilus influenza* type B.	[redacted]	Section 6.1.1.1 Screening Period Section 7.2.2 Exclusion Criteria, #30 (new) Table 1 Schedule of Events for Open-Label Treatment Period Section 9.2.1 Procedures Performed Only at the Screening/Baseline Visit
Replaced "U" with "X" in schedule of events.	This is a typographical correction. Urine pregnancy test will be performed, as indicated by the footnote.	Table 3 Schedule of Events (Optional Open-Label Extension Period)
Editorial change to include the Integrated Research Application System (IRAS) number.	This change was made to address a request from the ethics committee.	Title Page

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
AH50	Alternative pathway hemolytic activity assay
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
aHUS	Atypical hemolytic uremic syndrome
AUC	Area under the curve
C	Complement component (eg, C3, C5)
CBC	Complete blood count
CH50	Total complement hemolytic activity assay
CI	Confidence interval
COA	Clinical Outcome Assessment
COVID-19	Coronavirus Disease 2019
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CRP	C-reactive protein
CSR	Clinical study report
CTFG	Clinical Trial Facilitation Group
dL	Deciliter
DTD	Drug-target-drug
ECG	Electrocardiogram
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EORTC-QLQ-30	European Organization for Research and Treatment of Cancer Quality of Life of Cancer Patients Questionnaire-30
EOT	End of treatment
ESR	Erythrocyte sedimentation rate
ET	Early termination
EC	Ethics Committee
EU	European Union
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue

FAS	Full analysis set
FBR	Future biomedical research
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
g	Grams
GCP	Good Clinical Practice
GHS	Global health status
gMG	Generalized myasthenia gravis
GPI	Glycophosphatidylinositol
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
HSC	Hematopoietic stem cell
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council on Harmonisation
INR	International normalized ratio
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
kg	Kilogram
LAM	Lactational amenorrhea method
LDH	Lactate dehydrogenase
LTBI	Latent tuberculosis infection
mAb	Monoclonal antibody
MAC	Membrane attack complex
MAVE	Major adverse vascular event
mg	Milligram
MI	Multiple imputation
mRNA	messenger RNA
µg	Microgram
mL	Milliliter
MMRM	Multiple mixed-effect repeated measures

NOAEL	No observable adverse effect level
OLEP	Open-label extension period (an optional period)
OLTP	Open-label treatment period (main study period)
PD	Pharmacodynamic
PGIC	Patient Global Impression of Severity
PGIS	Patient Global Impression of Change
PIGA	Phosphatidylinositol glycan anchor biosynthesis class A
PK	Pharmacokinetic
PNH	Paroxysmal nocturnal hemoglobinuria
PT	Preferred term
Q2W	Every 2 weeks
Q4W	Every 4 weeks
Q8W	Every 8 weeks
QW	Every week
RBC	Red blood cell
RNA	Ribonucleic acid
RNase	Ribonuclease
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SC	Subcutaneous
SDV	Source data verification
siRNA	small interfering RNA
SOC	System organ class
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WOCBP	Women of childbearing potential
WOCF	Worst observation carried forward

TABLE OF CONTENTS

AMENDMENT HISTORY 2
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 10
CLINICAL STUDY PROTOCOL SYNOPSIS 20
1. INTRODUCTION 25
1.1. Background on Paroxysmal Nocturnal Hemoglobinuria 25
1.2. Background on Pozelimab 26
1.3. Background on Cemdisiran 28
1.4. Pozelimab + Cemdisiran: A Combination Approach 29
2. STUDY OBJECTIVES 29
2.1. Primary Objective 29
2.2. Secondary Objectives 29
2.3. Exploratory Objectives 30
3. HYPOTHESIS AND RATIONALE 30
3.1. Hypotheses 30
3.2. Rationale 30
3.2.1. Rationale for Study Design and Endpoints 30
3.2.2. Rationale for Dose Selection 32
3.3. Risk-Benefit 35
3.3.1. Infusion Reactions 35
3.3.2. Potential Risk of Neisseria Infection 35
3.3.3. Liver Function Test Abnormalities 36
3.3.4. Study Conduct in Response to Coronavirus Disease 2019 37
3.3.5. Other Risks 37
4. ENDPOINTS 37
4.1. Primary and Secondary Endpoints 37
4.1.1. Primary Endpoint 37
4.1.2. Secondary Endpoints 37
4.1.2.1. Secondary Endpoints for the Optional Open-Label Extension Period 39
4.1.3. Exploratory Endpoints 40
5. STUDY VARIABLES 41
5.1. Demographic and Baseline Characteristics 41

5.2. Efficacy Variables 41
5.2.1. Laboratory Variables for the Assessment of Efficacy 41
5.2.2. Transfusion Record 41
5.2.3. Clinical Outcome Assessments 41
5.3. Safety Variables 42
5.4. Pharmacokinetic Variables 42
5.5. Immunogenicity Variables 42
5.6. Pharmacodynamic and Other Biomarker Variables 42
6. STUDY DESIGN 43
6.1. Study Description and Duration 43
6.1.1. Study Periods 44
6.1.1.1. Screening Period 44
6.1.1.2. Open-Label Treatment Period 45
6.1.1.3. Optional Open-Label Extension Period 47
6.1.1.4. Post-Treatment Safety Follow-Up 47
6.1.1.5. End of Study Definition 47
6.1.2. Breakthrough Hemolysis 48
6.1.3. Treatment Intensification 48
6.1.4. Transfusion Algorithm 49
6.1.5. Large drug-target-drug immune complexes 49
6.2. Planned Interim Analysis 49
7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS 50
7.1. Number of Patients Planned 50
7.2. Study Population 50
7.2.1. Inclusion Criteria 50
7.2.2. Exclusion Criteria 50
7.3. Premature Withdrawal from the Study 53
7.4. Replacement of Patients 54
8. STUDY TREATMENTS 54
8.1. Investigational and Reference Treatments 54
8.1.1. Pozelimab 54
8.1.2. Cemdisiran 54
8.2. Background Treatments and Risk Mitigation 54

8.2.1. Meningococcal Vaccinations 54
8.2.2. Monitoring for Meningococcal Infection 55
8.2.3. Oral Antibiotics for Meningococcal Infection 55
8.2.4. Risk Management of *Neisseria Gonorrhea* 55
8.3. Dose Modification and Study Treatment Discontinuation Rules 56
8.3.1. Dose Modification 56
8.3.2. Treatment Intensification 56
8.3.3. Study Drug Discontinuation 56
8.3.3.1. Reasons for Permanent Discontinuation of Study Drug 57
8.3.3.2. Reasons for Temporary Discontinuation of Study Drug 57
8.4. Management of Acute Reactions 58
8.4.1. Acute Intravenous Infusion Reactions 58
8.4.1.1. Interruption of the Intravenous Infusion 58
8.4.1.2. Termination of the Intravenous Infusion 59
8.4.2. Acute Injection Reactions 59
8.4.2.1. Systemic Injection Reactions 59
8.4.2.2. Local Injection Site Reactions 59
8.5. Method of Treatment Assignment 59
8.6. Blinding 60
8.7. Treatment Logistics and Accountability 60
8.7.1. Packaging, Labeling, and Storage 60
8.7.2. Supply and Disposition of Treatments 60
8.7.3. Treatment Accountability 60
8.7.4. Treatment Compliance 60
8.8. Concomitant Medications 60
8.8.1. Prohibited Medications and Procedures 61
8.8.2. Permitted Medications and Procedures 61
8.9. Post-Trial Access to Study Treatment 61
9. STUDY SCHEDULE OF EVENTS AND PROCEDURES 62
9.1. Schedule of Events 62
9.1.1. Footnotes for the Schedule of Events Tables 71
9.1.1.1. Footnotes for Table 1 Schedule of Events (Open-Label Treatment Period) 71

9.1.1.2. Footnotes for Table 2 Schedule of Events (Open-Label Treatment Period for Patients on Intensified Therapy) 75
9.1.1.3. Footnotes for Table 3 Schedule of Events (for Optional Open-Label Extension Period) 77
9.1.1.4. Footnotes for Table 4 Schedule of Events (Post-Treatment Safety Follow-Up Period for All Patients) 79
9.1.2. Early Termination Visit 79
9.1.3. Unscheduled Visits 79
9.2. Study Procedures 80
9.2.1. Procedures Performed Only at the Screening/Baseline Visit 80
9.2.2. Efficacy Procedures 81
9.2.2.1. Laboratory Assessments of Efficacy 81
9.2.2.2. Clinical Outcome Assessments 81
9.2.3. Safety Procedures 83
9.2.3.1. Body-Weight 83
9.2.3.2. Vital Signs 83
9.2.3.3. Physical Examination 83
9.2.3.4. Electrocardiogram 83
9.2.3.5. Laboratory Testing (Safety and Other) 84
9.2.3.6. Blood Transfusion 86
9.2.3.7. Adverse Events 86
9.2.4. Drug Concentration and Measurements 86
9.2.4.1. Concentrations of Total Pozelimab, Eculizumab, and Total C5 86
9.2.4.2. Concentrations of Cemdisiran and Cemdisiran Metabolites 86
9.2.5. Immunogenicity Measurements and Samples 86
9.2.6. Pharmacodynamic and Exploratory Biomarker Procedures 87
9.2.7. Future Biomedical Research (Optional) 87
9.2.8. Pharmacogenomic Analysis (Optional) 88
10. SAFETY EVALUATION AND REPORTING 88
10.1. Recording and Reporting Adverse Events 88
10.1.1. General Guidelines 88
10.1.2. Reporting Procedure 89
10.1.3. Events that Require Expedited Reporting to Sponsor 90

10.1.4. Other Adverse Events of Special Interest that do not Require Expedited Reporting to Sponsor 91
10.2. Definitions 91
10.2.1. Adverse Event 91
10.2.2. Serious Adverse Event 91
10.2.3. Adverse Events of Special Interest 92
10.2.4. Infusion Reactions 92
10.2.5. Severity 92
10.2.6. Causality 93
10.3. Safety Monitoring 94
10.4. Notifying Health Authorities, Ethics Committee, and Investigators 95
11. STATISTICAL PLAN 95
11.1. Statistical Hypothesis 95
11.2. Justification of Sample Size 95
11.3. Analysis Sets 95
11.3.1. Efficacy Analysis Sets 95
11.3.2. Safety Analysis Sets 96
11.3.3. Pharmacokinetic Analysis Set 96
11.3.4. Immunogenicity Analysis Set 96
11.4. Statistical Methods 96
11.4.1. Patient Disposition 96
11.4.2. Demography and Baseline Characteristics 97
11.4.3. Efficacy Analyses 97
11.4.3.1. Secondary Efficacy Analysis 97
11.4.4. Control of Multiplicity 98
11.4.5. Safety Analysis 99
11.4.5.1. Adverse Events 99
11.4.5.2. Other Safety 100
11.4.5.3. Treatment Exposure 100
11.4.5.4. Treatment Compliance 100
11.4.6. Pharmacokinetics 101
11.4.6.1. Analysis of Drug Concentration Data 101
11.4.7. Analysis of Immunogenicity Data 101

11.4.8. Analysis of Pharmacodynamic and Exploratory Biomarker Data 101
11.5. Interim Analysis 101
11.6. Statistical Considerations Surrounding the Premature Termination of a Study 102
12. QUALITY CONTROL AND QUALITY ASSURANCE 102
12.1. Data Management and Electronic Systems 102
12.1.1. Data Management 102
12.1.2. Electronic Systems 102
12.2. Study Monitoring 103
12.2.1. Monitoring of Study Sites 103
12.2.2. Source Document Requirements 103
12.2.3. Case Report Form Requirements 103
12.3. Audits and Inspections 104
12.4. Study Documentation 104
12.4.1. Certification of Accuracy of Data 104
12.4.2. Retention of Records 104
13. ETHICAL AND REGULATORY CONSIDERATIONS 105
13.1. Good Clinical Practice Statement 105
13.2. Informed Consent 105
13.3. Patients Confidentiality and Data Protection 105
13.4. Institutional Review Board 106
13.5. Clinical Study Data Transparency 106
14. PROTOCOL AMENDMENTS 106
15. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE 107
15.1. Premature Termination of the Study 107
15.2. Close-out of a Site 107
16. CONFIDENTIALITY 107
17. FINANCING AND INSURANCE 107
18. PUBLICATION POLICY 107
19. REFERENCES 108
20. INVESTIGATOR'S AGREEMENT 111
SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS 112

LIST OF TABLES

Table 1: Schedule of Events for Open-Label Treatment Period....63
Table 2: Schedule of Events for Treatment Period (for Patients on Intensified Treatment in the OLTP)....66
Table 3: Schedule of Events (Optional Open-Label Extension Period)....68
Table 4: Schedule of Events for Post-Treatment Safety Follow-Up Period (All Patients)....70

LIST OF FIGURES

Figure 1: Study Flow Diagram....44

CLINICAL STUDY PROTOCOL SYNOPSIS

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
Site Location(s)	United Kingdom
Principal Investigator	Richard Kelly, MBChB, PhD
Objective(s)	The primary objective of the study is to evaluate the safety and tolerability of pozelimab and cemdisiran combination therapy in patients with paroxysmal nocturnal hemoglobinuria (PNH) who switch from eculizumab therapy. The secondary objectives of the study are: • To evaluate the effect of the combination treatment on the following parameters of intravascular hemolysis: lactate dehydrogenase (LDH) control, breakthrough hemolysis, and inhibition of complement hemolysis activity (CH50) • To evaluate the stability of LDH during the transition period from eculizumab monotherapy to combination with pozelimab and cemdisiran • To evaluate the effect on red blood cell (RBC) transfusion requirements • To evaluate the effect of the combination treatment on hemoglobin levels • To evaluate 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 evaluate the long-term safety and efficacy of the combination treatment in an optional open-label extension period (OLEP)
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, and a 52-week post-treatment safety follow-up period. The fourth period begins when a patient completes or permanently discontinues study treatment (eg, at the time of premature study drug discontinuation, at the completion of study treatment in the OLTP for patients who decline the optional OLEP, or at the completion of study treatment in the optional OLEP).

	Patients who fulfill all the eligibility criteria will be enrolled in the study and receive their first dose of study treatment on day 1 of the OLTP, which should occur on the day of the patient's scheduled treatment with eculizumab. Patients will be co-administered cemdisiran with eculizumab on day 1, and then receive eculizumab alone on the day of the patient's next planned dose (day 15 or earlier depending on the patient's usual dose frequency). The first dose of combination subcutaneous (SC) therapy with pozelimab and cemdisiran without background eculizumab will be administered on day 29 and every 4 weeks (Q4W) thereafter for 28 weeks. The first dose of combination SC therapy on day 29 will be preceded by an IV loading dose of pozelimab to achieve high concentrations of pozelimab rapidly in order to provide complete inhibition of C5 as soon as possible during the switch from eculizumab to pozelimab. The SC doses will be administered after at least 30 minutes following completion of the IV administration, and the patient should be observed during the interval. Patients will continue to be monitored for at least 30 minutes after completing the first SC injections for the pozelimab and cemdisiran combination. After the first SC dose of the pozelimab and cemdisiran combination on day 29, subsequent study treatment administrations may be continued by the site personnel, health care professional (if available) or administered by the patient or designated person at the patient's preferred location. These options for study treatment administration will depend on preference of the investigator and patient, local regulations as well as availability of healthcare professionals. During the study, a patient meeting breakthrough hemolysis criteria and inadequate LDH response will qualify for intensified treatment which consists of an initial IV loading dose of pozelimab and intensified pozelimab regimen to be administered Q2W along with cemdisiran at Q4W, for a period of 32 weeks. This regimen is proposed to provide extra C5 suppression that some patients may need and which cannot be managed adequately by the standard dose regimen (see Intensified Treatment section of this synopsis). The long-term safety and efficacy of the combination treatment will be assessed by providing the patients who complete the study treatment in the OLTP on combination treatment an option to participate in a long-term OLEP, in which patients shall continue to receive study treatment for an additional 52 weeks. For patients who complete the optional OLEP, post-trial access to treatment may be available. All patients who permanently stop study treatment will be asked to complete a 52-week safety follow-up period after the last dose of the study treatment. The safety follow-up period will begin when a patient completes or permanently discontinues study treatment (eg, at the time of premature study drug discontinuation, at the completion of study treatment in the OLTP for patients who decline the optional OLEP, or at the completion of the optional OLEP for patients who do not continue treatment in a post-trial access setting).
Study Duration	The screening period is up to 42 days in duration. The duration of the treatment period for individual patients is 32 weeks but will be longer for patients who are switched to intensified treatment. All patients who do not enter into the optional OLEP will be followed for an additional 52 weeks after the last dose of combination treatment. Patients opting to participate in the optional OLEP will continue open-label treatment for a 52-week period, to be followed by a 52-week safety follow-up period after the last dose of study treatment (the safety follow-up period is waived for patients who continue treatment in the post-trial access program).

End of Study Definition	The end of the main study is defined as the date of the last visit of the last patient in the OLTP, including patients who discontinued treatment during the OLTP and are being followed in the post-treatment safety follow-up period. The end of the optional OLEP is defined as the date of the last visit of the last patient in the optional OLEP, including patients who discontinued treatment during the optional OLEP and are being followed in the post-treatment safety follow-up period.
Population	
Sample Size:	Up to 12 patients
Target Population:	Patients will be men and women ≥18 years of age with a diagnosis of PNH, and currently on treatment with stable eculizumab therapy for at least 12 weeks prior to screening.
Treatments	All patients will receive pozelimab + cemdisiran combination treatment.
Study Drug	Pozelimab
Dose/Route/Schedule:	Initial dose (on day 29): 60 mg/kg IV loading dose (once) followed after 30 minutes by 400 mg SC. After initial dose of IV and SC pozelimab on day 29, patients will receive 400 mg SC Q4W. 30 mg/kg IV bolus as needed may be considered for patients who experience an LDH increase ≥2 x ULN due to an acute complement-activating conditions (see protocol for details)
Study Drug	Cemdisiran
Dose/Route/Schedule:	200 mg SC Q4W For the first approximately 2 weeks, patients will remain on eculizumab background treatment at their usual dose, and cemdisiran will be introduced: <u>Lead-in cemdisiran treatment and background concomitant treatment with eculizumab:</u> – Day 1 (the day of the scheduled eculizumab administration): cemdisiran 200 mg SC and eculizumab ≥900 mg IV (at the patient's usual dose) – Day 15 (or earlier): eculizumab ≥900 mg IV (patient's usual dose and frequency) The following dosage regimen of pozelimab/cemdisiran combination therapy will be administered during the switch from eculizumab treatment: <u>Pozelimab/cemdisiran combination treatment:</u> – Day 29 (week 4): pozelimab 60 mg/kg IV loading dose, followed by pozelimab 400 mg SC and cemdisiran 200 mg SC – Day 57 (week 8) to day 197 (week 28): pozelimab 400 mg SC and cemdisiran 200 mg SC Q4W (±7 days) maintenance regimen

Intensified Treatment/Route/Schedule: **(for patients who meet pre-specified criteria on LDH and breakthrough hemolysis)**	Single administration of pozelimab 30 mg/kg IV on the day of initiation of the new regimen, followed after 30 minutes by pozelimab 400 mg SC and cemdisiran 200 mg SC. Thereafter, pozelimab 400 mg will be administered SC Q2W (±3 days) along with cemdisiran 200 mg SC Q4W (±3 days).

Endpoint(s)

Primary: The primary study endpoint is the incidence and severity of treatment-emergent adverse events (TEAEs) through day 225 of the OLTP.

Secondary: The main secondary endpoints are:

- The percent change in LDH from pre-treatment (as defined by the mean of the LDH values at the screening visit and baseline (day 1 visit prior to drug administration) to end-of-treatment period (as defined by the mean of the LDH values at days 197 and 225 of the OLTP).
- The proportion of patients who are transfusion-free (defined as not requiring an RBC transfusion as per protocol algorithm, ie, transfusion avoidance) from baseline through day 225, and from day 29 through day 225, inclusive
- The proportion of patients with breakthrough hemolysis from baseline through day 225, and from day 29 through day 225, inclusive
- The proportion of patients who maintain adequate control of hemolysis, defined as 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
- 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 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, and from day 29 through day 225, inclusive
- Change in fatigue as measured by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) Scale from baseline to day 225
- 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)
- Concentrations of total pozelimab and eculizumab in serum, and total cemdisiran in plasma assessed throughout the study
- Change in total complement hemolytic activity assay (CH50) from baseline to day 225, inclusive
- 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
Procedures and Assessments	Safety procedures include measurement of body weight and routine safety assessments (vital signs, physical examination, electrocardiogram). Laboratory assessments of safety include coagulation panel, chemistry, hematology, urinalysis, and pregnancy (if applicable). Adverse events and concomitant medications and procedures will be monitored throughout the study. Efficacy procedures include laboratory assessments of efficacy (LDH, hemoglobin, and CH50), transfusion record update, and clinical outcome assessments (FACIT-Fatigue, EORTC QLQ-C30, Treatment Satisfaction Questionnaire for Medication [TSQM], Patient Global Impression of Severity [PGIS], Patient Global Impression of Change [PGIC], and PNH symptom-specific questionnaire). Other procedures include the collection of blood samples for biomarkers, drug concentrations, immunogenicity, and exploratory assessments.
Statistical Plan	**Justification of Sample Size** 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 from eculizumab at a dose higher than labeled and/or administered more frequently than labeled. Up to 12 patients with PNH will be enrolled to describe and explore the incidence and severity of TEAEs through day 225 of the OLTP. **Primary Analysis** The primary endpoint is the incidence and severity of TEAEs through day 225 of the OLTP. Descriptive summaries will be provided by treatment group. **Secondary Analysis** Secondary endpoints on efficacy will be descriptively summarized. **Timing of Statistical Analysis** The primary analysis will be conducted when all patients have completed the 32-week treatment period or have received intensified treatment or have prematurely discontinued the study during the OLTP. The analysis of the intensified OLTP will be conducted when all intensified patients have completed the 32-week intensified open label treatment period or have prematurely discontinued the study during the intensified OLTP. The OLEP analysis will be conducted when all patients have completed the 52-week OLEP or have prematurely discontinued the study. Additional safety data from the post-treatment safety follow-up period will be included in a subsequent analysis. An interim analysis may be conducted after 6 patients have completed at least 16 weeks of the open-label treatment period. Additional/other interim analyses may be performed to support regulatory interactions.

1. INTRODUCTION

1.1. Background on Paroxysmal Nocturnal Hemoglobinuria

Paroxysmal nocturnal hemoglobinuria (PNH) is a chronic, progressive, life-threatening and rare multisystem disease. It is characterized by uncontrolled complement activation on red blood cells (RBCs), resulting in intravascular hemolysis (Sahin, 2016), and on white blood cells (WBCs) and platelets, resulting in an increased risk of thrombosis. The estimated incidence of PNH is 1.3 cases per million individuals per year, and the estimated prevalence is 15.9 cases per million individuals per year (Preis, 2014).

Paroxysmal nocturnal hemoglobinuria originates from a multipotent, hematopoietic stem cell (HSC) that acquires a mutation of the phosphatidylinositol glycan anchor biosynthesis class A (PIGA) gene. The PIGA gene product is required for the biosynthesis of the glycophosphatidylinositol (GPI) anchor, a glycolipid moiety that attaches dozens of proteins to the plasma membrane of cells. Consequently, the PNH stem cell and all of its progeny have a reduction or absence of GPI-anchored proteins. The mature blood cells derived from the hematopoietic clone can have a complete deficiency (type III) or a partial deficiency (type II) of GPI-linked proteins (Hillmen, 2004). Two of the proteins that are affected by the absence of GPI anchors are CD55 and CD59, complement regulatory proteins. The CD55 protein regulates complement activation by inhibiting complement component 3 (C3) convertases, whereas CD59 inhibits the assembly of the membrane-attack complex (MAC) C5b-C9 by interacting with C8 and C9 (Brodsky, 2009). Their absence renders PNH erythrocytes susceptible to complement-mediated intravascular hemolysis. This intravascular hemolysis in patients with PNH causes anemia (frequently requiring blood transfusion) and hemoglobinuria. Complications of PNH include thrombosis, abdominal pain, dysphagia, erectile dysfunction, and pulmonary hypertension (Hillmen, 2006). Thromboembolism is the most common cause of mortality in patients with PNH and accounts for approximately 40% to 67% of attributable deaths. Potential mechanisms for thromboembolism include platelet activation, toxicity of free hemoglobin, nitric oxide depletion, absence of other GPI-linked proteins, and endothelial dysfunction (Hill, 2013). Paroxysmal nocturnal hemoglobinuria frequently occurs with autoimmune aplastic anemia (Luzzatto, 2018). Evidence suggests that loss of PIGA provides protection for the PNH clone against HSC loss by removing a putative GPI-anchored autoantigen serving as a target for an autoimmune response against the HSC.

The diagnosis of PNH is established using the internationally accepted definition of presence of increased PNH granulocyte clone size measured in peripheral blood by flow cytometry. An accepted definition of active disease is the presence of 1 or more of the following PNH-related signs or symptoms within 3 months: fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), anemia (hemoglobin <10 g/dL), history of a major adverse vascular event (MAVE; including thrombosis), dysphagia, or erectile dysfunction. Alternatively, activity can be established by a history of RBC transfusion due to PNH within 3 months.

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

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

While eculizumab has demonstrated to be an effective therapy for these patients, not all patients receive optimal therapeutic benefit. For example, approximately 25% of patients still need recurrent, albeit less frequent, blood transfusions and half of patients achieve LDH normalization (Lee, 2019). Up to 27% of eculizumab-treated patients may experience breakthrough hemolysis, which is a recurrence of the patient's intravascular hemolysis and associated signs and symptoms. Many patients experience breakthrough hemolysis due to inadequate C5 inhibition (Brodsky, 2017). Up to 20% of patients on eculizumab therapy require significant increases in dose or dose frequency due to breakthrough hemolysis secondary to incomplete inhibition of C5 (Hill, 2013)(Nakayama, 2016)(Peffault de Latour, 2015). Additionally, eculizumab is administered by intravenous (IV) infusion every 2 weeks (Q2W) and has been described as being burdensome for patients and may negatively impact quality of life (Groth, 2017). While the regulatory approval of ravulizumab has improved convenience with a dosing frequency of every 8 weeks, it is not available in most of the world and patients still experience some hemolytic breakthrough. Moreover, in rare instances, eculizumab, and presumably ravulizumab, is ineffective due to polymorphic variation in the gene encoding C5 such that the protein is not recognized by the 2 monoclonal antibodies (mAbs) (Nishimura, 2014) (Sheridan, 2018). The heterogeneity in these hematological responses may be related to underlying aplastic anemia, C3b-mediated extravascular hemolysis, or incomplete pharmacologic blockade of C5, and rare polymorphisms in the gene coding for C5 (Al-Ani, 2016). Thus, there remains an unmet medical need for patients with PNH.

Regeneron has developed a combination mAb/siRNA therapy, pozelimab-cemdisiran, that provides efficacy in patients with PNH, including those with polymorphic variant C5 protein which renders existing therapies ineffective, and offers the added convenience of subcutaneous/self-administration which may address the remaining unmet need.

1.2. Background on Pozelimab

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

Pozelimab was well-tolerated in a toxicology study in cynomolgus monkeys at doses up to 100 mg/kg/week following IV administration for 26 weeks, with a 13-week recovery period. The no observable adverse effect level (NOAEL) based on the results of this toxicology study was determined to be 100 mg/kg, the highest dose tested. Pozelimab was demonstrated to have low potential for cytokine release in cell-based, in-vitro experiments. Complexes of pozelimab and C5 did not result in the formation of immune complexes capable of binding to complement C1q.

Pozelimab has been evaluated in a Phase 1 randomized, placebo-controlled, double-blind study (R3918-HV-1659) in 56 healthy subjects in 7 dose cohorts (N=8, randomized 6:2 pozelimab:placebo for each cohort). Pozelimab was found to be generally well tolerated in ascending single doses of 1, 3, 10, 30 mg/kg IV, and 300 mg and 600 mg SC. The seventh cohort, a repeat-dose cohort of 4 weekly (QW) SC doses of 400 mg following a 15 mg/kg IV loading dose, resulted in 1 resolved serious adverse event (SAE) in the study, an episode of Salpingitis of undetermined microbial etiology. Dose-dependent inhibition of C5 was demonstrated for the single-dose cohorts using the total complement hemolysis activity assay (CH50), an ex-vivo measure of complement lytic activity. The repeat-dose cohort demonstrated complete complement inhibition throughout the dosing period. A threshold serum concentration of approximately 100 µg/mL of pozelimab was determined sufficient to achieve complete inhibition of CH50. To account for population-based variability in C5 levels and for transient increases in complement activity secondary to intercurrent illness, a desired minimum serum concentration of pozelimab greater than the threshold was used to establish a dosing regimen for pozelimab in patients with PNH: 30 mg/kg IV loading dose followed by 800 mg SC QW.

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

It is noted that the regimen represents relatively high doses for a biologic agent. The currently approved anti-C5 mAbs, eculizumab and ravulizumab, are similarly dosed at high levels (maintenance dose of 900 mg IV Q2W and 3000 mg to 3500 mg IV every 8 weeks [Q8W] for eculizumab and ravulizumab, respectively). For PNH, doses higher than 900 mg of eculizumab are sometimes used in practice. The requirement for such high anti-C5 mAb doses is driven by 2 factors. First, there is a need for 100% inhibition which can only be achieved with complete target engagement (Peffault de Latour, 2015) and C5 levels are high; second, in order to achieve 100% inhibition on a population basis, inter- and intra-patient variability of C5 concentrations and instances of enhanced complement activation (which may occur with intercurrent illness) must be considered.

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

1.3. Background on Cemdisiran

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

Cemdisiran has been evaluated in a phase 1/2 study in healthy subjects and patients with PNH who are naïve to anti-C5 treatment or on a background therapy of eculizumab (ALN-CC5-001). Cemdisiran had an acceptable safety profile in 32 healthy subjects following single injection at doses up to 900 mg SC or following repeated injections at doses up to 400 mg QW or 600 mg Q2W. In the 6 patients with PNH included in the study, safety of cemdisiran was acceptable at 200 mg and 400 mg QW, either alone or on a background of eculizumab at standard doses. Dose-dependent and durable reduction in C5 protein and complement activity were observed and the maximum reduction in C5 was between 90% to 99%. However, the maximum reduction in C5 levels achieved by cemdisiran monotherapy did not completely inhibit complement activity and was not sufficient in achieving adequate LDH reduction. Importantly, although cemdisiran monotherapy was insufficient in achieving adequate reduction in LDH, patients with PNH who were treated with cemdisiran co-administered with eculizumab were able to reduce their eculizumab dose and/or increase the interval between eculizumab doses while maintaining clinically meaningful inhibition of complement activity.

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

1.4. Pozelimab + Cemdisiran: A Combination Approach

The combination treatment of cemdisiran and pozelimab is being developed in patients with PNH due to unmet needs identified with current available treatments and a potential for added convenience in the dosing regimen. This study is designed to evaluate the safety, efficacy, and pharmacodynamic (PD) effects of the pozelimab and cemdisiran combination in patients with PNH who are currently on stable eculizumab therapy. Pharmacokinetic (PK)/PD modeling of observed data from both pozelimab and cemdisiran first-in-human studies in healthy subjects and patients with PNH (naïve to anti-C5 treatment or on a background therapy of eculizumab) suggests that, by combining cemdisiran and pozelimab, the desired C5 suppression may be durable with significantly lower doses of both agents and a longer dosing interval. An assessment of the risk-benefit of the pozelimab and cemdisiran combination for this study is provided in Section 3.3.

2. STUDY OBJECTIVES

2.1. Primary Objective

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

2.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the effect of the combination treatment on the following parameters of intravascular hemolysis: LDH control, breakthrough hemolysis, and inhibition of CH50
- To evaluate the effect of the combination treatment on the stability of LDH during the transition period from eculizumab monotherapy to combination with pozelimab and cemdisiran
- To evaluate the effect of the combination treatment on red blood cell (RBC) transfusion requirements
- To evaluate the effect of the combination treatment on hemoglobin levels
- To evaluate 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 evaluate the long-term safety and efficacy of the combination treatment in an optional open-label extension period (OLEP)

2.3. Exploratory Objectives

The exploratory objectives of the study are:

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

3. HYPOTHESIS AND RATIONALE

3.1. Hypotheses

The clinical hypothesis is that pozelimab and cemdisiran combination treatment has an acceptable safety and tolerability profile in patients with PNH who were previously treated with eculizumab.

3.2. Rationale

3.2.1. Rationale for Study Design and Endpoints

The current clinical study is a single-arm study of patients with PNH who are currently on eculizumab, and who will switch to pozelimab and cemdisiran combination therapy. As a single-arm, open-label study, patients and investigators will be aware of treatment allocation. The study does not include a placebo control, as it is considered unacceptable when there is a proven intervention (ie, eculizumab or ravulizumab) and patients with PNH who are not on C5 inhibition face risks of serious or irreversible harm from sequelae of the disease. The primary objective of

this study is to evaluate the safety and tolerability of pozelimab and cemdisiran combination therapy after 32 weeks of treatment in patients with PNH who switch from eculizumab therapy.

The primary endpoint for this study is an assessment of the incidence and severity of treatment-emergent adverse events, including adverse events of special interest (AESIs) and SAEs, throughout a 32-week treatment period. Both pozelimab and cemdisiran have been evaluated in healthy volunteers and patients with PNH as monotherapy. Additionally, cemdisiran has been studied in combination with eculizumab. The safety of each individual component has been deemed favorable to allow for continued development. This will be the first study in which the combination of pozelimab and cemdisiran is administered to patients with PNH who are taking eculizumab and will switch to the combination therapy.

Additional safety measures that will be evaluated include changes to vital signs, laboratory parameters, electrocardiogram parameters, and breakthrough hemolysis.

In addition to evaluation of safety, the study includes secondary efficacy endpoints to assess the effect of the combination treatment on control of intravascular hemolysis, as measured by LDH, which is central to the clinical monitoring of PNH (Rother, 2005), including during eculizumab therapy. Lactate dehydrogenase is an objective laboratory-based parameter that is unlikely to be biased by knowledge of treatment assignment. An LDH of at least 1.5 × ULN along with related clinical symptoms is considered an indication of active PNH, and for treatment with eculizumab (Sahin, 2016)(Soliris®, 2021). Furthermore, reductions in LDH below the 1.5 × ULN threshold with eculizumab therapy have been shown to correlate with improvement in a patient's symptoms, QoL measures, and transfusion requirements (Brodsky, 2008).

The use of LDH as a measure of intravascular hemolysis allows for an objective and precise means to gauge whether the control in intravascular hemolysis with eculizumab is sustained when patients switch to pozelimab and cemdisiran treatment. Thus, the absence of a clinically significant rise in LDH in patients switching from eculizumab to pozelimab and cemdisiran treatment supports the efficacy of the combination approach.

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

The study population includes patients with PNH currently being treated with eculizumab for at least the prior 12 weeks with any level of LDH. Eculizumab is administered as an IV infusion. Intravenous administration places a burden on the health care system as it requires administration in an infusion center or by a healthcare professional at the patient's home. Pozelimab and cemdisiran combination therapy is expected to remove the requirement for resource-consuming

visits to infusion centers or home nurse visits, and time off for the patient from their work/school and time away from their families. In addition, the inconvenience and interruptions associated with IV infusions may impact compliance, which is expected to be addressed with every-4-week (Q4W) self-administered pozelimab and cemdisiran combination therapy. Disruptions due to the COVID-19 pandemic and requirements from governments on travel restrictions, stay-at-home orders, and maintaining social distancing can impact IV-administered drugs such as eculizumab, whereas this impact would be minimized with self-administered pozelimab and cemdisiran combination therapy. Additionally, a delayed dose is expected to have less impact compared to patients treated with eculizumab based on an advantageous PK/PD profile with the combination. Finally, IV access issues may be encountered with infusions, making it difficult to complete the administration.

The study treatment duration of 32 weeks in the open-label treatment period (OLTP) is considered sufficient to provide an adequate understanding of the safety, efficacy, and PD effects of pozelimab and cemdisiran for continued development. It is expected that by weeks 28 to 32, there will be no contribution of eculizumab towards efficacy as assessed by LDH based on the known dosing interval and half-life of eculizumab. By the end-of-treatment period at week 32, the effect on LDH will be due to the sole contribution of the pozelimab and cemdisiran combination without any impact from the loading dose of pozelimab.

The long-term safety and efficacy of the combination treatment will be assessed by providing the patients who complete the main OLTP on combination treatment an opportunity to participate in an optional long-term OLEP, in which patients shall continue to receive study treatment for an additional 52 weeks. Patients who opt not to participate in the 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. Additional considerations on post-study treatment access are described in Section 8.9.

3.2.2. Rationale for Dose Selection

The proposed dosage regimen of pozelimab/cemdisiran combination therapy (Section 6.1) for patients with PNH, who switch from eculizumab treatment, was selected based on safety, efficacy, and PK/PD data from completed and ongoing studies for each individual agent in healthy subjects and in patients with PNH. The rationale for the chosen regimen is 1) to provide rapid and sustained complete C5 inhibition after the initiation of the combination treatment and throughout the dosing intervals, and 2) to mitigate the potential for the formation of high molecular weight (HMW) complexes of eculizumab-C5-pozelimab during the treatment switch.

Pozelimab

In the completed phase 1 study in healthy subjects (R3918-HV-1659), pozelimab was found to be generally well tolerated at single doses up to 30 mg/kg IV and 600 mg SC, or 4 weekly SC doses of 400 mg SC preceded by a 15 mg/kg IV loading dose. Maximum C5 inhibition with complete suppression of complement activity, as measured by a CH50 assay, was observed at higher doses (≥3 mg/kg IV dosing). The PK of total pozelimab appears non-linear at lower concentrations, becoming linear as concentrations increase. This is thought to be due to saturable, target-mediated elimination. In the ongoing Phase 2 study in patients with PNH naïve to anti-C5 treatment (R3918-PNH-1852), no safety signal has emerged following a loading dose of 30 mg/kg IV of pozelimab (day 1) followed by 800 mg SC QW (starting on day 8). Interim analysis showed that

efficacy, as measured by reducing LDH to below 1.5 ULN, was achieved in all 6 patients at day 57. More information regarding the results of the Phase 1 and 2 studies is provided in the Pozelimab IB.

Cemdisiran

Cemdisiran has been evaluated in a phase 1/2 study in healthy subjects and patients with PNH who are naïve to anti-C5 treatment or on a background therapy of eculizumab (ALN-CC5-001). Cemdisiran had an acceptable safety profile in healthy subjects following single injection at doses up to 900 mg SC or following repeated injections at doses up to 400 mg QW or 600 mg Q2W. In the 6 patients with PNH included in the study, safety of cemdisiran was acceptable at 200 mg and 400 mg QW, either alone or on a background of eculizumab at standard doses. Dose-dependent and durable reduction in C5 protein and complement activity were observed and the maximum reduction in C5 was between 90% to 99%. However, the maximum reduction in C5 levels achieved by cemdisiran monotherapy did not completely inhibit complement activity and was not sufficient in achieving adequate LDH reduction. More information regarding the results of the phase 1/2 study is provided in the Cemdisiran IB.

Pozelimab/Cemdisiran Combination

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

Mitigation of potential large drug-target-drug immune complex formations during treatment switch

While the overall goal of the proposed dosing regimen is to prevent hemolysis, the transition period of the combination treatment initiation is also designed to mitigate the potential for the formation of large drug-target-drug (DTD) immune complexes of eculizumab-C5-pozelimab during the treatment switch. As explained below, a lead-in cemdisiran dose plus a loading dose of pozelimab is proposed in order to minimize large DTD immune complex formation.

A previous clinical study reported adverse reactions (eg, serum sickness-like reactions, skin rash), upon switching from eculizumab to another anti-C5 mAb, crovalimab, attributed to the formation of immune complexes between C5 and the 2 non-competing C5 mAbs (Röth, 2018). Similarly, pozelimab has been shown to bind C5 non-competitively with eculizumab (R3918-PH-19074), and thus has the potential to form higher-order immune complexes in the presence of eculizumab and C5.

In vitro studies were conducted to simulate conditions that may occur when pozelimab is administered to a patient previously dosed with eculizumab. The sponsor generated an ‘in-house eculizumab’ to conduct in vitro studies, which has the same amino acid sequence and binds to the same epitope on C5 as eculizumab. Neither pozelimab nor ‘in-house eculizumab’ individually formed higher order multimers larger than a 1:2 mAb:C5 complex. Pozelimab was added to pre-formed in-house eculizumab:C5 complexes under conditions of excess pozelimab

(5:1:1 pozelimab: in-house eculizumab:C5) and equimolar amounts of total mAb to C5 (1:1:2 pozelimab: in-house eculizumab:C5). The latter conditions were expected to promote formation of large DTD immune complexes. Under conditions of pozelimab excess, the majority of complexes observed (~86%) were either trimeric or pentameric (2:1 or 3:2 mAb:C5 molar ratios, respectively), with the remainder comprising large DTD immune complexes. At an equimolar ratio of total mAb and C5, the majority of the samples (~86%) consisted of heterogeneous large DTD immune complexes larger than pentamers. In summary, while 'in-house eculizumab' and pozelimab in combination were able to form heteromeric complexes with C5, the presence of excess pozelimab reduced the formation of higher-order immune complexes relative to conditions where total mAb and C5 were present at equimolar concentrations.

In the current study, a 4-week lead-in period with a dose of cemdisiran 200 mg SC is provided. [redacted] reduce C5 production and consequently lower the total C5 (eculizumab-C5 complexes plus free C5) level (about 86% reduction of total C5 on day 29 compared to day 1), before the initiation of the pozelimab/cemdisiran combination treatment. Consequently, the potential for the formation of the large DTD immune complexes should be significantly reduced. To further minimize the risk of formation of large DTD immune complexes upon initiating pozelimab/cemdisiran combination treatment, a loading dose of pozelimab 60 mg/kg IV is provided. Based on reported mean trough concentrations of eculizumab of 97 mg/L (Soliris®, 2021) and predicted pozelimab concentration over time, the molar concentrations of pozelimab are expected to be in excess of eculizumab following the IV loading dose with an estimated ratio of approximately 17:1. Indeed, crovalimab was noted to have transient reductions of concentrations in serum during the switch period in patients receiving eculizumab, and this issue was addressed with an optimized dosing regimen (a loading dose series before the maintenance doses). A lead-in cemdisiran dose plus a loading dose of pozelimab is considered the best solution to address this concern.

Provide rapid and sustained maximum C5 inhibition after the initiation of the combination treatment and throughout the dosing intervals

In addition to being part of the approach to mitigate the potential for the formation of large DTD immune complexes, the IV loading dose of pozelimab 60 mg/kg is proposed to ensure rapid and complete inhibition of C5 to avoid any breakthrough hemolysis that could occur during the treatment transition. Based on simulations, the dosage regimen of the IV loading dose followed by the SC maintenance dose of pozelimab/cemdisiran 400 mg/200 mg Q4W starting on day 29 is expected to result in rapid and sustained suppression of C5 to biologically inactive levels. [redacted] The CH50 assay will be used to confirm complete inhibition of complement activity has been achieved throughout the dosing interval in patients with PNH.

Treatment Intensification

A modified regimen consisting of an intensified regimen of pozelimab is included to provide extra C5 suppression that some patients may need to achieve adequate control of intravascular hemolysis and is intended to be used as an intensified regimen in the planned phase 3 studies. See Section 6.1.3.

3.3. Risk-Benefit

A risk-benefit statement with respect to the overall development program is provided in the IB for pozelimab and the IB for cemdisiran. The combination treatment of cemdisiran and pozelimab is being developed in patients with PNH for the following reasons: (1) both drugs work via a complementary approach on a validated pathway with the possibility of complete inhibition of the pathway, which may translate into optimal efficacy in nearly all patients and anticipated better control of breakthrough hemolysis; (2) cemdisiran is insufficient to treat PNH as monotherapy; (3) pozelimab was effective as monotherapy in treatment of PNH in a phase 2 study, but the regimen was considered potentially burdensome; (4) pozelimab and cemdisiran combination therapy will address significant unmet needs for patients and provide for reduced treatment burden with self-administration Q4W which should translate into benefit for patients who have to take therapy for long-term duration; (5) pozelimab and cemdisiran combination therapy is not expected to be associated with any increased risk beyond that of the individual agents, whereby the individual agents have similar risk profiles and may be associated with a decrease in the number of injection site reactions due to reduced frequency of administration; and (6) efficacy is [redacted] in patients with C5 variant protein, which renders eculizumab or ravulizumab ineffective.

The following sections describe potential risks and strategies for mitigation.

3.3.1. Infusion Reactions

The loading dose of 60 mg/kg IV is expected to be well tolerated. There were no infusion reactions, and pozelimab was well tolerated in healthy subjects who received IV doses of up to 30 mg/kg and in patients with PNH naïve to complement inhibitor therapy, who received an IV loading dose of 30 mg/kg. In the 13- and 26-week toxicology studies dosed up to 100 mg/kg/week in cynomolgus monkeys, no adverse effects were reported (See Pozelimab IB).

3.3.2. Potential Risk of Neisseria Infection

An established risk of blocking C5 complement activity is increased susceptibility to infections, specifically to encapsulated organisms, the most potentially severe of which is infection with *Neisseria meningitidis* (Figueroa, 1991). The risk for meningococcal infection is largely driven by the degree of inhibition of C5. Two different agents acting on C5 through independent pathways are not expected to increase the risk for meningococcal infection above that of each of the individual agents. This expectation is based on the goal of complement inhibition therapy and human genetic data. The objective of pozelimab and cemdisiran combination therapy is complete inhibition of C5 activity. Once this is achieved, then further inhibition is not possible and the anticipated risk is not expected to increase further. Human genetic data reveal that the increased risk of infections with *Neisseria* spp. occurs when there is homozygous loss of complement factor 5 (C5). Importantly, individuals who are C5 heterozygous loss of function do not have increased risk of infections with *Neisseria* spp. (Platonov, 1997).

Experience with eculizumab suggests that pretreatment with appropriate vaccinations covering multiple serotypes and concurrent therapy with oral antibiotics is effective at substantially mitigating this risk (Hillmen, 2013)(McNamara, 2017)(NHS England, 2013)(Soliris®, 2021). Current treatment guidelines for PNH and the eculizumab package insert recommend such vaccinations prior to dosing. Because vaccination does not provide 100% coverage to all strains and there are no proven titer levels associated with 100% protection, prophylactic oral antibiotics are also commonly given to patients with genetic or pharmacologic deficiency in terminal complement activity. In various disease settings such as asplenia in sickle cell disease, and with terminal complement deficiency, use of long-term prophylactic antibiotics has been safely implemented for the prevention of encapsulated organisms, including *N. meningitidis* (Gaston, 1986)(Wedzicha, 2008).

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

Recently, serious infections with *Neisseria* species (other than *N. meningitidis*), including disseminated gonococcal infections, have been reported during eculizumab treatment (Soliris®, 2021). Therefore, patients will undergo a risk assessment and counseling regarding the potential risk of *Neisseria gonorrhea* as per the investigator's local guidelines. Patients will be counseled about *N. gonorrhea* prevention, and regular testing will be advised for at-risk patients. A risk-factor assessment will be based on local practice or national guidelines to determine if the patient is at risk, which would lead to further management of prevention, testing, and treatment of *N. gonorrhea* (Section 8.2.4).

3.3.3. Liver Function Test Abnormalities

Liver function test abnormalities are noted as a potential risk due to the targeted delivery of cemdisiran to hepatocytes and were carefully followed in the cemdisiran program. No signal has emerged from the phase 1 and 2 clinical studies to date. In the healthy volunteer study with cemdisiran, about 30% to 40% of healthy subjects had asymptomatic, transient, mild elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) that were $< 3 \times$ ULN in the cemdisiran dosing arms. In patients with PNH (n=6), 1 patient had a related AE of increased transaminases with ALT and AST $\geq 3 \times$ ULN. The patient had several underlying contributing factors, and the AE resolved within 120 days of onset in the setting of ongoing cemdisiran pharmacology. The patient was rechallenged in a compassionate use setting, and no increase ALT or AST ≥3 X ULN has been reported. Additional details may be found in the Cemdisiran IB.

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

3.3.4. Study Conduct in Response to Coronavirus Disease 2019

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

3.3.5. Other Risks

Other risks are described under *Safety Considerations* in Section 6.1.1.2.

4. ENDPOINTS

4.1. Primary and Secondary Endpoints

4.1.1. Primary Endpoint

The primary study endpoint is the incidence and severity of TEAEs through day 225 of the OLTP.

4.1.2. Secondary Endpoints

The secondary 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, ie, transfusion avoidance) from baseline through day 225, and from day 29 through day 225, inclusive
- The rate and number of units of RBCs transfused from baseline through day 225, and from day 29 through day 225, inclusive.

- The proportion of patients with breakthrough hemolysis from baseline through day 225, and from day 29 through day 225, inclusive
- The proportion of patients who maintain adequate control of hemolysis, defined as LDH ≤1.5 x ULN from post-baseline (on day 1) through day 225, and 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, and from 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, and from day 29 through day 225, inclusive
- The 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 total 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
- Incidence and severity of TEAEs for patients who receive dose intensification through day 225r

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

The secondary endpoints for the optional OLEP are:

- Incidence and severity of TEAEs during the 52-week OLEP in patients treated with pozelimab and cemdisiran combination therapy
- Change and percent change of LDH from day 1e (baseline of the OLEP) to week 24e and week 52e
- 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 (ie, 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
- The 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

4.1.3. Exploratory Endpoints

The exploratory endpoints for the OLTP are:

- Proportion of patients who require treatment intensification throughout the study
- Incidence of MAVE, defined as adverse events of special interest that include thrombophlebitis/deep vein thrombosis, pulmonary embolus, myocardial infarction, unstable angina, renal vein or artery thrombosis, acute peripheral vascular occlusion, hepatic vein thrombosis, portal vein thrombosis, mesenteric/visceral vein thrombosis or infarction, mesenteric/visceral arterial thrombosis or infarction, transient ischemic attack, cerebral arterial occlusion/cerebrovascular accident, cerebral venous occlusion, gangrene (nontraumatic; non-diabetic), amputation (nontraumatic; non-diabetic) 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)
- Change in PNH symptoms as measured by the de novo PNH Symptom-Specific Questionnaire from baseline to day 225
- Change in Patient Global Impression of Severity (PGIS) from baseline to day 225, including questions on PNH symptoms, impacts, and fatigue
- Patient Global Impression of Change (PGIC) at day 225, including questions on PNH symptoms, impacts, and fatigue
- Identify any potential differences that influence efficacy and safety via genotyping and gene expression analysis (by RNA sequencing)

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

5. STUDY VARIABLES

5.1. Demographic and Baseline Characteristics

In accordance with local regulations, baseline characteristics will be collected and will include standard demographic information (eg, age, gender, race, ethnicity, etc), disease characteristics, medical history, and medication history for each patient. The data will be used to describe the patient population under study and may inform whether there are differences in the safety or efficacy profile based on the defined patient characteristics. In addition, collection of data on race and ethnicity is required by certain regulatory agencies, such as the FDA.

5.2. Efficacy Variables

5.2.1. Laboratory Variables for the Assessment of Efficacy

Efficacy in this study is evaluated by the following laboratory assessments:

- LDH (serum)
- Hemoglobin
- CH50

These laboratory variables are relevant to the characterization and disease mechanisms of PNH (Brodsky, 2014). Lactate dehydrogenase as a measure of intravascular hemolysis allows for an objective and precise means to gauge whether the control of intravascular hemolysis with eculizumab is sustained when the patients are switched to pozelimab and cemdisiran combination treatment. The CH50 assay will be used to confirm complete inhibition of complement activity has been achieved throughout the dosing interval in patients with PNH.

5.2.2. Transfusion Record

Hemolytic anemia is a clinical manifestation of PNH, and patients often require blood transfusion for symptomatic management. The frequency of blood transfusion has been used in other studies of PNH to assess efficacy (Hillmen, 2006) (Röth, 2018).

5.2.3. Clinical Outcome Assessments

The following clinical outcome assessments (described in Section 9.2.2.2) will be completed by the patient:

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

5.3. Safety Variables

The safety variables in this study include:

- TEAEs
- Body weight
- Vital signs
- Electrocardiogram (ECG)
- Physical examination
- Routine safety laboratory tests (hematology, chemistry, urinalysis, and pregnancy testing [for women of childbearing potential or WOCBP])
- Concomitant medications and treatments

5.4. Pharmacokinetic Variables

The PK variables are the concentration of total pozelimab, cemdisiran, cemdisiran metabolites, total eculizumab, total C5, and time.

5.5. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, and time point/visit.

5.6. Pharmacodynamic and Other Biomarker 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: ie, haptoglobin, reticulocyte count, and bilirubin
- AH50, serum
- Complement activation markers: ie, sC5b-9
- PNH clone size: ie, PNH erythrocytes and granulocytes

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

6. STUDY DESIGN

6.1. Study Description and Duration

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 is planned to be conducted in a single center in the United Kingdom, but if needed, additional sites/countries may be included. Patients who are currently receiving eculizumab at the labeled dosing regimen (900 mg IV Q2W) or who are currently receiving eculizumab at a dose higher than the labeled dose (>900 mg IV) or more frequently than labeled will be enrolled. A study schematic is provided in Figure 1.

The study consists of 4 periods: a screening period of up to 42 days, a 32-week OLTP (this main study period will be longer for patients who require intensified treatment), an optional 52-week OLEP, and a 52-week post-treatment safety follow-up period. The fourth period begins when a patient completes or permanently discontinues study treatment (eg, at the time of premature study drug discontinuation, at the completion of study treatment in the OLTP for patients who decline the optional OLEP, or at the completion of study treatment in the optional OLEP for patients who do not continue study treatment in a post-trial access program immediately following the study). The treatment period begins from the first dose of study drug and ends after the completion of the dosing interval of the last dose to account for the treatment effect of the final dose of study drug.

For the first approximately 2 weeks, patients will remain on eculizumab background treatment at their usual dose/frequency, and cemdisiran alone will be introduced:

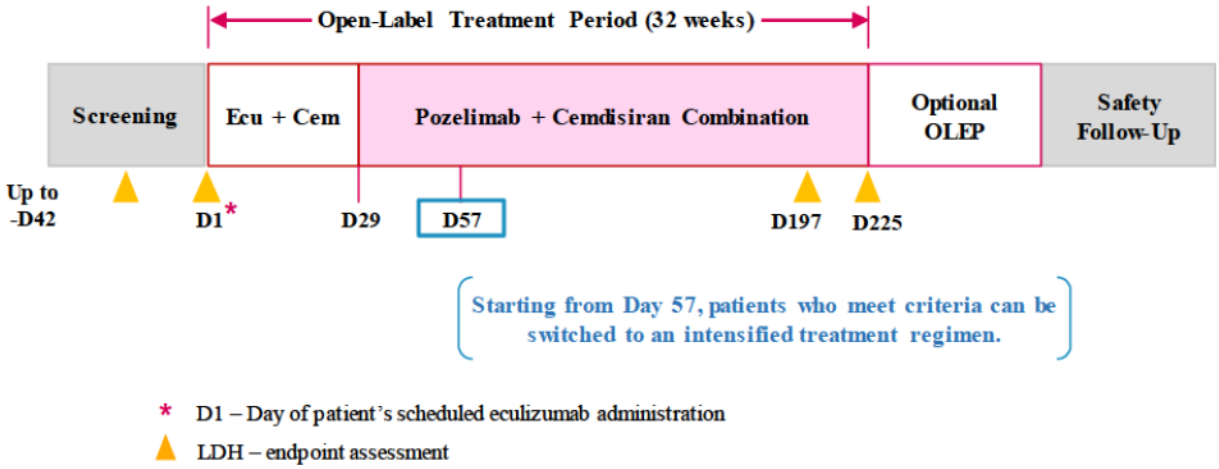
- Lead-in cemdisiran treatment and background concomitant treatment with eculizumab:
  - **Day 1** (the day of patient's scheduled eculizumab administration): cemdisiran 200 mg SC and eculizumab ≥900 mg IV (patient's usual dose). Note: eculizumab may be administered up to 2 days after cemdisiran if not administered with cemdisiran on day 1.
  - **Day 15**:
    - For patients on eculizumab Q14 days (labeled dose regimen): day 15 (±2 days), ie, day 13 to day 17
    - For patients on eculizumab more frequently than Q14 days: patients should be dosed within 2 days of their usual planned dose

The following dosage regimen of pozelimab/cemdisiran combination therapy will be administered during the switch from eculizumab treatment:

- Pozelimab/cemdisiran combination treatment:
  - **Day 29** (week 4): pozelimab 60 mg/kg IV loading dose, followed (after a delay of at least 30 minutes) by pozelimab 400 mg SC and cemdisiran 200 mg SC
  - **Day 57** (week 8) to day 197 (week 28): pozelimab 400 mg SC and cemdisiran 200 mg SC Q4W maintenance regimen (±7 days)

Details of all dose administration windows are provided in Table 1 (footnotes #9, 10, 11, and 12).

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.

6.1.1. Study Periods

6.1.1.1. Screening Period

The screening period will evaluate patients to establish their eligibility to enter the study.

The screening visit should take place up to 42 days prior to day 1 (a day that the patient is scheduled to be administered eculizumab). An additional interim screening visit(s) may take place as needed, for instance, in order to obtain the LDH value for pretreatment assessment on the day of (or if not possible, one day before) eculizumab administration, and prior to eculizumab dosing.

Historical data will be collected including, but not limited to, eculizumab administration, concomitant medications, hemolytic parameters, and transfusions. Data will also be collected on PNH signs and symptoms during the screening period.

Patients will require vaccination/revaccination for *N. meningitidis* unless documentation is provided of prior immunization in the past 5 years prior to screening, or less than 5 years if required according to current national vaccination guidelines for vaccination use with complement inhibitors or local practice. For patients who require meningococcal vaccination during the screening period, administration should occur preferably at least 2 weeks prior to day 1, unless local practice or national guidelines specify a different vaccination protocol. If vaccination precedes the initiation of study treatment by less than 2 weeks, then the patient must receive antibiotic prophylaxis for a minimum of 2 weeks from the date of vaccine administration (Section 8.2.1).

During screening, patients who have not been vaccinated against *Streptococcus pneumoniae* and *Haemophilus influenza* type B according to current national/local vaccination guidelines will be required to be vaccinated to be eligible for the study (Section 7.2.2).

In addition to *N. meningitidis*, fatal or serious infections with *N. gonorrhea* have been reported in patients taking eculizumab. Therefore, a risk assessment and counseling regarding the potential risk of *N. gonorrhea* infection will be conducted per local practice (Section 8.2.4).

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

In addition to screening procedures, patients will be asked to complete a PNH Symptom-Specific Questionnaire daily for at least 14 consecutive days prior to the day 1 visit.

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

6.1.1.2. Open-Label Treatment Period

Patients who fulfill all the eligibility criteria will be enrolled in the study and receive their first dose of study drug on day 1, which should occur on the day of the patient's scheduled treatment with eculizumab. As described in Section 6.1, patients will be administered cemdisiran with eculizumab on day 1 (note: eculizumab may be administered up to 2 days after day 1 cemdisiran in order to accommodate the logistical complexities associated with its administration). Eculizumab will be administered alone on day 15 (+2 days or earlier, according to the patient's usual dosing frequency (refer to Section 6.1). The first dose of combination SC therapy with pozelimab and cemdisiran without background eculizumab will be administered on day 29 and continue Q4W thereafter. The first dose of combination SC therapy on day 29 will be preceded by an IV loading dose of pozelimab to achieve high concentrations of pozelimab rapidly in order to provide complete inhibition of C5, as soon as possible, during the switch from eculizumab to pozelimab. The SC doses should not be given until at least 30 minutes after completion of the IV administration, and the patient should be observed during the interval. Patients will also be monitored for at least 30 minutes after completing the first SC injections for the pozelimab and cemdisiran combination.

After the first SC dose of the pozelimab and cemdisiran combination on day 29, subsequent study treatment administrations may be continued by the site personnel, a healthcare professional if available, or administered by the patient or designated person at the patient's preferred location. These options for study treatment administration will depend on preference of the investigator and patient, local regulations, and availability of healthcare professional. If self-administration (or administration by a designated person) is undertaken, then sufficient injection training at the scheduled administration(s) with a pozelimab and cemdisiran maintenance regimen will be provided by the investigator or qualified study staff designee. After training, observation of self-administration (or administration by designated person) will be conducted by clinical site personnel and may be conducted in person at the patient's home or via telemedicine. Once this

observation is considered satisfactory, the pozelimab and cemdisiran maintenance regimen can be subsequently administered independently by patient/designated person for the remainder of the study. A patient diary will be provided prior to initiation of self-administration for recording data on study treatment administration. The diary should be completed upon each study drug administration.

Safety Considerations

Breakthrough hemolysis is assessed by the investigator throughout the study and is defined in Section 6.1.2. During the study, a patient meeting criteria for breakthrough hemolysis or inadequate LDH response may qualify for treatment intensification as described in Section 6.1.3.

The decision to transfuse with RBCs during the study should proceed according to the predefined criteria in Section 6.1.4.

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

During intravenous infusion of pozelimab, due to concern of potential IV infusion reactions, patients should be observed for at least 30 minutes after the infusion. In addition, emergency equipment and medication for the treatment of infusion reactions must be available at the clinical site for immediate use. All infusion reactions must be reported as adverse events (AEs) and graded using the grading scales provided in Section 10.2.5. Patients should also be observed for at least 30 minutes after completing the first SC injections of the pozelimab and cemdisiran combination.

During the transition of therapy from eculizumab to pozelimab, investigators should have heightened awareness for possible AEs as a result of the risk of formation of large multimers of complexes of eculizumab-C5-pozelimab (ie, large DTD immune complexes) (See Section 6.1.5).

Study Procedures

Study procedures in the treatment period include laboratory assessments of efficacy (LDH, hemoglobin, and CH50), transfusion record update, clinical outcome assessments, body weight, and routine safety assessments (vital signs, physical examination, ECG, safety laboratory testing). Treatment-emergent adverse events and concomitant medications will be monitored throughout the study. Patients will provide blood samples for biomarkers, drug concentration for potential PK and PD assessment, immunogenicity, and exploratory assessments. Study procedures are listed by visit in Table 1 and described in Section 9.2. Study procedures, including sample collection for laboratory analysis, may be performed at the study clinic or at another location that is more convenient for the patient (including home visits), if this option is available and with sponsor approval. The last doses of study treatment for patients who do not receive dose intensification are administered on day 197 (week 28). Patients will return for safety, efficacy, and other assessments at the end of treatment (EOT) visit at week 32. For patients who restarted on intensified treatment during the study, the last dose of study treatment is administered at week 30. Patients will return for safety, efficacy, and other assessments at the EOT visit at week 32 (Table 2).

6.1.1.3. Optional Open-Label Extension Period

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

During the optional OLEP, patients who are not on intensified treatment who meet the pre-defined criteria for treatment intensification will follow the dosing regimen as described in Section 8.3.2 with the new regimen starting on the day of intensification, and will continue their visit schedule at the next OLEP visit.

This means that starting the day of intensification (day pre-defined criteria have been met), the patient will receive a single administration of pozelimab 30 mg/kg IV followed by SC administration of pozelimab and cemdisiran the same day. Thereafter, the patients will receive pozelimab 400 mg Q2W and cemdisiran 200 mg Q4W starting from the day of intensification (±3 days). The visit schedule for the OLEP will remain unchanged.

For patients who complete the optional OLEP, post-trial access to treatment may be available (Section 8.9).

6.1.1.4. Post-Treatment Safety Follow-Up

Patients who permanently discontinue study treatment for any reason (including patients who decline continuation in the optional OLEP and patients who complete the OLEP but do not continue treatment in a post-trial access setting) will undergo an off-treatment follow-up period until 52 weeks after the last dose of study treatment as described in Table 4. The post-treatment follow-up monitors the safety of the patient as the study drugs are eliminated gradually from the body.

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

6.1.1.5. End of Study Definition

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

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

The safety follow-up period is waived for patients who continue treatment in the post-trial access program.

6.1.2. Breakthrough Hemolysis

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

- An increase in LDH occurs when:
  - LDH ≥2 x ULN if pre-treatment LDH is ≤1.5 x ULN or
  - LDH ≥2 x ULN subsequent to initial achievement of LDH ≤1.5 x ULN if pre-treatment LDH is >1.5 x ULN

  Note: pre-treatment LDH is defined by the mean of the LDH values at the screening visit and day 1 visit
- The signs or symptoms should correspond to those known to be associated with intravascular hemolysis due to PNH, limited to the following: new onset or worsening fatigue, headache, dyspnea, hemoglobinuria, abdominal pain, scleral icterus, erectile dysfunction, chest pain, confusion, dysphagia, new thrombotic event, anemia including hemoglobin value significantly lower (ie, ≥2 g/dL decrease) as compared to patient's known baseline hemoglobin values.

6.1.3. Treatment Intensification

An intensified regimen is proposed to provide extra C5 suppression that some patients may need and which cannot be managed adequately by the standard dose regimen. Patients will receive intensification of their pozelimab treatment from day 57 onward as described in Section 8.3.2 if they meet both criteria below:

- Breakthrough hemolysis that is not due to a complement-activating condition (ie intercurrent infection) **and**
- Inadequate LDH response (ie, LDH >1.5 x ULN) that is sustained (ie, on 2 consecutive measurements spanning at least 2 weeks).

During the OLTP, patients who undergo treatment intensification may require unscheduled visit(s) before initiation. The day of initiation of the intensified regimen should be re-anchored to baseline of the Intensified Treatment Period in the OLTP (day 1r) and thereafter following a similar schedule of subsequent visits and assessments as newly enrolled patients (see Table 2). Patients who are on intensified treatment will be considered to have completed the OLTP once they finish the 32-week treatment period on the intensified regimen.

During the optional OLEP, patients who are not on intensified treatment who meet criteria for treatment intensification will follow the dosing regimen described in Section 8.3.2 with the new regimen starting on the day of intensification and for the remainder of the OLEP. Patients will continue their visit schedule at the next OLEP visit (Table 3).

Patients are eligible to receive intensification of pozelimab only once (whether during the main treatment period or the optional OLEP), beyond which no further intensification will be permitted.

Note: After day 29, patients who have an LDH increase ≥2 x ULN due to an acute complement-activating condition during the OLTP, intensified OLTP or optional OLEP may receive an IV pozelimab dose of 30 mg/kg IV at the discretion of the investigator and in consultation with the

sponsor (see Section 8.3.2). An assessment of the patient's weight should be performed on the day of the IV pozelimab load in order to calculate the appropriate dose. This is not considered treatment intensification as there will be no change in regimen and no requirement to reset their schedule to day 1.

6.1.4. Transfusion Algorithm

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

- Transfuse with RBC(s) if the hemoglobin level is ≤9 g/dL with new onset or worsening signs or symptoms resulting from anemia that are of sufficient severity to warrant transfusion or
- Transfuse with RBC(s) if the hemoglobin level is ≤7 g/dL with or without signs or symptoms of anemia.

6.1.5. Large drug-target-drug immune complexes

During the transition of therapy from eculizumab to pozelimab, investigators should have heightened awareness for possible AEs as a result of the risk of formation of large multimers of complexes of eculizumab-C5-pozelimab (ie, large DTD immune complexes). Patients may present with a variety of signs and symptoms such as fever, malaise, rash, and polyarthralgia. Investigators should also consider meningococcal infection as the cause of the aforementioned symptoms. If a rash does develop, the site may consider taking pictures of the skin lesions as allowed based on local requirements and/or perform a skin biopsy if clinically indicated. If photos are obtained, then copies should be kept as source documents, which may later be collected by the sponsor. If there is a suspicion of an AE potentially due to large DTD immune complexes, an unscheduled laboratory test should be obtained and at minimum will include a complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), chemistry, C3, C4, and urinalysis (including microscopic evaluation). It is recommended that the investigator consult with a rheumatologist or nephrologist if needed and inform the sponsor. However, further investigations are at the discretion of the investigator. Investigators should consider treatment with an additional dose of pozelimab 30 mg/kg IV. This additional dose will establish conditions of pozelimab excess in the circulation and minimize the risk of further formation of immune complexes. Further management should be based on clinical experience with type III hypersensitivity reactions (ie, serum sickness) which includes antihistamines, non-steroidal anti-inflammatory drugs, topical corticosteroids for localized skin rash, and systemic corticosteroids for generalized skin rash or systemic manifestations.

6.2. Planned Interim Analysis

An interim analysis may be conducted after 6 patients have completed at least 16 weeks of the OLTP (Section 11.5). Additional/other interim analyses may be performed to support regulatory interactions.

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

7.1. Number of Patients Planned

Up to 12 patients.

7.2. Study Population

7.2.1. Inclusion Criteria

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

1. Male or female ≥18 years of age at the time of consent
2. Diagnosis of paroxysmal nocturnal hemoglobinuria confirmed by a history of high-sensitivity flow cytometry from prior testing
3. Treated with stable (ie, no change in dose or frequency) eculizumab therapy at the labeled dosing regimen or a higher dose and/or more frequently administered than labeled for at least 12 weeks prior to screening visit
4. Provide informed consent signed by study patient
5. Willing and able to comply with clinic/remote visits and study-related procedures
6. Able to understand and complete study-related questionnaires

7.2.2. Exclusion Criteria

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

1. History of bone marrow transplantation or receipt of an organ transplant
2. Body weight <40 kg at screening
3. Current plans for modification (initiation, discontinuation, or dose/dosing interval change) of the following background concomitant medications, as applicable, during screening and treatment period: erythropoietin, immunosuppressive drugs, corticosteroids, anti-thrombotic agents, anticoagulants, iron supplements, and folic acid
4. Any use of complement inhibitor therapy other than eculizumab in the 12 weeks prior to the screening visit or planned use during the study
5. Any 2 of the following 3 abnormalities at the screening visit (one repeat measurement is allowed during screening period):
   a. Peripheral blood absolute neutrophil count (ANC) <500/μL [<0.5 x 10^9/L] or
   b. Peripheral blood platelet count <20,000/μL or
   c. Peripheral blood reticulocyte count abnormality defined as <20,000/μL or < 1%
6. Known hypocellular bone marrow based on a history of reduced age-adjusted bone marrow cellularity and/or bone marrow cellularity ≤25%.

7. No documented meningococcal vaccination within 5 years prior to screening visit unless it is documented that vaccination has been administered during the screening period and prior to initiation of study treatment
8. Unable to take antibiotics for meningococcal prophylaxis, if required by local standard of care
9. Any active, ongoing infection or a recent infection requiring ongoing systemic treatment with antibiotics, antivirals, or antifungals within 2 weeks of screening or during the screening period
10. Documented history of systemic fungal disease or unresolved tuberculosis (TB), or evidence of active or latent tuberculosis infection (LTBI) during screening period. Assessment for active TB and LTBI should be according with local practice or guidelines, including those pertaining to risk assessment, and the use of tuberculin skin test or T-cell interferon gamma release assay
11. Positive hepatitis B surface antigen or hepatitis C virus RNA during screening.

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

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

19. Anticipated need for major surgery during the study.
20. History of cancer within the past 5 years, except for adequately treated basal cell skin cancer, squamous cell skin cancer, or in situ cervical cancer
21. Known hypersensitivity to pozelimab, cemdisiran, or to any components of the respective formulations
22. Known or documented functional or anatomic asplenia
23. Any clinically significant abnormality identified at the time of screening that in the judgment of the investigator or any sub-investigator would preclude safe completion of the study or constrain endpoints assessment such as major systemic diseases, or patients with short life expectancy
24. Considered by the investigator or any sub-investigator as inappropriate for this study for any reason, including but not limited to the following:
    - Deemed unable to meet specific protocol requirements, such as scheduled visits
    - Deemed unable to administer or tolerate long-term injections
    - Presence of any other conditions (eg, geographic, social), actual or anticipated, that the investigator feels would restrict or limit the patient's participation for the duration of the study
    - Part of a vulnerable population such as the institutionalized
25. Members of the clinical site study team and/or his/her immediate family, unless prior approval granted by the sponsor
26. Pregnant or breastfeeding women
27. Women of childbearing potential (WOCBP)* who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 52 weeks after the last dose. Highly effective contraceptive measures include:
    a. stable use of combined (estrogen- and progestogen-containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening;
    b. intrauterine device (IUD); intrauterine hormone-releasing system (IUS);
    c. bilateral tubal ligation;
    d. vasectomized partner (provided that the male vasectomized partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has obtained medical assessment of surgical success for the procedure); and/or
    e. sexual abstinence†, ‡.

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

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

†Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drugs. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

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

28. Participation in another interventional clinical study or use of any experimental therapy within 30 days before screening visit or within 5 half-lives of that investigational product, whichever is greater.
29. Patients with a history of significant multiple intolerability and/or severe allergies (including latex gloves) or patients who have had an anaphylactic reaction or significant multiple intolerability to prescription or non-prescription drugs.
30. Patients who have not been vaccinated against *Streptococcus pneumoniae* and *Haemophilus influenza* type B if recommended by current national/local vaccination guidelines. (Note that patients who were not previously vaccinated shall receive these vaccinations during screening, if recommended by current national/local vaccination guidelines.)

7.3. Premature Withdrawal from the Study

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

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

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

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

7.4. Replacement of Patients

Patients prematurely withdrawn from the study drug can be replaced, if needed, to ensure that at least 6 patients complete 32 weeks of treatment. The medical/study director, in cooperation with the study biostatistician, will decide whether or not to replace a withdrawn patient.

8. STUDY TREATMENTS

See Section 6.1 for details on treatment regimen.

8.1. Investigational and Reference Treatments

8.1.1. Pozelimab

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

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

8.1.2. Cemdisiran

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

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

8.2. Background Treatments and Risk Mitigation

Enrolled patients will be on background concomitant treatment with eculizumab at the patient's usual dose and interval until they are switched to the study drug combination.

8.2.1. Meningococcal Vaccinations

Patients will have had previous documented vaccination for meningococcus (serotypes A, C, Y, W, and serotype B if available) and should be re-vaccinated if prior immunization was more than 5 years prior to screening, or less than 5 years prior to screening if required according to current national vaccination guidelines for vaccination use with complement inhibitors or local practice.

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

8.2.2. Monitoring for Meningococcal Infection

Patients should be closely monitored for early signs and symptoms of meningococcal infection and evaluated immediately if an infection is suspected.

Patients will be provided with a patient safety card describing signs and symptoms of meningococcal infection, along with instructions in case of a potential meningococcal infection, as well as information for the non-investigator healthcare provider.

8.2.3. Oral Antibiotics for Meningococcal Infection

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

Ultimately, the decision to administer prophylaxis with oral antibiotics, the start day of administration, the duration of prophylaxis, and the choice and dosing regimen of antibiotics will be at the discretion of the investigator and should be consistent with local guidelines, unless the patient receives vaccination within 2 weeks from day 1, in which case the patient must receive antibiotic prophylaxis for a minimum of 2 weeks from the date of vaccination. Oral antibiotics will be sourced locally by the investigator or designee and reimbursed by the sponsor.

8.2.4. Risk Management of *Neisseria Gonorrhea*

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

A risk-factor assessment should be based on local practice or national guidelines. The investigator should make his/her own assessment of risk (and if needed, consultation with other healthcare provider) to determine if the patient is at risk, which would lead to further management of prevention, testing, and treatment of *N. gonorrhea*.

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

General preventive measures include abstinence and use of a condom. Additional preventive measures should be considered based on local practice or national guidelines.

8.3. Dose Modification and Study Treatment Discontinuation Rules

8.3.1. Dose Modification

Dose modification for an individual patient is not allowed, unless the patient meets the criteria for intensified treatment as described in Section 6.1.3.

8.3.2. Treatment Intensification

Patients who meet criteria for treatment intensification (Section 6.1.3) will receive a single administration of pozelimab 30 mg/kg IV on the day of initiation (can be initiated from day 57 onward) in addition to a maintenance regimen with a shortened frequency of pozelimab administration 400 mg SC Q2W along with cemdisiran 200 mg SC Q4W (±3 days) for a period of 32 weeks starting on the day of initiation.

An assessment of the patient's weight should be performed on the day of the IV pozelimab load in order to calculate the appropriate dose. The IV dose should be administered first. The SC doses should be given at least 30 minutes after completion of the IV administration.

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

In the event of an LDH increase ≥2 x ULN due to an acute complement-activating condition (ie, intercurrent infection) after day 29 in the OLTP, intensified OLTP or at any time in the optional OLEP, an IV loading dose of pozelimab 30 mg/kg IV may be given at the discretion of the investigator and in consultation with the sponsor. An assessment of the patient's weight should be performed on the day of the IV pozelimab load in order to calculate the appropriate dose . This is not considered treatment intensification. No other changes will be made to the study treatment regimen (ie, the regular dose and frequency of pozelimab and cemdisiran will proceed unchanged). Patients will continue onto the next visit of their current visit schedule.

8.3.3. Study Drug Discontinuation

Patients who permanently discontinue from study treatment either in the OLTP or the intensified OLTP should be encouraged to remain in the study. Those who agree and do not withdraw from the study will be asked to return to the clinic for all remaining study visits per the visit schedule, including safety follow-up until 52 weeks after their last dose of study treatment (Table 4).

Patients who permanently discontinue from study treatment and who opt to withdraw from the study should return for an early termination (ET) visit consisting of applicable assessments at the EOT visit for the corresponding study period, per Section 9.1.2.

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

8.3.3.1. Reasons for Permanent Discontinuation of Study Drug

Study drug dosing of an individual patient will be permanently stopped in the event of:

- Evidence of pregnancy
- Serious or severe allergic reactions considered related to pozelimab or cemdisiran
  - Please note that AEs potentially due to large DTD immune complexes are not considered as an automatic reason for permanent treatment discontinuation. The investigator should review the particular case and consult with the medical monitor prior to deciding on permanent treatment discontinuation.
- Liver impairment as evidence by 1 or more of the following criteria and no other reason can be found to explain the following lab abnormalities, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; PNH-related complication; or another drug capable of causing the observed injury:
  - ALT or AST >8 × ULN, or
  - ALT or AST >5 × ULN for more than 2 weeks, or
  - ALT or AST >3 × ULN and total bilirubin >2 × ULN (or international normalized ratio [INR] >1.5)
- Patient withdrawal of consent
- Patient noncompliance as determined by the investigator (eg, not complying with protocol-required visits, assessments, and/or dosing instructions)
- Investigator's clinical judgment that it is in the best interest of the patient

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

8.3.3.2. Reasons for Temporary Discontinuation of Study Drug

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

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

Note regarding infection with SARS-CoV-2: If, in the investigator's medical judgement, it is in the patient's best interest to interrupt treatment with pozelimab and cemdisiran until the patient recovers from SARS-CoV-2, then it is advisable that 2 repeat COVID-19 PCR tests, or equivalent tests depending on regional recommendations, be conducted to confirm the patient is negative for SARS-CoV-2. If COVID-19 PCR testing is not feasible, it is advised that at least 3 months have transpired since the initial diagnosis. The investigator may resume treatment with pozelimab and cemdisiran under close clinical monitoring if the investigator feels that the benefit of resuming therapy outweighs the risks and the patient has no new contraindications to treatment. Input from the sponsor regarding the permissible duration of interruption to allow resumption of treatment may be sought.

8.4. Management of Acute Reactions

8.4.1. Acute Intravenous Infusion Reactions

During intravenous infusion of pozelimab, due to concern of potential reactions, patients should be observed for at least 30 minutes after the infusion.

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

8.4.1.1. Interruption of the Intravenous Infusion

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

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

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

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

8.4.1.2. Termination of the Intravenous Infusion

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

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

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

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

8.4.2. Acute Injection Reactions

8.4.2.1. Systemic Injection Reactions

Patients should be observed for at least 30 minutes after the first SC injection. Additionally, emergency equipment and medication for the treatment of systemic reactions must be available at the clinical site for immediate use. All injection reactions must be reported as AEs (as defined in Section 10.2.1) and graded using the grading scales as instructed in Section 10.2.5.

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

8.4.2.2. Local Injection Site Reactions

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

8.5. Method of Treatment Assignment

Not applicable as this is a single-arm study.

8.6. Blinding

Not applicable as this is an open-label study.

8.7. Treatment Logistics and Accountability

8.7.1. Packaging, Labeling, and Storage

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

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

8.7.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2ºC to 8ºC to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be destroyed/returned to the sponsor or designee.

8.7.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication

- Dispensed to each patient
- Returned from each patient (if applicable), and
- Disposed of at the site or returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

8.7.4. Treatment Compliance

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

8.8. Concomitant Medications

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

8.8.1. Prohibited Medications and Procedures

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

- 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 transition of switch to combination treatment
- Other investigational treatments during the course of the study
- In addition, the patient should not consume any alcohol and, if possible, refrain from strenuous exercise within 24 hours prior to each clinic visit when blood is drawn

8.8.2. Permitted Medications and Procedures

The following medications and procedures will be permitted, under the following conditions:

- Any medication required to treat an AE, including systemic corticosteroids, at the discretion of the investigator
- Meningococcal vaccination, as described in Section 8.2.1
- Oral antibiotic prophylaxis as recommended, as described in Section 8.2.3
- Oral contraceptives and hormone-replacement therapy may continue
- Acetaminophen/paracetamol, aspirin, or ibuprofen at the recommended dose per the local prescribing information
- Concomitant administration of erythropoietin, immunosuppressive drugs, corticosteroids, anti-thrombotic agents, anticoagulants, iron supplements, and folic acid are permitted and if possible, should be kept constant throughout the study. Any changes to these concomitant medications will be at the discretion of the investigator and consistent with practice in the prior 26 weeks from enrollment into this study, when possible. Any other medications may undergo dose adjustment or discontinuation at the discretion of the investigator.
- Any other medication required for the treatment of the patient's background medical conditions

8.9. Post-Trial Access to Study Treatment

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

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. Schedule of Events

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

Study assessments and procedures are presented by visit in Table 1 (OLTP), Table 2 (treatment period for patients who require intensified therapy in the OLTP), Table 3 (optional OLEP), and Table 4 (post-treatment safety follow-up period). Study procedures, including sample collection for laboratory analysis, may be performed at the study clinic or at another location that is more convenient for the patient (including home visits), if this option is available and with sponsor approval.

Table 1: Schedule of Events 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	
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---------->												

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
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
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

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
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 2: 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
Electrocardiogram											X		X
Adverse events	<-----							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
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 3: 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 4: 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		

9.1.1. Footnotes for the Schedule of Events Tables

9.1.1.1. Footnotes for Table 1 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.

9.1.1.2. Footnotes for Table 2 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.

9.1.1.3. Footnotes for Table 3 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. 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).

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

1. 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 (eg, 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.
2. 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.
3. Daily oral antibiotic prophylaxis against *N. meningitidis* is recommended until 52 weeks after discontinuation of study treatment.

9.1.2. Early Termination Visit

During the OLTP, patients who permanently discontinue from study treatment and who opt to withdraw from the study should return for an ET visit consisting of the assessments as described in the week 32 (EOT) visit in Table 1 and Table 2 (for patients on intensified therapy).

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

9.1.3. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal/uninterpretable laboratory results, for follow-up of AEs, to evaluate events of breakthrough hemolysis (Section 6.1.2), to provide intensified treatment (Section 6.1.3), or for any other reason, as warranted. In the event of suspected treatment-related SAEs, such as anaphylaxis or hypersensitivity, additional drug concentration and immunogenicity samples may be collected at or near the onset and the resolution of the event.

9.2. Study Procedures

9.2.1. Procedures Performed Only at the Screening/Baseline Visit

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

- Obtain informed consent (including optional sub-studies)
- Review inclusion/exclusion criteria
- 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. Ongoing PNH symptoms and signs will also be collected.
- Record prior medications (within 12 weeks prior to screening), and detailed eculizumab administration history (past 26 weeks)
- Record demographics
- Measure height
- Administration of vaccination for *N. meningitidis* or documentation of meningococcal vaccination within the past 5 years (or less than 5 years if required according to national vaccination guidelines for vaccination use with complement inhibitors or local practice)
- Vaccination against *Streptococcus pneumoniae* and *Haemophilus influenza* type B (if needed for eligibility requirement). Vaccinations should be given according to the current national/local guidelines and may be reimbursed by the sponsor.
- Titers to measure *N. meningitidis* (only if required per local practice/regulations)
- 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.
- Risk factor assessment for *N. gonorrhea* is recommended, and counseling is advised for at-risk patients
- Provide patient safety card for meningococcal infection and review instructions. This card will be provided to the patient at baseline or any other visit when needed.
- Sample to assess FSH (to determine postmenopausal status, if applicable)
- Sample for hepatitis B and C

At the discretion of the investigator, additional visits during the screening period may be scheduled as needed to complete screening procedures. Patients may be rescreened up to 2 times after discussion between the investigator and the sponsor.

9.2.2. Efficacy Procedures

9.2.2.1. Laboratory Assessments of Efficacy

Laboratory assessments of efficacy will be performed at scheduled visits according to Table 1 (OLTP),Table 2 (for patients on intensified treatment), and Table 3 (optional OLEP).

9.2.2.1.1. Lactate Dehydrogenase

Samples for LDH testing are collected as part of the blood chemistry panel (Section 9.2.3.5) and will be collected prior to study drug administration at scheduled visits. Levels of LDH in serum will be analyzed by a central laboratory.

Care must be taken with the collection of LDH as it is the primary endpoint in the study. During blood collection, handling, and processing, the same methodology will be applied across study visits, as best as possible. **Every precaution must be taken to avoid hemolysis.** Detailed instructions for collecting samples for LDH are provided in the study-related documents provided to the study site and should be reviewed prior to each collection.

9.2.2.1.2. Hemoglobin

Samples for hemoglobin testing are collected as part of the hematology panel (Section 9.2.3.5) and will be collected prior to study drug administration at scheduled visits.

9.2.2.1.3. Total Complement Hemolytic Activity

Samples for CH50 testing will be collected prior to study drug administration at scheduled visits.

9.2.2.2. Clinical Outcome Assessments

The following clinical outcome assessments are self-reported and will be completed by the patient at time points according to Table 1 and Table 2 (for patients on intensified treatment) and Table 3 (optional OLEP).

9.2.2.2.1. Functional Assessment of Chronic Illness Therapy-Fatigue

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

9.2.2.2.2. European Organization for the Research and Treatment of Cancer: Quality of Life of Cancer Patients Questionnaire-30

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

9.2.2.2.3. Treatment Satisfaction Questionnaire for Medication

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

9.2.2.2.4. PNH Symptom-Specific Questionnaire

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

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

9.2.2.2.5. Patient Global Impression of Severity/Patient Global Impression of Change

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

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

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

9.2.3. Safety Procedures

The following safety procedures will be measured at visits and time points according Table 1, Table 2 (for patients on intensified treatment), Table 3 (optional OLEP), and Table 4 (safety follow-up period).

9.2.3.1. Body-Weight

Body weight will be recorded at scheduled visits. Body weight should be obtained with the patient wearing undergarments or very light clothing and no shoes. If possible, the same type/model of scale should be used throughout the study.

9.2.3.2. Vital Signs

Vital signs (temperature, sitting blood pressure, and pulse) will be collected predose at scheduled visits.

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

9.2.3.3. Physical Examination

A physical examination will be performed at scheduled visits. Each physical examination will include an evaluation of the head and neck, lungs, heart, abdomen, extremities, and skin. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

9.2.3.4. Electrocardiogram

A standard 12-lead ECG will be performed locally at scheduled visits. Electrocardiograms should be performed before blood is drawn during visits requiring blood draws.

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

The ECG will be interpreted locally by the investigator. Any new and/or clinically significant changes in ECG parameters should be immediately rechecked for confirmation before making any decision for the concerned patient.

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

9.2.3.5. Laboratory Testing (Safety and Other)

Samples for laboratory testing will be collected at scheduled visits. The coagulation blood sample must always be collected first, followed by the blood chemistry sample.

During blood collection, handling, and processing, the same methodology will be applied across study visits, as best as possible, to preserve the quality of the sample and avoid hemolysis (Section 9.2.2.1.1). Detailed instructions for blood sample collection, including the sequence in which blood draws must be performed, are in the laboratory manual provided to study sites.

Unscheduled visits may be scheduled to collect blood samples as part of safety monitoring (Section 9.1.3).

Hematology, chemistry, and urinalysis samples are planned to be analyzed by a central laboratory whenever possible. A local laboratory may be acceptable in special circumstances (eg, for eligibility) after discussion and agreement from the sponsor. Pregnancy testing may be performed at a central or a local laboratory.

Other testing (eg, total C5, CH50, AH50) will be done by a specialized laboratory as outlined in study-related documents provided to the site.

Blood Chemistry

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

* Obtain total, direct, and indirect bilirubin
** In addition, the estimated glomerular filtration rate will be calculated with the CKD-EPI equation (Levey, 2009)

Hematology

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

Urinalysis*

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

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

Other Laboratory Tests

Other laboratory tests include:

- Coagulation panel: prothrombin time and activated partial thromboplastin time (aPTT)
- Hepatitis B and C testing
- Pregnancy testing (WOCBP only): serum human chorionic gonadotrophin pregnancy testing at screening, and urine pregnancy testing at all subsequent scheduled visits. Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.
- Unscheduled blood collection for drug hypersensitivity events including suspicion of an AE potentially due to large DTD immune complexes. At minimum to include: CBC, ESR, CRP, chemistry, C3, C4, and urinalysis (including microscopic evaluation).
- Unscheduled blood collection for suspected breakthrough hemolysis events should include, at a minimum, CBC, reticulocyte count, chemistry, coagulation parameters, D-dimer, total C5, CH50, ADA (against pozelimab), and drug concentrations of pozelimab and eculizumab, as applicable.
- Titers to measure *N. meningitidis* (only if required per local practice/regulations)
- Drug concentration measurements (Section 9.2.4)
- Immunogenicity measurements (Section 9.2.5)
- Pharmacodynamic and exploratory biomarkers (Section 9.2.6)
- Optional: pharmacogenomic and future biomarker research (Section 9.2.7 and Section 9.2.8)

Abnormal Laboratory Values and Laboratory Adverse Events

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

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

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

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

9.2.3.6. Blood Transfusion

Transfusions with RBCs during the study should proceed according to the predefined criteria in Section 6.1.4. Any blood transfusion will be captured in the transfusion record CRF.

9.2.3.7. Adverse Events

At every visit, AEs will be collected and assessed as described in Section 10.

9.2.4. Drug Concentration and Measurements

Detailed instructions for blood sample collection are included in the laboratory manual provided to the study site. The exact sampling time must be recorded, as allowed per local regulation.

Any unused samples may be used for future exploratory research if the patient has provided consent for optional research, and as allowed per local regulation.

9.2.4.1. Concentrations of Total Pozelimab, Eculizumab, and Total C5

Samples to measure the concentration of total pozelimab, eculizumab, and total C5 will be collected at time points specified in Table 1 (OLTP), Table 2 (for patients on intensified treatment), and Table 3 (optional OLEP).

On day 29, obtain blood samples prior to IV administration of pozelimab and within 15 minutes after the end of the IV infusion. At other visits, obtain blood samples prior to any SC study drug administration.

9.2.4.2. Concentrations of Cemdisiran and Cemdisiran Metabolites

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

9.2.5. Immunogenicity Measurements and Samples

Blood samples for immunogenicity assessment will be collected for pozelimab and for cemdisiran prior to any study drug administration at time points listed in Table 1 (OLTP), Table 2 (for patients on intensified treatment), and Table 3 (optional OLEP).

9.2.6. Pharmacodynamic and Exploratory Biomarker Procedures

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

- CH50 (serum) is the principal PD marker for the study and is also an efficacy measure in this study.
- Parameters of intravascular hemolysis: ie, haptoglobin, reticulocyte count, and bilirubin
- Free hemoglobin
- AH50 (serum)
- Complement activation markers: ie, sC5b-9
- PNH clone size: ie, PNH erythrocytes and granulocytes

Biomarker measurements will be performed in the specified matrices to determine effects of pozelimab and cemdisiran on relevant physiological and pathogenic processes. The list may be altered or expanded, as it is recognized that more relevant or novel biomarkers may be discovered during the process of this study. The biomarkers studied will be ones believed to be relevant to the pathophysiology of PNH, target engagement, pozelimab and cemdisiran mechanism of action, and possible toxicities. Any unused or leftover samples, collected for any purpose from this study, may be used for exploratory research.

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

9.2.7. Future Biomedical Research (Optional)

Patients who agree to participate in the future biomedical research (FBR) sub-study will be required to consent to this optional sub-study before samples are banked for FBR. Additional samples will be collected for FBR. Residual biomarker samples for study-related research, as well as unused drug concentration and immunogenicity samples, will be stored for up to 15 years after the final date of the database lock (or for a shorter time period if required per regional laws and regulations). The samples may be utilized for FBR that may or may not be directly related to the study, including being used as reference samples and assay development or validation. The results of these FBR analyses will not be presented in the CSR.

9.2.8. Pharmacogenomic Analysis (Optional)

Patients who agree to participate in the genomics sub-study will be required to consent to this optional sub-study before collection of the samples. Whole blood samples for DNA extraction should be collected on day 1/baseline (predose), but can be collected at a later study visit. Whole blood samples for RNA extraction will be collected at time points according to Table 1 (OLTP) and Table 3 (optional OLEP). DNA and RNA samples will be collected for pharmacogenomics analyses to understand the genetic determinants of efficacy and safety associated with the treatments in this study and the molecular basis of PNH and related diseases. These samples will be single-coded as defined by the International Council on Harmonisation (ICH) guideline E15. Samples will be stored for up to 15 years after the final date of the database lock (or for a shorter time period if required per regional laws and regulations). If there are specific site or country requirements involving the pharmacogenomic analyses, which the sponsor is unable to comply with, samples will not be collected at those sites.

The purpose of the pharmacogenomic analyses is to identify genomic associations with clinical or biomarker response to pozelimab and/or cemdisiran, other PNH clinical outcome measures, and possible AEs. In addition, associations between genomic variants and prognosis or progression of PNH, as well as related complement-mediated diseases, may also be studied. These data may be used or combined with data collected from other studies to identify and validate genomic markers related to the study drug, target pathway, or PNH and related diseases.

Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Other methods, including whole-exome sequencing, whole-genome sequencing, DNA copy number variation, and transcriptome sequencing (or other methods for quantitating RNA expression) may also be performed. The list of methods may be expanded to include novel methodology that may be developed during the course of this study or sample storage period. Results from the genomic analyses will not be reported in the CSR.

10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

10.1.1. General Guidelines

The investigator (or designee) must promptly record all adverse events occurring during the study data collection, from the time of signing the ICF to the end of the study. Medical conditions that existed or were diagnosed prior to the signing of the Informed Consent will be recorded as part of medical history. Abnormal laboratory values and vital signs observed at the time of Informed Consent should also be recorded as medical history. Any subsequent worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug should also be recorded as an AE.

At each visit, the investigator will determine whether any AEs have occurred by evaluating the patient. Adverse events may be directly observed, reported spontaneously by the patient, or by questioning the patient at each study visit. Patients should be questioned in a general way, without asking about the occurrence of any specific symptoms. The investigator must assess all AEs to

determine seriousness, severity, and causality, in accordance with the definitions in Section 10.2. The investigator's assessment must be clearly documented in the site's source documentation with the investigator's signature. The investigator should follow up on SAEs (and AESIs) until they have resolved or are considered clinically stable; AEs should be followed until they are resolved or until last study visit, whichever comes first.

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

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

For events that are serious due to resulting in hospitalization, the reason for hospitalization must be reported as the serious adverse event (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the Informed Consent Form) procedures, treatments requiring hospitalization for pre-existing conditions that do not worsen in severity, and admission for palliative or social care should not be reported as SAEs (see Section 10.2 for Definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any SAE that may occur subsequent to the reporting period (end of the study) that the investigator assesses as related to study drug should also be reported.

All AEs, serious adverse events (SAEs), AESIs, and pregnancy reports are to be reported according to the procedures in Section 10.1.3.

10.1.2. Reporting Procedure

All events (serious and non-serious) must be reported with investigator's assessment of the event's seriousness, severity, and causality to the study drug. For SAEs and AESIs, a detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided on the AE CRF. Specific or estimated dates of event onset, treatment, and resolution should be included, when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed and include the results if available. Information not available at the time of the initial report must be documented in a follow-up report. Source documents (including hospital or medical records, diagnostic reports, etc) will be summarized in the narrative on the AE CRF, and retained at the study center and available upon request.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

10.1.3. Events that Require Expedited Reporting to Sponsor

The following events require reporting to the sponsor (or designee) within 24 hours of learning of the event:

- **SAEs** (see definition in Section 10.2.2).
- **Selected Adverse Events of Special Interest** (AESI [see definition in Section 10.2.3]; serious and nonserious**:** adverse events of special interest for this study include the following:
  - Suspected Neisseria infection
  - Moderate or severe infusion reactions
  - Any MAVE: Includes thrombophlebitis/deep vein thrombosis, pulmonary embolus, myocardial infarction, unstable angina, renal vein or artery thrombosis, acute peripheral vascular occlusion, hepatic vein thrombosis, portal vein thrombosis mesenteric/visceral vein thrombosis or infarction, mesenteric/visceral arterial thrombosis or infarction, transient ischemic attack, cerebral arterial occlusion/cerebrovascular accident, cerebral venous occlusion, gangrene(nontraumatic; non-diabetic), amputation (nontraumatic; non-diabetic)
  - 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

    Note: This AESI must be reported to the sponsor within 24 hours once the investigator confirms the abnormal laboratory value.
- **Pregnancy:** although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female patient during the study or within 52 weeks of the last dose of study drug. Any complication of pregnancy affecting a female study patient and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.
- **Symptomatic overdose of study drug:** accidental or intentional overdose of at least 2 times the intended dose of study drug within the intended therapeutic window, if associated with an AE.

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

Although these AESIs do not require expedited reporting to the sponsor, the following events are of interest and will involve specific data collection to characterize better:

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

10.2. Definitions

10.2.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

10.2.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger)
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as a hospital admission (any duration) or an emergency room visit for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions)
- Is a **congenital anomaly/birth defect**
- Is an **important medical event**. Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

Criteria for reporting SAEs must be followed for these events.

10.2.3. Adverse Events of Special Interest

An adverse event of special interest (AESI; serious or non-serious) is one of scientific and medical interest specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Adverse events of special interest for this study are listed in Section 10.1.3 and Section 10.1.4.

10.2.4. Infusion Reactions

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

10.2.5. Severity

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

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

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

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

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

Infusion Reactions

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

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

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

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

Injection Site Reactions

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

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

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

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

10.2.6. Causality

The investigator must provide causality assessment as to whether or not there is a reasonable possibility that the drug caused the adverse event, based on evidence or facts, his/her clinical judgment, and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

The following factors should be considered when assessing causality:

- Temporal relationship: time to onset versus time drug was administered
- Nature of the reactions: immediate versus long term
- Clinical and pathological features of the events
- Existing information about the drug and same class of drugs
- Concomitant medications
- Underlying and concurrent illnesses
- Response to dechallenge (drug discontinuation) or dose reduction
- Response to rechallenge (re-introduction of the drug) or dose increase, when applicable
- Patient's medical and social history

Causality to the study drug (including study drug administration):

- Related:
  - The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.

  or

  - The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its class of drugs, or is predicted by known pharmacology.
- Not Related:
  - The AE does not follow a reasonable sequence from study drug administration, or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

Causality to the study conduct (protocol-specified procedure):

- Related:
  - The AE follows a reasonable temporal sequence from a protocol-specified procedure, and cannot be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.
- Not Related:
  - The AE does not follow a reasonable sequence from a protocol-specified procedure, or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

10.3. Safety Monitoring

The investigator will monitor the safety of the study patient at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The medical/study director will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, GPS; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic, cumulative aggregate basis.

10.4. Notifying Health Authorities, Ethics Committee, and Investigators

During the study, the sponsor and/or the contract research organization (CRO) will inform health authorities, the Ethics Committee (EC), and the participating investigators of any SUSARs (Suspected Unexpected Serious Adverse Reactions) occurring in other study centers or other studies of the active study drug (pozelimab and cemdisiran), as appropriate per local reporting requirements. In addition, the sponsor and/or CRO will comply with any additional local safety reporting requirements.

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

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

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

11. STATISTICAL PLAN

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

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

11.1. Statistical Hypothesis

No formal statistical hypothesis is to be tested.

11.2. Justification of Sample Size

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.

Up to 12 patients with PNH will be enrolled to describe and explore the incidence and severity of TEAEs through day 225 of the OLTP.

11.3. Analysis Sets

11.3.1. Efficacy Analysis Sets

The full analysis set (FAS) includes all enrolled patients who received any amount of study drugs and have at least 1 post-baseline 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 assessment in the OLEP.

11.3.2. Safety Analysis Sets

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.

11.3.3. Pharmacokinetic Analysis Set

The PK analysis population 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.

11.3.4. Immunogenicity Analysis Set

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

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

11.4. Statistical Methods

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

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

11.4.1. Patient Disposition

The following will be provided:

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

11.4.2. Demography and Baseline Characteristics

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

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

11.4.3. Efficacy Analyses

11.4.3.1. Secondary Efficacy Analysis

There are no primary efficacy endpoints in this study.

For secondary efficacy endpoints that are defined by the change from baseline to a time point in a variable, the analysis set will consist of all treated patients who have a non-missing baseline measurement of the variable. Secondary endpoints include:

- 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 EOT period (as defined by the mean of the LDH values at days 197 and 225 in the OLTP)
- Percent change in LDH from pre-treatment to day 29
- Change in CH50 levels from baseline to day 225, inclusive
- Change in hemoglobin levels from baseline to day 225, inclusive
- Change from baseline in concentration of total C5 assessed throughout the study
- Change in fatigue as measured by the FACIT-Fatigue Scale from baseline to day 225, inclusive
- Change from baseline to day 225 in GHS and PF scores on the EORTC QLQ-C30

To assess the above secondary endpoints, summary statistics will be presented by visit for the percent change from baseline (for LDH) and change from baseline (for the remaining variables) as described above, along with 95% confidence intervals. In addition, summary statistics will be presented for values at all visits up to day 225.

These summaries will be repeated for any of the following subgroups that have at least 3 patients:

- Patients who switched from eculizumab administration at the labeled dosing regimen
- Patients who switched from eculizumab at a dose higher than labeled and/or more frequently than labeled

For binary secondary endpoints, all treated patients will be analyzed. The binary secondary endpoints are as follows:

- Proportion of patients who maintain adequate control of hemolysis, defined as LDH ≤1.5 x ULN from post-baseline (on day 1) through day 225, and from day 57 through day 225, inclusive (a patient will be treated as not achieving adequate control if he/she is missing >25% of scheduled LDH measurements, missing any 2 consecutive LDH measurements, has received intensified treatment, or has permanently discontinued treatment. For other patients, LDH measurements will be assessed by non-missing LDH measurements).
- Proportion of patients with adequate control of hemolysis at each visit from post-baseline (on day 1) through day 225, inclusive
- 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
- Proportion of patients with breakthrough hemolysis from baseline through day 225 and from day 29 through day 225, inclusive (non-responder imputation will be applied for patients who receive intensified treatment).
- Proportion of patients with hemoglobin stabilization (defined as patients who do not receive an RBC transfusion and have no decrease in hemoglobin level ≥ 2 g/dL) from baseline through day 225, and from day 29 through day 225, inclusive.
- Proportion of patients who are transfusion-free (defined as not requiring an RBC transfusion as per protocol algorithm) from baseline through day 225, and from day 29 through day 225, inclusive (ie, transfusion avoidance).

For these endpoints, observed proportions and 95% confidence intervals using the Clopper-Pearson exact method will be reported.

For the rate and number of units of RBCs transfused from baseline through day 225, and from day 29 through day 225, inclusive, the analysis set will consist of all treated patients who never received the intensified regimen during treatment. The rate of units of transfusion for a patient will be calculated based on the duration of treatment exposure of the patient. Means and 95% confidence intervals will be reported for all patients and for the 2 patient subgroups named above, if applicable.

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

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

11.4.4. Control of Multiplicity

Not applicable.

11.4.5. Safety Analysis

The primary endpoint in this study is the incidence and severity of TEAEs through 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. Additional safety analysis will be provided as a supplement once all treatment-discontinued patients complete their safety follow-up.

11.4.5.1. Adverse Events

Definitions

For safety variables, 3 observation periods are defined:

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

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

Analysis

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). Coding will be to lowest-level terms. The preferred term (PT), and the primary system organ class (SOC) will be listed.

Summaries of all TEAEs will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 10.2.5), presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT
- Treatment-emergent AESIs (defined with a PT or a prespecified grouping)

Deaths and other SAEs will be listed and summarized.

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

11.4.5.2. Other Safety

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.

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 all patients and separately for patients in whom the PCSV criterion was normal or missing at baseline.

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

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

ECG

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 point.

Listings will be provided with flags indicating PCSVs.

11.4.5.3. Treatment Exposure

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)
- (Date of last administration of study drug - date of the first administration of study drug for the study period) + 14 days (for Q2W)

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

11.4.5.4. Treatment Compliance

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

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

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

11.4.6. Pharmacokinetics

11.4.6.1. Analysis of Drug Concentration Data

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

No formal statistical hypothesis testing will be performed.

11.4.7. Analysis of Immunogenicity Data

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

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

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

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

11.4.8. Analysis of Pharmacodynamic and Exploratory Biomarker Data

Analysis of CH50 is described in Section 11.4.3.1. Analysis of other biomarker data is defined in the SAP. The results of exploratory biomarkers might not be presented in the CSR.

11.5. 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. Data will be summarized descriptively.

11.6. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in Section 15.1.

12. QUALITY CONTROL AND QUALITY ASSURANCE

In accordance with ICH E6, the sponsor is responsible for quality assurance to ensure that the study is conducted and the data generated, recorded, and reported in compliance with the protocol, GCP, and any applicable regulatory requirement(s). The planned quality assurance and quality control procedures for the study are described in this section.

12.1. Data Management and Electronic Systems

12.1.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation [quality-checking], cleaning, correcting, releasing) will be maintained and stored at Regeneron (sponsor).

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

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

12.1.2. Electronic Systems

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

- IVRS/IWRS system – enrollment, study drug supply
- EDC system – data capture – Medidata Rave
- Statistical Analysis System (SAS) – statistical review and analysis
- Pharmacovigilance safety database
- eCOA system – capture COA

12.2. Study Monitoring

12.2.1. Monitoring of Study Sites

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

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements.

12.2.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents). The site is responsible to ensure quality within their records and systems and is accountable for ensuring that all source data and CRF data are timely, accurate, and complete.

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

12.2.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on eCRFs within the EDC system by trained site personnel. All required CRFs must be completed for each and every patient enrolled in the study. The investigator must ensure the accuracy, completeness, and timeliness of the data reported to the sponsor in the CRFs. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each patient CRF casebook is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

Corrections to the CRF will be entered in the CRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the EDC system. For corrections made via data queries, a reason for any alteration must be provided.

12.3. Audits and Inspections

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

12.4. Study Documentation

12.4.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the CRF/eCRF must be signed electronically by the investigator. This signed declaration accompanies each set of patient final CRFs/eCRFs that will be provided to the sponsor.

12.4.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer, if a longer period is required by relevant regulatory authorities. The investigator must obtain written approval from the sponsor before discarding or destroying any essential study documents during the retention period following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor (written notification) and the relevant records will be transferred to a mutually agreed-upon destination.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

13.2. Informed Consent

The principles of informed consent are described in ICH guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate EC. A copy of the EC-approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in language that he/she can understand. The ICF should be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Patients who can understand but who can neither write nor read will have the ICF read to them in the presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the patient.

If new safety information results in significant changes in the risk/benefit assessment, or if there are significant changes to the study procedures, the ICF must be reviewed and updated appropriately. All study patients must be informed of the new information and provide their written consent if they wish to continue in the study. The original, signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient.

13.3. Patients Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study patient will be maintained. Patients should be identified by a patient identification number only, on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF) must be kept in strict confidence.

The patient's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

13.4. Institutional Review Board

An appropriately constituted EC, as described in ICH guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the patients (eg, advertising) before any patient may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patient, in which case the EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the EC should be informed of any event likely to affect the safety of patients or the continued conduct of the clinical study.

A copy of the EC approval letter with a current list of the EC members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

13.5. Clinical Study Data Transparency

Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations. Treatment codes will be disseminated to each investigation site thereafter.

14. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design of the protocol or ICF without an EC-approved amendment. Where required per local legislation, regulatory authority approval will also be sought.

15. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

15.1. Premature Termination of the Study

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

15.2. Close-out of a Site

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

Investigator's Decision

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

Sponsor's Decision

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

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

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

16. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

17. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

18. PUBLICATION POLICY

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

19. REFERENCES

Al-Ani F, Chin-Yee I, Lazo-Langner A. Eculizumab in the management of paroxysmal nocturnal hemoglobinuria: patient selection and special considerations. Ther Clin Risk Manag 2016; 12:1161-70.

Atkinson MJ, Kumar R, Cappelleri JC, Hass SL. Hierarchical construct validity of the treatment satisfaction questionnaire for medication (TSQM version II) among outpatient pharmacy consumers. Value Health 2005; 8 Suppl 1:S9-S24.

Atkinson MJ, Sinha A, Hass SL, Colman SS, Kumar RN, Brod M, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health Qual Life Outcomes 2004; 2:12.

Brodsky RA. Eculizumab: another breakthrough. Blood 2017; 129(8):922-3.

Brodsky RA. How I treat paroxysmal nocturnal hemoglobinuria. Blood 2009; 113(26):6522-7.

Brodsky RA. Paroxysmal nocturnal hemoglobinuria. Blood 2014; 124(18):2804-11.

Brodsky RA, Young NS, Antonioli E, Risitano AM, Schrezenmeier H, Schubert J, et al. Multicenter phase 3 study of the complement inhibitor eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria. Blood 2008; 111(4):1840-7.

Cocks K, Cohen D, Wisloff F, Sezer O, Lee S, Hippe E, et al. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-MY20) in assessing the quality of life of patients with multiple myeloma. Eur J Cancer 2007; 43(11):1670-8.

CTFG. 2020. Recommendations related to contraception and pregnancy testing in clinical trials. Vol. v1.1. Clinical Trials Facilitation and Coordination Group.

FDA. 2009. Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.

Figueroa JE, Densen P. Infectious diseases associated with complement deficiencies. Clin Microbiol Rev 1991; 4(3):359-95.

Gaston MH, Verter JI, Woods G, Pegelow C, Kelleher J, Presbury G, et al. Prophylaxis with oral penicillin in children with sickle cell anemia. A randomized trial. N Engl J Med 1986; 314(25):1593-9.

Griffin M, Munir T. Management of thrombosis in paroxysmal nocturnal hemoglobinuria: a clinician's guide. Ther Adv Hematol 2017; 8(3):119-26.

Groth M, Singer S, Niedeggen C, Petermann-Meyer A, Roth A, Schrezenmeier H, et al. Development of a disease-specific quality of life questionnaire for patients with aplastic anemia and/or paroxysmal nocturnal hemoglobinuria (QLQ-AA/PNH)-report on phases I and II. Ann Hematol 2017; 96(2):171-81.

Hill A, Kelly RJ, Hillmen P. Thrombosis in paroxysmal nocturnal hemoglobinuria. Blood 2013; 121(25):4985-96; quiz 5105.

Hillmen P, Hall C, Marsh JC, Elebute M, Bombara MP, Petro BE, et al. Effect of eculizumab on hemolysis and transfusion requirements in patients with paroxysmal nocturnal hemoglobinuria. N Engl J Med 2004; 350(6):552-9.

Hillmen P, Muus P, Roth A, Elebute MO, Risitano AM, Schrezenmeier H, et al. Long-term safety and efficacy of sustained eculizumab treatment in patients with paroxysmal nocturnal haemoglobinuria. Br J Haematol 2013; 162(1):62-73.

Hillmen P, Young NS, Schubert J, Brodsky RA, Socie G, Muus P, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med 2006; 355(12):1233-43.

Lee JW, Sicre de Fontbrune F, Wong Lee Lee L, Pessoa V, Gualandro S, Fureder W, et al. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. Blood 2019; 133(6):530-9.

Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; 150(9):604-12.

Luzzatto L, Risitano AM. Advances in understanding the pathogenesis of acquired aplastic anaemia. Br J Haematol 2018; 182(6):758-76.

McNamara LA, Topaz N, Wang X, Hariri S, Fox L, MacNeil JR. High Risk for Invasive Meningococcal Disease Among Patients Receiving Eculizumab (Soliris) Despite Receipt of Meningococcal Vaccine. MMWR Morb Mortal Wkly Rep 2017; 66(27):734-7.

Nakayama H, Usuki K, Echizen H, Ogawa R, Orii T. Eculizumab Dosing Intervals Longer than 17 Days May Be Associated with Greater Risk of Breakthrough Hemolysis in Patients with Paroxysmal Nocturnal Hemoglobinuria. Biol Pharm Bull 2016; 39(2):285-8.

NHS England. 2013. B05/S(HSS)/a. 2013/14 NHS Standard Contract for Paroxysmal Nocturnal Haemoglobinuria Service (Adults and Adolescents).

Nishimura J, Yamamoto M, Hayashi S, Ohyashiki K, Ando K, Brodsky AL, et al. Genetic variants in C5 and poor response to eculizumab. N Engl J Med 2014; 370(7):632-9.

Patrick DL, Burke LB, Gwaltney CJ, Leidy NK, Martin ML, Molsen E, et al. Content validity--establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO Good Research Practices Task Force report: part 2--assessing respondent understanding. Value Health 2011; 14(8):978-88.

Peffault de Latour R, Fremeaux-Bacchi V, Porcher R, Xhaard A, Rosain J, Castaneda DC, et al. Assessing complement blockade in patients with paroxysmal nocturnal hemoglobinuria receiving eculizumab. Blood 2015; 125(5):775-83.

Platonov AE, Shipulin GA, Shipulina OJ, Vershinina IV, Densen P. Heterozygous C8beta complement deficiency does not predispose to meningococcal disease. Clin Exp Immunol 1997; 108(3):497-9.

Preis M, Lowrey CH. Laboratory tests for paroxysmal nocturnal hemoglobinuria. Am J Hematol 2014; 89(3):339-41.

Röth A, Rottinghaus ST, Hill A, Bachman ES, Kim JS, Schrezenmeier H, et al. Ravulizumab (ALXN1210) in patients with paroxysmal nocturnal hemoglobinuria: results of 2 phase 1b/2 studies. Blood Adv 2018; 2(17):2176-85.

Rother RP, Bell L, Hillmen P, Gladwin MT. The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin: a novel mechanism of human disease. JAMA 2005; 293(13):1653-62.

Sahin F, Akay OM, Ayer M, Dal MS, Ertop S, Ilhan O, et al. Pesg PNH diagnosis, follow-up and treatment guidelines. Am J Blood Res 2016; 6(2):19-27.

Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Jr., Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006; 117(2):391-7.

Sheridan D, Yu ZX, Zhang Y, Patel R, Sun F, Lasaro MA, et al. Design and preclinical characterization of ALXN1210: A novel anti-C5 antibody with extended duration of action. PLoS One 2018; 13(4):e0195909.

Soliris®. 2021. Prescribing information for eculizumab. Alexion Pharmaceuticals, Inc.

Stead ML, Brown JM, Velikova G, Kaasa S, Wisloff F, Child JA, et al. Development of an EORTC questionnaire module to be used in health-related quality-of-life assessment for patients with multiple myeloma. European Organization for Research and Treatment of Cancer Study Group on Quality of Life. Br J Haematol 1999; 104(3):605-11.

Wedzicha JA. Antibiotics at COPD exacerbations: the debate continues. Thorax 2008; 63(11):940-2.

Weitz I, Meyers G, Lamy T, Cahn JY, Uranga MT, Garcia Vela JA, et al. Cross-sectional validation study of patient-reported outcomes in patients with paroxysmal nocturnal haemoglobinuria. Intern Med J 2013; 43(3):298-307.

20. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: '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' and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Medical/Study Director, Regulatory Representative, Clinical Study Lead, and Biostatistician)

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

Study Title: A 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

Protocol Number: R3918-PNH-20105

Protocol Version: R3918-PNH-20105 Amendment 3

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison

See appended electronic signature page

Sponsor's Responsible Clinical Study Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00172377 v1.0

Approval/eSignature	[redacted] 03-Dec-2021 21:39:03 GMT+0000

Approval/eSignature	[redacted] 06-Dec-2021 15:41:10 GMT+0000

Approval/eSignature	[redacted] 06-Dec-2021 17:44:07 GMT+0000

Approval/eSignature	[redacted] 06-Dec-2021 21:30:10 GMT+0000

Signature Page for VV-RIM-00172377 v1.0 Approved