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

Summary

EudraCT number	2020-005005-17
Trial protocol	HU
Global end of trial date	18 October 2023

Results information

Result version number	v1 (current)
This version publication date	02 November 2024
First version publication date	02 November 2024

Trial information

Trial identification

Sponsor protocol code	R3918-PNH-2092

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04811716
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Regeneron Pharmaceuticals, Inc.
Sponsor organisation address	777 Old Saw Mill River Road, Tarrytown, NY, United States, 10591
Public contact	Clinical Trials Administrator, Regeneron Pharmaceuticals, Inc., 001 844-734-6643, clinicaltrials@regeneron.com
Scientific contact	Clinical Trials Administrator, Regeneron Pharmaceuticals, Inc., 001 844-734-6643, clinicaltrials@regeneron.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 October 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 October 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the safety and tolerability of 2 dosing regimens of pozelimab and cemdisiran combination therapy during the open-label treatment period (OLTP)

Protection of trial subjects:

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.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	29 July 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Hong Kong: 1
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Korea, Republic of: 12
Country: Number of subjects enrolled	Malaysia: 4
Country: Number of subjects enrolled	Taiwan: 4
Country: Number of subjects enrolled	United Kingdom: 2
Worldwide total number of subjects	24
EEA total number of subjects	1

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	19
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Twenty-four participants were screened and randomized.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Pozelimab Q2W + Cemdisiran

Arm description:

Pozelimab administered by subcutaneous (SC) injection every 2 weeks (Q2W) and cemdisiran administered by subcutanous (SC) injection. The first dose of the combination treatment (pozelimab Q2W + cemdisiran) was administered on day 1 of the open-label treatment period (OLTP). In the open¬ label extension period (OLEP), participants received a regimen of pozelimab + cemdisiran, regardless of their treatment assignment in the OLTP.

Arm type	Experimental
Investigational medicinal product name	Pozelimab
Investigational medicinal product code	REGN3918
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered by subcutaneous (SC) injection

Arm title	Pozelimab Q4W + Cemdisiran

Arm description:

Pozelimab administered by subcutaneous (SC) injection every 4 weeks (Q4W) and cemdisiran administered by subcutanous (SC) injection. The first dose of the combination treatment was administered on day 1 of the OLTP. In the OLEP, participants received a regimen of pozelimab Q4W + cemdisiran, regardless of their treatment assignment in the OLTP.

Arm type	Experimental
Investigational medicinal product name	Cemdisiran
Investigational medicinal product code	ALN-CC5
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered by subcutaneous (SC) injection

Number of subjects in period 1	Pozelimab Q2W + Cemdisiran	Pozelimab Q4W + Cemdisiran
Started	12	12
Completed	10	12
Not completed	2	0
Consent withdrawn by subject	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Pozelimab Q2W + Cemdisiran
Reporting group description:	
Pozelimab administered by subcutaneous (SC) injection every 2 weeks (Q2W) and cemdisiran administered by subcutanous (SC) injection. The first dose of the combination treatment (pozelimab Q2W + cemdisiran) was administered on day 1 of the open-label treatment period (OLTP). In the open¬ label extension period (OLEP), participants received a regimen of pozelimab + cemdisiran, regardless of their treatment assignment in the OLTP.	
Reporting group title	Pozelimab Q4W + Cemdisiran
Reporting group description:	
Pozelimab administered by subcutaneous (SC) injection every 4 weeks (Q4W) and cemdisiran administered by subcutanous (SC) injection. The first dose of the combination treatment was administered on day 1 of the OLTP. In the OLEP, participants received a regimen of pozelimab Q4W + cemdisiran, regardless of their treatment assignment in the OLTP.	

Reporting group values	Pozelimab Q2W + Cemdisiran	Pozelimab Q4W + Cemdisiran	Total
Number of subjects	12	12	24
Age Categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: years			
arithmetic mean	41.4	53.2	
standard deviation	± 16.89	± 16.38	-
Gender Categorical Units: Subjects			
Female	5	6	11
Male	7	6	13
Race, Customized Units: Subjects			
White	1	1	2
Black or African American	0	0	0
Asian	10	11	21
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Not Reported	1	0	1
Ethnicity (NIH/OMB) Units: Subjects			

Hispanic or Latino	0	0	0
Not Hispanic or Latino	12	12	24

End points

End points reporting groups

Reporting group title	Pozelimab Q2W + Cemdisiran

Reporting group description:

Pozelimab administered by subcutaneous (SC) injection every 2 weeks (Q2W) and cemdisiran administered by subcutanous (SC) injection. The first dose of the combination treatment (pozelimab Q2W + cemdisiran) was administered on day 1 of the open-label treatment period (OLTP). In the open¬ label extension period (OLEP), participants received a regimen of pozelimab + cemdisiran, regardless of their treatment assignment in the OLTP.

Reporting group title	Pozelimab Q4W + Cemdisiran

Reporting group description:

Pozelimab administered by subcutaneous (SC) injection every 4 weeks (Q4W) and cemdisiran administered by subcutanous (SC) injection. The first dose of the combination treatment was administered on day 1 of the OLTP. In the OLEP, participants received a regimen of pozelimab Q4W + cemdisiran, regardless of their treatment assignment in the OLTP.

Subject analysis set title	Pozelimab Q4W + Cemdisiran
Subject analysis set type	Full analysis

Subject analysis set description:

Pozelimab administered by subcutaneous (SC) injection every 4 weeks (Q4W) and cemdisiran administered by subcutanous (SC) injection. The first dose of the combination treatment was administered on day 1 of the OLTP. In the OLEP, participants received a regimen of pozelimab Q4W + cemdisiran, regardless of their treatment assignment in the OLTP.

Subject analysis set title	Pozelimab Q4W + Cemdisiran
Subject analysis set type	Full analysis

Subject analysis set description:

Pozelimab administered by subcutaneous (SC) injection every 4 weeks (Q4W) and cemdisiran administered by subcutanous (SC) injection. The first dose of the combination treatment was administered on day 1 of the OLTP. In the OLEP, participants received a regimen of pozelimab Q4W + cemdisiran, regardless of their treatment assignment in the OLTP.

Primary: Percentage of participants with treatment emergent adverse events (TEAEs)

End point title	Percentage of participants with treatment emergent adverse events (TEAEs)[1]

End point description:

Safety analysis set (SAS) included all randomized participants who received any amount of study drug and was based on the treatment received (as treated); Here 'number analyzed' = the number of evaluable participants at a specified timepoint

End point type	Primary

End point timeframe:

Through Week 28

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

End point values	Pozelimab Q2W + Cemdisiran	Pozelimab Q4W + Cemdisiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: Percentage of participants				
number (not applicable)				
Participants with any TEAE	66.7	41.7		
Participants with serious TEAE	16.7	0		

Participants with severe TEAE	16.7	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change of Lactate dehydrogenase (LDH) from pre-treatment to end-of-treatment period

End point title	Percent change of Lactate dehydrogenase (LDH) from pre-treatment to end-of-treatment period

End point description:

OLTP
Pre-treatment (mean of LDH values prior to combination dosing); End-of-treatment (mean of LDH value at week 24- through week 28); Full analysis set (FAS) = included all randomized participants who received any amount of study drug & had at least 1 post-baseline assessment; based on treatment allocated (as randomized); percentage of change in Upper Limit of Normal (xULN); Here 'number analyzed' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

End of treatment period, approximately 28 Weeks

End point values	Pozelimab Q2W + Cemdisiran	Pozelimab Q4W + Cemdisiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: Percentage of change				
arithmetic mean (standard deviation)	2.93 (± 36.575)	3.65 (± 13.608)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Maintaining Adequate Control of Hemolysis from Baseline (Day 1) through Week 28

End point title	Percentage of Participants Maintaining Adequate Control of Hemolysis from Baseline (Day 1) through Week 28

End point description:

OLTP
Adequate control of hemolysis is defined as LDH values ≤1.5 x Upper limit of normal (ULN) from baseline (day 1) to week 28; Full analysis set (FAS) = included all randomized participants who received any amount of study drug & had at least 1 post-baseline assessment; based on treatment allocated (as randomized); Here 'number analyzed' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1) through Week 28

End point values	Pozelimab Q2W + Cemdisiran	Pozelimab Q4W + Cemdisiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: Percentage of participants				
number (not applicable)	75.0	91.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Maintaining Adequate Control of Hemolysis from Week 4 through Week 28

End point title	Percentage of Participants Maintaining Adequate Control of Hemolysis from Week 4 through Week 28

End point description:

OLTP
Full analysis set (FAS) = included all randomized participants who received any amount of study drug & had at least 1 post-baseline assessment; based on treatment allocated (as randomized); Here 'number analyzed' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Week 4 through Week 28

End point values	Pozelimab Q2W + Cemdisiran	Pozelimab Q4W + Cemdisiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: Percentage of participants				
number (not applicable)	83.3	91.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Adequate Control of Hemolysis at Each Visit from Baseline (Day 1) through Week 28

End point title	Percentage of Participants with Adequate Control of Hemolysis at Each Visit from Baseline (Day 1) through Week 28

End point description:

OLTP; Adequate control at a visit is defined as having LDH <=1.5 x ULN at that visit; FAS = included all randomized participants who received any amount of study drug & had at least 1 post-baseline assessment; based on treatment allocated (as randomized); Here 'number analyzed' = number of

evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1) through Week 28

End point values	Pozelimab Q2W + Cemdisiran	Pozelimab Q4W + Cemdisiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: Percentage of participants				
number (not applicable)				
Baseline Visit (Day 1) n=12,12	100.0	100.0		
Pre-treatment n=12,12	100.0	100.0		
Week 1 n=12,12	100.0	100.0		
Week 2 n=12,12	100.0	100.0		
Week 4 n=12,12	83.0	100.0		
Week 6 n=12,12	92.0	100.0		
Week 8 n=12,11	100.0	100.0		
Week 10 n=11,12	100.0	100.0		
Week 12 n=12,12	100.0	92.0		
Week 16 n=12,12	100.0	100.0		
Week 20 n=12,12	100.0	100.0		
Week 24 n=12,12	100.0	100.0		
Week 28 n=12,12	92.0	100.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Normalization of LDH at Each Visit from Baseline (Day 1) through Week 28

End point title	Percentage of Participants with Normalization of LDH at Each Visit from Baseline (Day 1) through Week 28

End point description:

OLTP; Normalization of LDH was defined as LDH ≤1.0 × ULN at each visit; FAS = included all randomized participants who received any amount of study drug & had at least 1 post-baseline assessment; based on treatment allocated (as randomized); Here 'number analyzed' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1) through Week 28

End point values	Pozelimab Q2W + Cemdisiran	Pozelimab Q4W + Cemdisiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: Percentage of participants				
number (not applicable)				
Baseline (Day 1) n=12,12	92.0	75.0		
Pre-treatment n=12,12	92.0	83.0		
Week 1 n=12,12	100.0	92.0		
Week 2 n=12,12	92.0	83.0		
Week 4 n=12,12	83.0	83.0		
Week 6 n=12,12	83.0	75.0		
Week 8 n=12,11	100.0	82.0		
Week 10 n=11,12	100.0	83.0		
Week 12 n=12,12	92.0	83.0		
Week 16 n=12,12	92.0	75.0		
Week 20 n=12,12	100.0	92.0		
Week 24 n=12,12	100.0	92.0		
Week 28 n=12,12	83.0	83.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the curve (AUC) of LDH over time from Baseline (Day 1) through Week 28

End point title	Area under the curve (AUC) of LDH over time from Baseline (Day 1) through Week 28

End point description:

OLTP; FAS = included all randomized participants who received any amount of study drug & had at least 1 post-baseline assessment; based on treatment allocated (as randomized); Here 'number analyzed' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1) through Week 28

End point values	Pozelimab Q2W + Cemdisiran	Pozelimab Q4W + Cemdisiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: Units per Liter (U/L)				
arithmetic mean (standard deviation)	238.18 (± 44.006)	244.42 (± 39.085)		

Statistical analyses

No statistical analyses for this end point

Secondary: AUC of LDH over time from Week 4 through Week 28

End point title	AUC of LDH over time from Week 4 through Week 28

End point description:

OLTP; FAS = included all randomized participants who received any amount of study drug & had at least 1 post-baseline assessment; based on treatment allocated (as randomized); Here 'number analyzed' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Week 4 through Week 28

End point values	Pozelimab Q2W + Cemdisiran	Pozelimab Q4W + Cemdisiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: U/L				
arithmetic mean (standard deviation)	202.49 (± 38.272)	211.28 (± 34.280)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Transfusion Avoidance from Baseline (Day 1) through Week 28

End point title	Percentage of Participants with Transfusion Avoidance from Baseline (Day 1) through Week 28

End point description:

OLTP
Not requiring a red blood cell (RBC) transfusion as per protocol algorithm; FAS = included all randomized participants who received any amount of study drug & had at least 1 post-baseline assessment; based on treatment allocated (as randomized); Here 'number analyzed' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 28

End point values	Pozelimab Q2W + Cemdisiran	Pozelimab Q4W + Cemdisiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: Percentage of participants				
number (not applicable)	83.3	100.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Hemoglobin Stabilization from Baseline (Day 1) through Week 28

End point title	Percentage of Participants with Hemoglobin Stabilization from Baseline (Day 1) through Week 28

End point description:

OLTP
Hemoglobin stabilization was defined as participants who did not receive an RBC transfusion and had no decrease in hemoglobin level of ≥2 grams per deciLiter (g/dL). FAS = included all randomized participants who received any amount of study drug & had at least 1 post-baseline assessment; based on treatment allocated (as randomized); Here 'number analyzed' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1) through Week 28

End point values	Pozelimab Q2W + Cemdisiran	Pozelimab Q4W + Cemdisiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: Percentage of participants				
number (not applicable)	75.0	91.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Breakthrough hemolysis from Baseline (Day 1) through Week 28

End point title	Percentage of Participants with Breakthrough hemolysis from Baseline (Day 1) through Week 28

End point description:

OLTP; Breakthrough hemolysis = increase in LDH with concomitant signs or symptoms associated with hemolysis:
• Increase in LDH occurs when:
− LDH ≥2 × ULN if pre-treatment LDH is ≤1.5 × ULN or
− LDH ≥2 × ULN after initial achievement of LDH ≤1.5 × ULN if pre-treatment LDH is >1.5 × ULN
Signs/symptoms should correspond to those known to be associated with intravascular hemolysis due to Paroxysmal nocturnal hemoglobinuria (PNH) limited to the following: new onset or worsening fatigue, headache, dyspnea, hemoglobinuria, abdominal pain, scleral icterus, erectile dysfunction, chest pain, confusion, dysphagia, anemia including hemoglobin value significantly lower (ie, ≥2g/dL decrease) compared to participant's baseline hemoglobin value, & thrombotic event. FAS = all randomized

participants who received any study drug & had at least 1 post-baseline assessment; based on treatment allocated (as randomized); Here 'number analyzed' = number of evaluable participants at specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1) through Week 28

End point values	Pozelimab Q2W + Cemdisiran	Pozelimab Q4W + Cemdisiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: Percentage of participants				
number (not applicable)	8.3	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Hemoglobin Levels from Baseline (Day 1) through Week 28

End point title	Change in Hemoglobin Levels from Baseline (Day 1) through Week 28

End point description:

OLTP; FAS = included all randomized participants who received any amount of study drug & had at least 1 post-baseline assessment; based on treatment allocated (as randomized); Here 'number analyzed' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 28

End point values	Pozelimab Q2W + Cemdisiran	Pozelimab Q4W + Cemdisiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: grams per Liter (g/L)				
arithmetic mean (standard deviation)	-1.3 (± 13.77)	10.3 (± 7.41)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Total complement hemolysis activity assay (CH50) from Baseline (Day 1) through Week 28

End point title	Change in Total complement hemolysis activity assay (CH50) from Baseline (Day 1) through Week 28

End point description:

OLTP; FAS = included all randomized participants who received any amount of study drug & had at least 1 post-baseline assessment; based on treatment allocated (as randomized); Here 'number analyzed' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 28

End point values	Pozelimab Q2W + Cemdisiran	Pozelimab Q4W + Cemdisiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: Units per milliliter (U/mL)				
arithmetic mean (standard deviation)	0.0 (± 0.0)	-0.1 (± 0.29)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in fatigue as measured by Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) Scale from Baseline (Day 1) through Week 28

End point title	Change in fatigue as measured by Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) Scale from Baseline (Day 1) through Week 28

End point description:

OLTP
FACIT fatigue is a 13-item scale and for each item 4 is not at all fatigued to 0 very much fatigued. Higher FACIT-Fatigue scores indicate less fatigue (scores range from 0-52). A 5-point change is considered clinically meaningful; FAS = included all randomized participants who received any amount of study drug & had at least 1 post-baseline assessment; based on treatment allocated (as randomized); Here 'number analyzed' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 28

End point values	Pozelimab Q2W + Cemdisiran	Pozelimab Q4W + Cemdisiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: Score on a scale				
arithmetic mean (standard deviation)	-6.0 (± 10.09)	-2.09 (± 4.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Red Blood Cells (RBCs) transfused from Baseline (Day 1) to Week 28

End point title	Rate of Red Blood Cells (RBCs) transfused from Baseline (Day 1) to Week 28

End point description:

OLTP
Rate of RBCs transfused is defined as number of events per patient-years. For each participant, the participant-years are the time from first dose date to week 28 (or early terminations visit if subject discontinued the study early) in the OLTP. FAS = included all randomized participants who received any amount of study drug & had at least 1 post-baseline assessment; based on treatment allocated (as randomized); Here 'number analyzed' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 28

End point values	Pozelimab Q2W + Cemdisiran	Pozelimab Q4W + Cemdisiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: Per participant-year of treatment				
number (confidence interval 95%)	1.284 (0.169 to 9.760)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Per-Protocol RBC Units Transfused from Baseline (Day 1) through Week 28

End point title	Number of Per-Protocol RBC Units Transfused from Baseline (Day 1) through Week 28

End point description:

OLTP; FAS = included all randomized participants who received any amount of study drug & had at least 1 post-baseline assessment; based on treatment allocated (as randomized); Here 'number analyzed' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 28

End point values	Pozelimab Q2W + Cemdisiran	Pozelimab Q4W + Cemdisiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: Units				
arithmetic mean (standard deviation)	1.5 (± 3.73)	0.0 (± 0.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in global health status/quality of life scale (GHS/QoL) on the European Organization for Research and Treatment of Cancer: Quality-of-Life Questionnaire core 30 items (EORTC QLQ-C30) from Baseline (Day 1) through Week 28

End point title	Change in global health status/quality of life scale (GHS/QoL) on the European Organization for Research and Treatment of Cancer: Quality-of-Life Questionnaire core 30 items (EORTC QLQ-C30) from Baseline (Day 1) through Week 28

End point description:

OLTP; EORTC QLQ-C30 has 30 items (i.e. single questions), 24 of which are aggregated into 9 multi-item scales: 5 functioning scales (physical, role, cognitive, emotional & social), 3 symptom scales (fatigue, pain & nausea/vomiting) & 1 global health status scale. The remaining 6 single-item (dyspnoea, appetite loss, sleep disturbance, constipation, diarrhoea & the financial impact) scales assess symptoms. All of the scales & single-item measures range in score from 0-100. Higher score for functioning scales & global health status equal a better level of functioning (i.e. a better state of participant), while higher scores on the symptom & single-item scales indicate a higher level of symptoms (i.e. a worse state of the participant); FAS = included all randomized participants who received any amount of study drug & had at least 1 post-baseline assessment; based on treatment allocated (as randomized); Here 'number analyzed' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 28

End point values	Pozelimab Q2W + Cemdisiran	Pozelimab Q4W + Cemdisiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: Score on a scale				
arithmetic mean (standard deviation)	-9.4 (± 23.33)	-1.9 (± 13.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of Total Pozelimab in Serum on Week 28

End point title	Concentrations of Total Pozelimab in Serum on Week 28

End point description:

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

End point type	Secondary

End point timeframe:

On Week 28

End point values	Pozelimab Q2W + Cemdisiran	Pozelimab Q4W + Cemdisiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: mg/L				
arithmetic mean (standard deviation)	131 (± 74.8)	58.2 (± 31.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of Total C5 on Week 28

End point title	Concentrations of Total C5 on Week 28

End point description:

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

End point type	Secondary

End point timeframe:

On Week 28

End point values	Pozelimab Q2W + Cemdisiran	Pozelimab Q4W + Cemdisiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: mg/L				
median (inter-quartile range (Q1-Q3))	0 (0 to 13.8)	0 (0 to 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of Cemdisiran in Plasma on Week 28

End point title	Concentrations of Cemdisiran in Plasma on Week 28

End point description:

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

End point type	Secondary

End point timeframe:

On Week 28

End point values	Pozelimab Q2W + Cemdisiran	Pozelimab Q4W + Cemdisiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: mg/L				
arithmetic mean (standard deviation)	0 (± 0)	0 (± 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in physical function (PF) scores on the EORTC QLQ-C30 from Baseline (Day 1) through Week 28

End point title	Change in physical function (PF) scores on the EORTC QLQ-C30 from Baseline (Day 1) through Week 28

End point description:

OLTP; The EORTC QLQ-C30 is a 30-item, self-administered, generic questionnaire that assesses health-related QoL across multiple domains, including GHS, global QoL, 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). EORTC QLQ-C30 domain scales range from 0 to 100, with lower scores indicating worse QoL and higher scores for symptom scales indicating worse symptoms. A 10-point change is considered meaningful; Full analysis set (FAS) = included all randomized participants who eceived any amount of study drug & had at least 1 post-baseline assessment; based on treatment allocated (as randomized); Here 'n' = the number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 28

End point values	Pozelimab Q2W + Cemdisiran	Pozelimab Q4W + Cemdisiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: Score on a scale				
arithmetic mean (standard deviation)	-6.7 (± 19.19)	0.7 (± 9.09)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Cemdisiran Anti-Drug Antibody (ADA) Responses Over Time

End point title	Number of Participants with Cemdisiran Anti-Drug Antibody (ADA) Responses Over Time

End point description:

OLTP and OLEP; Anti-Drug Antibodies (ADA) Analysis Set; Here 'n' = the number of evaluable participants at a certain timepoint

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Pozelimab Q2W + Cemdisiran	Pozelimab Q4W + Cemdisiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: Participants				
number (not applicable)				
Treatment-Boosted Response	0	0		
Treatment-Emergent Response	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Pozelimab Anti-Drug Antibody (ADA) Responses Over Time

End point title	Number of Participants with Pozelimab Anti-Drug Antibody (ADA) Responses Over Time

End point description:

OLTP and OLEP; Anti-Drug Antibodies (ADA) Analysis Set; Here 'n' = the number of evaluable participants at a certain timepoint

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Pozelimab Q2W + Cemdisiran	Pozelimab Q4W + Cemdisiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: Participants				
number (not applicable)				
Treatment-Boosted Response	0	0		

Treatment-Emergent Response	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with TEAEs for participants who received treatment intensification

End point title	Percentage of participants with TEAEs for participants who received treatment intensification

End point description:

OLTP
No participants received dose intensification during the study; Therefore, assessment of the safety of pozelimab + cemdisiran combination therapy in participants requiring dose intensification was not conducted; Safety analysis set (SAS) included all randomized participants who received any amount of study drug and was based on the treatment received (as treated); Here 'n' = the number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Through Week 28

End point values	Pozelimab Q2W + Cemdisiran	Pozelimab Q4W + Cemdisiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: Percentage of participants				
number (not applicable)				
Participants with any TEAE Participants with any serious TEAE Participants with any severe TEAE				

Notes:

[2] - No participants received dose intensification; assessment was not conducted

[3] - No participants received dose intensification; assessment was not conducted

Statistical analyses

No statistical analyses for this end point

Secondary: Change of LDH from Baseline (Day 1e) to Week 52e

End point title	Change of LDH from Baseline (Day 1e) to Week 52e

End point description:

OLEP; OLEP FAS included all participants who participated in the OLEP who received any amount of study drug in the OLEP and had at least 1 post-baseline efficacy assessment in the OLEP; Here 'n' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1e) to Week 52e

End point values	Pozelimab Q4W + Cemdisiran			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: U/L				
arithmetic mean (standard deviation)	-14.5 (± 105.90)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change of LDH from OLEP Baseline (Day 1e) to Week 24e

End point title	Percent Change of LDH from OLEP Baseline (Day 1e) to Week 24e

End point description:

OLEP; OLEP FAS included all participants who participated in the OLEP who received any amount of study drug in the OLEP and had at least 1 post-baseline efficacy assessment in the OLEP; Here 'n' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1e) to Week 24e

End point values	Pozelimab Q4W + Cemdisiran			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Percentage of change				
arithmetic mean (standard deviation)	-0.7 (± 20.60)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change of LDH from Baseline (Day 1e) to Week 24e

End point title	Change of LDH from Baseline (Day 1e) to Week 24e

End point description:

Optional Open-Label Extension Period (OLEP); OLEP FAS included all participants who participated in the OLEP who received any amount of study drug in the OLEP and had at least 1 post-baseline efficacy assessment in the OLEP; Here 'n' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1e) to Week 24e

End point values	Pozelimab Q4W + Cemdisiran			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: U/L				
arithmetic mean (standard deviation)	-18.2 (± 108.40)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Maintaining Adequate Control of Hemolysis from Baseline (Day 1e) through Week 24e

End point title	Percentage of Participants Maintaining Adequate Control of Hemolysis from Baseline (Day 1e) through Week 24e

End point description:

OLEP; OLEP FAS included all participants who participated in the OLEP who received any amount of study drug in the OLEP and had at least 1 post-baseline efficacy assessment in the OLEP; Here 'n' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1e) through Week 24e

End point values	Pozelimab Q4W + Cemdisiran			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Percentage of Participants				
number (not applicable)	95.7			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Maintaining Adequate Control of Hemolysis from Baseline (Day 1e) through Week 52e

End point title	Percentage of Participants Maintaining Adequate Control of Hemolysis from Baseline (Day 1e) through Week 52e

End point description:

OLEP; OLEP FAS included all participants who participated in the OLEP who received any amount of

study drug in the OLEP and had at least 1 post-baseline efficacy assessment in the OLEP; Here 'n' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1e) through Week 52e

End point values	Pozelimab Q4W + Cemdisiran			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Percentage of Participants				
number (not applicable)	95.7			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Adequate Control of Hemolysis at Each Visit from Baseline (Day 1e) through Week 52e

End point title	Percentage of Participants with Adequate Control of Hemolysis at Each Visit from Baseline (Day 1e) through Week 52e

End point description:

OLEP; Adequate control at a visit is defined as having LDH <=1.5 x ULN at that visit; OLEP FAS included all participants who participated in the OLEP who received any amount of study drug in the OLEP and had at least 1 post-baseline efficacy assessment in the OLEP; Here 'n' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1e) through Week 52e

End point values	Pozelimab Q4W + Cemdisiran			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Percentage of participants				
number (not applicable)				
OLEP Baseline (Day 1e)	96.0			
Week 8e	100.0			
Week 16e	100.0			
Week 24e	100.0			
Week 32e	100.0			
Week 40e	100.0			
Week 52e	100.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change of LDH from Baseline (Day 1e) to Week 52e

End point title	Percent change of LDH from Baseline (Day 1e) to Week 52e

End point description:

OLEP; OLEP FAS included all participants who participated in the OLEP who received any amount of study drug in the OLEP and had at least 1 post-baseline efficacy assessment in the OLEP; Percentage of change for units per liter (U/L); Here 'n' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1e) to Week 52e

End point values	Pozelimab Q4W + Cemdisiran			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Percentage of change				
arithmetic mean (standard deviation)	0.2 (± 19.49)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Normalization of LDH at Each Visit from Baseline (Day 1e) through Week 52e

End point title	Percentage of Participants with Normalization of LDH at Each Visit from Baseline (Day 1e) through Week 52e

End point description:

OLEP; OLEP FAS included all participants who participated in the OLEP who received any amount of study drug in the OLEP and had at least 1 post-baseline efficacy assessment in the OLEP; Here 'n' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1e) through week 52e

End point values	Pozelimab Q4W + Cemdisiran			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Percentage of participants				
number (not applicable)				
OLEP Baseline (Day 1e)	87.0			
Week 8e	83.0			
Week 16e	82.0			
Week 24e	82.0			
Week 32e	86.0			
Week 40e	86.0			
Week 52e	82.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Breakthrough hemolysis from Baseline (Day 1e) through Week 24e

End point title	Percentage of Participants with Breakthrough hemolysis from Baseline (Day 1e) through Week 24e

End point description:

OLEP; OLEP FAS included all participants who participated in the OLEP who received any amount of study drug in the OLEP and had at least 1 post-baseline efficacy assessment in the OLEP; Here 'n' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1e) through Week 24e

End point values	Pozelimab Q4W + Cemdisiran			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Percentage of Participants				
number (not applicable)	4.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Breakthrough hemolysis from Baseline (Day 1e) through Week 52e

End point title	Percentage of Participants with Breakthrough hemolysis from Baseline (Day 1e) through Week 52e

End point description:

OLEP; OLEP FAS included all participants who participated in the OLEP who received any amount of study drug in the OLEP and had at least 1 post-baseline efficacy assessment in the OLEP; Here 'n' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1e) through Week 52e

End point values	Pozelimab Q4W + Cemdisiran			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Percentage of participants				
number (not applicable)	4.3			

Statistical analyses

No statistical analyses for this end point

Secondary: AUC of LDH over time from Baseline (Day 1e) through Week 52e

End point title	AUC of LDH over time from Baseline (Day 1e) through Week 52e

End point description:

OLEP; OLEP FAS included all participants who participated in the OLEP who received any amount of study drug in the OLEP and had at least 1 post-baseline efficacy assessment in the OLEP; Here 'n' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1e) through Week 52e

End point values	Pozelimab Q4W + Cemdisiran			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: U/L				
arithmetic mean (standard deviation)	154.63 (± 38.231)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Hemoglobin Stabilization from Baseline (Day 1e) through Week 24e

End point title	Percentage of Participants with Hemoglobin Stabilization from Baseline (Day 1e) through Week 24e

End point description:

OLEP
Participants who do not receive RBC transfusion and have no decrease in hemoglobin levels; OLEP FAS included all participants who participated in the OLEP who received any amount of study drug in the OLEP and had at least 1 post-baseline efficacy assessment in the OLEP; Here 'n' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1e) through Week 24e

End point values	Pozelimab Q4W + Cemdisiran			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Percentage of participants				
number (not applicable)	78.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Hemoglobin Stabilization from Baseline (Day 1e) through Week 52e

End point title	Percentage of Participants with Hemoglobin Stabilization from Baseline (Day 1e) through Week 52e

End point description:

OLEP
Participants who do not receive RBC transfusion and have no decrease in hemoglobin levels; OLEP FAS included all participants who participated in the OLEP who received any amount of study drug in the OLEP and had at least 1 post-baseline efficacy assessment in the OLEP; Here 'n' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1e) through Week 52e

End point values	Pozelimab Q4W + Cemdisiran			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Percentage of participants				
number (not applicable)	69.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in hemoglobin levels from Baseline (Day 1e) to Week 24e

End point title	Change in hemoglobin levels from Baseline (Day 1e) to Week 24e

End point description:

OLEP; OLEP FAS included all participants who participated in the OLEP who received any amount of study drug in the OLEP and had at least 1 post-baseline efficacy assessment in the OLEP; Here 'n' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1e) to Week 24e

End point values	Pozelimab Q4W + Cemdisiran			
Subject group type	Subject analysis set			
Number of subjects analysed	21			
Units: g/L				
arithmetic mean (standard deviation)	0.8 (± 15.63)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Per-Protocol Transfusion Avoidance from Baseline (Day 1e) through Week 52e

End point title	Percentage of Participants with Per-Protocol Transfusion Avoidance from Baseline (Day 1e) through Week 52e

End point description:

OLEP
Not requiring a RBC transfusion as per protocol algorithm; OLEP FAS included all participants who participated in the OLEP who received any amount of study drug in the OLEP and had at least 1 post-baseline efficacy assessment in the OLEP; Here 'n' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1e) to Week 52e

End point values	Pozelimab Q4W + Cemdisiran			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Percentage of Participants				
number (not applicable)	87.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in hemoglobin levels from Baseline (Day 1e) to Week 52e

End point title	Change in hemoglobin levels from Baseline (Day 1e) to Week 52e

End point description:

OLEP; OLEP FAS included all participants who participated in the OLEP who received any amount of study drug in the OLEP and had at least 1 post-baseline efficacy assessment in the OLEP; Here 'n' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1e) to Week 52e

End point values	Pozelimab Q4W + Cemdisiran			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: g/L				
arithmetic mean (standard deviation)	-0.6 (± 12.60)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Per-Protocol Transfusion Avoidance from Baseline (Day 1e) through Week 24e

End point title	Percentage of Participants with Per-Protocol Transfusion Avoidance from Baseline (Day 1e) through Week 24e

End point description:

OLEP
Not requiring a RBC transfusion as per protocol algorithm; OLEP FAS included all participants who participated in the OLEP who received any amount of study drug in the OLEP and had at least 1 post-baseline efficacy assessment in the OLEP; Here 'n' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1e) through Week 24e

End point values	Pozelimab Q4W + Cemdisiran			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Percentage of Participants				
number (not applicable)	87.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of units of RBCs transfused from Baseline (Day 1e) to Week 24e

End point title	Number of units of RBCs transfused from Baseline (Day 1e) to Week 24e

End point description:

OLEP; OLEP FAS included all participants who participated in the OLEP who received any amount of study drug in the OLEP and had at least 1 post-baseline efficacy assessment in the OLEP; Here 'n' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1e) to Week 24e

End point values	Pozelimab Q4W + Cemdisiran			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Units				
arithmetic mean (standard deviation)	0.4 (± 1.47)			

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of RBCs transfused from Baseline (Day 1e) to Week 52e

End point title	Rate of RBCs transfused from Baseline (Day 1e) to Week 52e

End point description:

OLEP; OLEP FAS included all participants who participated in the OLEP who received any amount of study drug in the OLEP and had at least 1 post-baseline efficacy assessment in the OLEP; Here 'n' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1e) to Week 52e

End point values	Pozelimab Q4W + Cemdisiran			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Per participant-year of treatment				
number (confidence interval 95%)	0.506 (0.092 to 2.773)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in CH50 from Baseline (Day 1e) to Week 16e

End point title	Change in CH50 from Baseline (Day 1e) to Week 16e

End point description:

OLEP; OLEP FAS included all participants who participated in the OLEP who received any amount of study drug in the OLEP and had at least 1 post-baseline efficacy assessment in the OLEP; Here 'n' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1e) to Week 16e

End point values	Pozelimab Q4W + Cemdisiran			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: U/mL				
arithmetic mean (standard deviation)	0.0 (± 0.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of RBCs transfused from Baseline (Day 1e) to Week 24e

End point title	Rate of RBCs transfused from Baseline (Day 1e) to Week 24e

End point description:

OLEP; OLEP FAS included all participants who participated in the OLEP who received any amount of study drug in the OLEP and had at least 1 post-baseline efficacy assessment in the OLEP; Here 'n' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1e) to Week 24e

End point values	Pozelimab Q4W + Cemdisiran			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Per participant-year of treatment				
number (confidence interval 95%)	0.591 (0.143 to 2.445)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in CH50 from Baseline (Day 1e) to Week 24e

End point title	Change in CH50 from Baseline (Day 1e) to Week 24e

End point description:

OLEP; OLEP FAS included all participants who participated in the OLEP who received any amount of study drug in the OLEP and had at least 1 post-baseline efficacy assessment in the OLEP; Here 'n' = number of evaluable participants at a specified timepoint; Since all participants have 0 values at baseline for CH50, the percentage change is not appropriate and undefined. Therefore, this endpoint is not able to be calculated.

End point type	Secondary

End point timeframe:

Baseline (Day 1e) to Week 24e

End point values	Pozelimab Q4W + Cemdisiran			
Subject group type	Subject analysis set			
Number of subjects analysed	0[4]			
Units: U/mL				
arithmetic mean (standard deviation)	()			

Notes:

[4] - All participants have 0 values at baseline, percentage change is undefined and cannot be calculated.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of units of RBCs transfused from Baseline (Day 1e) to Week 52e

End point title	Number of units of RBCs transfused from Baseline (Day 1e) to Week 52e

End point description:

OLEP; OLEP FAS included all participants who participated in the OLEP who received any amount of study drug in the OLEP and had at least 1 post-baseline efficacy assessment in the OLEP; Here 'n' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1e) to Week 52e

End point values	Pozelimab Q4W + Cemdisiran			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Units				
arithmetic mean (standard deviation)	0.9 (± 3.95)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in GHS/QoL on the EORTC QLQ-C30 from Baseline (Day 1e) to Week 52e

End point title	Change in GHS/QoL on the EORTC QLQ-C30 from Baseline (Day 1e) to Week 52e

End point description:

OLEP; The EORTC QLQ-C30 is a 30-item, self-administered, generic questionnaire that assesses health-related QoL across multiple domains, including GHS, global QoL, 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). EORTC QLQ-C30 domain scales range from 0 to 100, with lower scores indicating worse QoL and higher scores for symptom scales indicating worse symptoms. A 10-point change is considered meaningful. OLEP FAS included all participants who participated in the OLEP who received any amount of study drug in the OLEP and had at least 1 post-baseline efficacy assessment in the OLEP; Here 'n' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1e) to Week 52e

End point values	Pozelimab Q4W + Cemdisiran			
Subject group type	Subject analysis set			
Number of subjects analysed	21			
Units: Score on a scale				
arithmetic mean (standard deviation)	6.0 (± 13.73)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in fatigue as measured by Functional Assessment of Chronic

Illness Therapy-Fatigue (FACIT-Fatigue) scale from Baseline (Day 1e) to Week 52e

End point title	Change in fatigue as measured by Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale from Baseline (Day 1e) to Week 52e

End point description:

OLEP; The FACIT-Fatigue is a 13-item, self-administered assessment of an individual's level of fatigue during their usual daily activities over the past week. This questionnaire is part of the FACIT measurement system, a compilation of questions measuring health-related QoL in participants with cancer and other chronic illnesses. The FACIT-Fatigue items are measured with 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 less fatigue. A 5-point change is considered clinically meaningful. OLEP FAS included all participants who participated in the OLEP who received any amount of study drug in the OLEP and had at least 1 post-baseline efficacy assessment in the OLEP; Here 'n' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1e) to Week 52e

End point values	Pozelimab Q4W + Cemdisiran			
Subject group type	Subject analysis set			
Number of subjects analysed	21			
Units: Score on a scale				
arithmetic mean (standard deviation)	-0.9 (± 5.95)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in CH50 from Baseline (Day 1e) to Week 52e

End point title	Change in CH50 from Baseline (Day 1e) to Week 52e

End point description:

OLEP; OLEP FAS included all participants who participated in the OLEP who received any amount of study drug in the OLEP and had at least 1 post-baseline efficacy assessment in the OLEP; Here 'n' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1e) to Week 52e

End point values	Pozelimab Q4W + Cemdisiran			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: U/mL				
arithmetic mean (standard deviation)	0.0 (± 0.21)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in CH50 from Baseline (Day 1e) to Week 16e

End point title	Percent change in CH50 from Baseline (Day 1e) to Week 16e

End point description:

OLEP; OLEP FAS included all participants who participated in the OLEP who received any amount of study drug in the OLEP and had at least 1 post-baseline efficacy assessment in the OLEP; Here 'n' = number of evaluable participants at a specified timepoint; Since all participants have 0 values at baseline for CH50, the percentage change is not appropriate and undefined. Therefore, this endpoint is not able to be calculated.

End point type	Secondary

End point timeframe:

Baseline (Day 1e) to Week 16e

End point values	Pozelimab Q4W + Cemdisiran			
Subject group type	Subject analysis set			
Number of subjects analysed	0[5]			
Units: Percentage of change				
number (not applicable)				

Notes:

[5] - All participants have 0 values at baseline, percentage change is undefined and cannot be calculated.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in CH50 from Baseline (Day 1e) to Week 52e

End point title	Percent change in CH50 from Baseline (Day 1e) to Week 52e

End point description:

OLEP; OLEP FAS included all participants who participated in the OLEP who received any amount of study drug in the OLEP and had at least 1 post-baseline efficacy assessment in the OLEP; Here 'n' = number of evaluable participants at a specified timepoint; Since all participants have 0 values at baseline for CH50, the percentage change is not appropriate and undefined. Therefore, this endpoint is not able to be calculated.

End point type	Secondary

End point timeframe:

Baseline (Day 1e) to Week 52e

End point values	Pozelimab Q4W + Cemdisiran			
Subject group type	Subject analysis set			
Number of subjects analysed	0[6]			
Units: Percentage of change				
number (not applicable)				

Notes:

[6] - All participants have 0 values at baseline, percentage change is undefined and cannot be calculated.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in CH50 from Baseline (Day 1e) to Week 24e

End point title	Percent change in CH50 from Baseline (Day 1e) to Week 24e

End point description:

OLEP; OLEP FAS included all participants who participated in the OLEP who received any amount of study drug in the OLEP and had at least 1 post-baseline efficacy assessment in the OLEP; Here 'n' = number of evaluable participants at a specified timepoint; Since all participants have 0 values at baseline for CH50, the percentage change is not appropriate and undefined. Therefore, this endpoint is not able to be calculated.

End point type	Secondary

End point timeframe:

Baseline (Day 1e) to Week 24e

End point values	Pozelimab Q4W + Cemdisiran			
Subject group type	Subject analysis set			
Number of subjects analysed	0[7]			
Units: Percentage of change				
number (not applicable)				

Notes:

[7] - All participants have 0 values at baseline, percentage change is undefined and cannot be calculated.

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of Total Pozelimab in Serum on Week 52

End point title	Concentrations of Total Pozelimab in Serum on Week 52

End point description:

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

End point type	Secondary

End point timeframe:

On Week 52

End point values	Pozelimab Q2W + Cemdisiran	Pozelimab Q4W + Cemdisiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: mg/L				
arithmetic mean (standard deviation)	63.4 (± 35.6)	58.6 (± 28.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in PF scores on the EORTC QLQ-C30 from Baseline (Day 1e) to Week 52e

End point title	Change in PF scores on the EORTC QLQ-C30 from Baseline (Day 1e) to Week 52e

End point description:

OLEP; The EORTC QLQ-C30 is a 30-item, self-administered, generic questionnaire that assesses health-related QoL across multiple domains, including GHS, global QoL, 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). EORTC QLQ-C30 domain scales range from 0 to 100, with lower scores indicating worse QoL and higher scores for symptom scales indicating worse symptoms. A 10-point change is considered meaningful.; OLEP FAS included all participants who participated in the OLEP who received any amount of study drug in the OLEP and had at least 1 post-baseline efficacy assessment in the OLEP; Here 'n' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Baseline (Day 1e) to Week 52e

End point values	Pozelimab Q4W + Cemdisiran			
Subject group type	Subject analysis set			
Number of subjects analysed	21			
Units: Score on a scale				
arithmetic mean (standard deviation)	-0.3 (± 3.93)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with TEAEs Up to Week 52

End point title	Percentage of Participants with TEAEs Up to Week 52

End point description:

OLEP; SAS; Here 'n' = number of evaluable participants at a specified timepoint

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Pozelimab Q4W + Cemdisiran			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Percentage of participants				
number (not applicable)				
Participants with any TEAE	73.9			
Participants with serious TEAE	8.7			
Participants with severe TEAE	4.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of Total C5 on Week 52

End point title	Concentrations of Total C5 on Week 52

End point description:

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

End point type	Secondary

End point timeframe:

On Week 52

End point values	Pozelimab Q2W + Cemdisiran	Pozelimab Q4W + Cemdisiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: mg/L				
median (inter-quartile range (Q1-Q3))	0 (0 to 8.05)	0 (0 to 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of Cemdisiran in Plasma on Week 52

End point title	Concentrations of Cemdisiran in Plasma on Week 52

End point description:

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

End point type	Secondary

End point timeframe:

On Week 52

End point values	Pozelimab Q2W + Cemdisiran	Pozelimab Q4W + Cemdisiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: mg/L				
arithmetic mean (standard deviation)	0 (± 0)	0 (± 0)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

1. OLTP (from first dose up to Week 28 + follow-up of participant without OLE, total 24 participants)
2. OLEP (from Week 28 EOT up to Week 52 OLEP and up to Week 52 follow-up EOS, total 23 participants)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	OLTP_Pozelimab Q2W + Cemdisiran

Reporting group description:

Pozelimab administered by subcutaneous (SC) injection every 2 weeks (Q2W) and cemdisiran administered by subcutanous (SC) injection. The first dose of the combination treatment (pozelimab Q2W + cemdisiran) was administered on day 1 of the open-label treatment period (OLTP). In the open¬ label extension period (OLEP), participants received a regimen of pozelimab + cemdisiran, regardless of their treatment assignment in the OLTP.

Reporting group title	OLEP_Pozelimab Q4W + Cemdisiran

Reporting group description:

In the open-label extension period (OLEP), participants received a regimen of pozelimab SC Q4W + cemdisiran SC, regardless of their treatment assignment in the OLTP.

Reporting group title	OLTP_Pozelimab Q4W + Cemdisiran

Reporting group description:

Pozelimab administered by subcutaneous (SC) injection every 4 weeks (Q4W) and cemdisiran administered by subcutanous (SC) injection. The first dose of the combination treatment was administered on day 1 of the OLTP. In the OLEP, participants received a regimen of pozelimab Q4W + cemdisiran, regardless of their treatment assignment in the OLTP.

Serious adverse events	OLTP_Pozelimab Q2W + Cemdisiran	OLEP_Pozelimab Q4W + Cemdisiran	OLTP_Pozelimab Q4W + Cemdisiran
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 12 (25.00%)	2 / 23 (8.70%)	0 / 12 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Blood and lymphatic system disorders			
Haemolysis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 23 (4.35%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Anal fistula			

subjects affected / exposed	0 / 12 (0.00%)	1 / 23 (4.35%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	0 / 12 (0.00%)	1 / 23 (4.35%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	OLTP_Pozelimab Q2W + Cemdisiran	OLEP_Pozelimab Q4W + Cemdisiran	OLTP_Pozelimab Q4W + Cemdisiran
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 12 (66.67%)	10 / 23 (43.48%)	5 / 12 (41.67%)
Investigations			
Free haemoglobin present			
subjects affected / exposed	0 / 12 (0.00%)	0 / 23 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Electrocardiogram ST segment depression			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Transaminases increased			

subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 23 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Injection site reaction			
subjects affected / exposed	2 / 12 (16.67%)	3 / 23 (13.04%)	2 / 12 (16.67%)
occurrences (all)	6	4	4
Blood and lymphatic system disorders			
Haemolysis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Breakthrough haemolysis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Anaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Ear and labyrinth disorders			
Inner ear disorder			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Anal fistula			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Abdominal pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 23 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1

Renal and urinary disorders			
Paroxysmal nocturnal haemoglobinuria			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 23 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Arthralgia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 23 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Muscle spasms			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
COVID-19			
subjects affected / exposed	2 / 12 (16.67%)	4 / 23 (17.39%)	1 / 12 (8.33%)
occurrences (all)	2	4	1
Upper respiratory tract infection			
subjects affected / exposed	2 / 12 (16.67%)	4 / 23 (17.39%)	0 / 12 (0.00%)
occurrences (all)	2	5	0
Subcutaneous abscess			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Chlamydial infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 23 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 December 2021	The main purpose of this amendment was to modify the timing of the interim analysis and to align endpoints with other studies.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported