Clinical trial results:
A Phase III, Randomized, Multicenter, Open-Label, Active-Comparator Controlled Study to Evaluate the Efficacy and Safety of APL-2 in Patients With Paroxysmal Nocturnal Hemoglobinuria (PNH)

Summary

EudraCT number	2017-004268-36
Trial protocol	DE BE ES NL FR GB IT
Global end of trial date	13 August 2020

Results information

Result version number	v1 (current)
This version publication date	12 November 2021
First version publication date	12 November 2021

Trial information

Trial identification

Sponsor protocol code	APL2-302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03500549
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Apellis Pharmaceuticals, Inc
Sponsor organisation address	100 5th Avenue, Waltham, Massachusetts, United States, MA 02451
Public contact	Apellis Clinical Trial Information Line, Apellis Pharmaceuticals, Inc, 1 833-284-6361, clinicaltrials@apellis.com
Scientific contact	Apellis Clinical Trial Information Line, Apellis Pharmaceuticals, Inc, 1 833-284-6361, clinicaltrials@apellis.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	13 August 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluation of the efficacy and safety of pegcetacoplan (APL-2) compared with those of eculizumab in subjects with paroxysmal nocturnal hemoglobinuria (PNH) who continued to have Hb levels <10.5 grams per deciliter (g/dL) despite treatment with eculizumab (Soliris®).

Protection of trial subjects:

This research was carried out in accordance with the protocol, applicable regulations, the ethical principles set forth in the Declaration of Helsinki, and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Harmonised Guideline for Good Clinical Practice E6 Revision 2. An external, independent data monitoring committee (IDMC) assessed the progress and cumulative safety/tolerability data of the study. The IDMC had the responsibility to conduct a thorough safety assessment at regular predefined intervals during the randomized controlled period (RCP) and open-label treatment phases of the study.

Background therapy: -

Evidence for comparator:

PNH is caused by complement-mediated lysis of erythrocyte clones lacking functional CD55 and CD59 on their surface to protect them against this process. These erythrocytes are particularly susceptible to the membrane attack complex (MAC) and have been shown to lyse readily in the presence of complement activation. Eculizumab is a monoclonal anti-C5 antibody that inhibits the formation of the MAC, and has been approved for the treatment of PNH.

Actual start date of recruitment	14 June 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 14
Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	Japan: 10
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Russian Federation: 2
Country: Number of subjects enrolled	Korea, Republic of: 1

Worldwide total number of subjects	80
EEA total number of subjects	33

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)	63
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a Phase 3, randomized, multicenter, open-label, active-comparator controlled study. The treatment period of the study consisted of 3 parts: a 4-week run-in period, a 16-week RCP, and a 32-week open-label period.

Pre-assignment

Screening details:

Of the 102 subjects screened, 80 subjects met all the inclusion criteria and none of the exclusion criteria and entered the run-in period. Randomization was stratified by the number of packed red blood cell (PRBC) transfusions within the 12 months prior to Day –28 and platelet count at screening.

Period 1

Period 1 title	Run-in Period (Day -28 to ≤Day 1)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Run-in Period: Pegcetacoplan

Arm description:

During the 4-week run-in period (Day –28 to ≤Day 1) all subjects received twice-weekly subcutaneous (SC) doses of pegcetacoplan 1080 milligrams (mg) in addition to their current dosage of eculizumab treatment.

Arm type	Experimental
Investigational medicinal product name	Eculizumab
Investigational medicinal product code	
Other name	Soliris
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dosage of eculizumab treatment continued as prescribed regardless of study visit scheduling or the pegcetacoplan administration schedule (ie, it was not required that eculizumab dosing aligned with pegcetacoplan dosing or study visits).

Investigational medicinal product name	Pegcetacoplan
Investigational medicinal product code	APL2-302
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Pegcetacoplan was administered as a 20 mL SC infusion.

Arm title	Run-in Period: Eculizumab

Arm description:

During the 4-week run-in period (Day –28 to ≤Day 1) all subjects received twice-weekly SC doses of pegcetacoplan 1080 mg in addition to their current dosage of eculizumab treatment.

Arm type	Active comparator
Investigational medicinal product name	Eculizumab
Investigational medicinal product code	
Other name	Soliris
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dosage of eculizumab treatment continued as prescribed regardless of study visit scheduling or the pegcetacoplan administration schedule (ie, it was not required that eculizumab dosing aligned with pegcetacoplan dosing or study visits).

Investigational medicinal product name	Pegcetacoplan
Investigational medicinal product code	APL2-302
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Pegcetacoplan was administered as a 20 mL SC infusion.

Number of subjects in period 1	Run-in Period: Pegcetacoplan	Run-in Period: Eculizumab
Started	41	39
Completed	41	39

Period 2

Period 2 title	RCP (Day 1 - Week 16)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	RCP: Pegcetacoplan

Arm description:

On Day 1, the subjects were randomized to receive monotherapy with SC infusions of pegcetacoplan 1080 mg twice-weekly or every 3 days up to the end of the open-label period (Week 48).

Arm type	Experimental
Investigational medicinal product name	Pegcetacoplan
Investigational medicinal product code	APL2-302
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Pegcetacoplan was administered as a 20 mL SC infusion.

Arm title	RCP: Eculizumab

Arm description:

On Day 1, the subjects were randomized to receive monotherapy with their pre-screening stable dose of eculizumab via intravenous infusion every 2 weeks up to the end of the RCP (Week 16).

Arm type	Active comparator

Investigational medicinal product name	Eculizumab
Investigational medicinal product code	
Other name	Soliris
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dosage of eculizumab treatment continued as prescribed regardless of study visit scheduling or the pegcetacoplan administration schedule (ie, it was not required that eculizumab dosing aligned with pegcetacoplan dosing or study visits).

Number of subjects in period 2	RCP: Pegcetacoplan	RCP: Eculizumab
Started	41	39
Completed	38	39
Not completed	3	0
Adverse event, non-fatal	3	-

Period 3

Period 3 title	Open-label Period (Week 17 to Week 48)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Open-label Period: Continue Pegcetacoplan

Arm description:

On Day 1 of the RCP, the subjects were randomized to receive monotherapy with SC infusions of pegcetacoplan 1080 mg twice-weekly or every 3 days up to the end of the open-label period (Week 48).

Arm type	Experimental
Investigational medicinal product name	Pegcetacoplan
Investigational medicinal product code	APL2-302
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Pegcetacoplan was administered as a 20 mL SC infusion.

Arm title	Open-label Period: Crossover to Pegcetacoplan

Arm description:

Subjects entered the open-label run-in period where they received pegcetacoplan 1080 mg twice-weekly in addition to eculizumab for 4 weeks (Week 17 to Week 20) before receiving monotherapy with SC infusions of pegcetacoplan 1080 mg twice-weekly or every 3 days up to the end of the open-label period (Week 48).

Arm type	Experimental

Investigational medicinal product name	Pegcetacoplan
Investigational medicinal product code	APL2-302
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Pegcetacoplan was administered as a 20 mL SC infusion.

Investigational medicinal product name	Eculizumab
Investigational medicinal product code	
Other name	Soliris
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dosage of eculizumab treatment continued as prescribed regardless of study visit scheduling or the pegcetacoplan administration schedule (ie, it was not required that eculizumab dosing aligned with pegcetacoplan dosing or study visits).

Number of subjects in period 3	Open-label Period: Continue Pegcetacoplan	Open-label Period: Crossover to Pegcetacoplan
Started	38	39
Completed	35	32
Not completed	3	7
Adverse event, non-fatal	3	7

Baseline characteristics

Reporting groups	
Reporting group title	Run-in Period: Pegcetacoplan
Reporting group description:	
During the 4-week run-in period (Day –28 to ≤Day 1) all subjects received twice-weekly subcutaneous (SC) doses of pegcetacoplan 1080 milligrams (mg) in addition to their current dosage of eculizumab treatment.	
Reporting group title	Run-in Period: Eculizumab
Reporting group description:	
During the 4-week run-in period (Day –28 to ≤Day 1) all subjects received twice-weekly SC doses of pegcetacoplan 1080 mg in addition to their current dosage of eculizumab treatment.	

Reporting group values	Run-in Period: Pegcetacoplan	Run-in Period: Eculizumab	Total
Number of subjects	41	39	80
Age categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	31	32	63
>=65 years	10	7	17
Gender categorical Units: Subjects			
Female	27	22	49
Male	14	17	31
Ethnicity Units: Subjects			
Hispanic or Latino	2	1	3
Not Hispanic or Latino	29	32	61
Unknown or Not Reported	10	6	16
Race Units: Subjects			
Asian	5	7	12
Black or African American	2	0	2
White	24	25	49
Other	0	1	1
Not Reported	10	6	16
Number of transfusions in the last 12 months prior to Day −28 Units: Subjects			
<4	20	16	36
≥4	21	23	44
Platelet count at screening Units: Subjects			
<100,000 (count/ cubic millimeter [mm^3])	12	9	21
≥100,000 (count/ mm^3)	29	30	59

End points

End points reporting groups

Reporting group title	Run-in Period: Pegcetacoplan
Reporting group description:	
During the 4-week run-in period (Day –28 to ≤Day 1) all subjects received twice-weekly subcutaneous (SC) doses of pegcetacoplan 1080 milligrams (mg) in addition to their current dosage of eculizumab treatment.	
Reporting group title	Run-in Period: Eculizumab
Reporting group description:	
During the 4-week run-in period (Day –28 to ≤Day 1) all subjects received twice-weekly SC doses of pegcetacoplan 1080 mg in addition to their current dosage of eculizumab treatment.	
Reporting group title	RCP: Pegcetacoplan
Reporting group description:	
On Day 1, the subjects were randomized to receive monotherapy with SC infusions of pegcetacoplan 1080 mg twice-weekly or every 3 days up to the end of the open-label period (Week 48).	
Reporting group title	RCP: Eculizumab
Reporting group description:	
On Day 1, the subjects were randomized to receive monotherapy with their pre-screening stable dose of eculizumab via intravenous infusion every 2 weeks up to the end of the RCP (Week 16).	
Reporting group title	Open-label Period: Continue Pegcetacoplan
Reporting group description:	
On Day 1 of the RCP, the subjects were randomized to receive monotherapy with SC infusions of pegcetacoplan 1080 mg twice-weekly or every 3 days up to the end of the open-label period (Week 48).	
Reporting group title	Open-label Period: Crossover to Pegcetacoplan
Reporting group description:	
Subjects entered the open-label run-in period where they received pegcetacoplan 1080 mg twice-weekly in addition to eculizumab for 4 weeks (Week 17 to Week 20) before receiving monotherapy with SC infusions of pegcetacoplan 1080 mg twice-weekly or every 3 days up to the end of the open-label period (Week 48).	
Subject analysis set title	Treatment Period: Pegcetacoplan
Subject analysis set type	Full analysis
Subject analysis set description:	
During the 4-week run-in period (Day –28 to ≤Day 1) all subjects received twice-weekly SC doses of pegcetacoplan 1080 mg in addition to their current dosage of eculizumab treatment. On Day 1, the subjects were randomized to receive monotherapy with SC infusions of pegcetacoplan 1080 mg twice-weekly or every 3 days up to the end of the open-label period (Week 48).	
Subject analysis set title	Treatment Period: Eculizumab
Subject analysis set type	Full analysis
Subject analysis set description:	
During the 4-week run-in period (Day –28 to ≤Day 1) all subjects received twice-weekly SC doses of pegcetacoplan 1080 mg in addition to their current dosage of eculizumab treatment. On Day 1, the subjects were randomized to receive monotherapy with their pre-screening stable dose of eculizumab via intravenous infusion every 2 weeks up to the end of the RCP (Week 16). Subjects then entered the open-label run-in period where they received pegcetacoplan 1080 mg twice-weekly in addition to eculizumab for 4 weeks (Week 17 to Week 20) before receiving monotherapy with SC infusions of pegcetacoplan 1080 mg twice-weekly or every 3 days up to the end of the open-label period (Week 48).	
Subject analysis set title	Open-label Run-in Period: Crossover to Pegcetacoplan
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects in the open-label run-in period received pegcetacoplan 1080 mg twice-weekly in addition to eculizumab for 4 weeks (Week 17 to Week 20).	

Primary: Least Squares (LS) Mean Change From Baseline to Week 16 in Hemoglobin (Hb) Level During the RCP

End point title	Least Squares (LS) Mean Change From Baseline to Week 16 in Hemoglobin (Hb) Level During the RCP

End point description:

Baseline was the average of measurements recorded before taking the first dose of pegcetacoplan, which included local and central laboratory values during the screening period. Analysis excluded data before the RCP and was censored for transfusions. The ITT set included all randomized subjects.

End point type	Primary

End point timeframe:

Baseline and Week 16

End point values	RCP: Pegcetacoplan	RCP: Eculizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	39		
Units: g/dL				
least squares mean (standard error)	2.37 (± 0.363)	-1.47 (± 0.666)		

Statistical analyses

Statistical analysis title	Pegcetacoplan Versus Eculizumab

Statistical analysis description:

The primary endpoint analysis was a between-treatment-group comparison using a mixed effect model for repeated measures (MMRM). The difference between pegcetacoplan and eculizumab LS mean Hb changes from Baseline at Week 16 was calculated along with its 2-sided 95% confidence interval (CI) and associated P-value from the MMRM model for the ITT set, censored for transfusions.

Comparison groups	RCP: Pegcetacoplan v RCP: Eculizumab
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	3.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.33
upper limit	5.34

Notes:

[1] - Superiority was tested at the 5% level. MRMM includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of randomization stratification factors.

Secondary: Percentage of Subjects Who Did Not Require a Transfusion (Transfusion Avoidance) During the RCP

End point title	Percentage of Subjects Who Did Not Require a Transfusion (Transfusion Avoidance) During the RCP

End point description:

Subjects who experienced more than 1 transfusion during the RCP are only counted once. Subjects who did not have a transfusion but withdrew before Week 16 were considered as having a transfusion in the analysis of transfusion avoidance. The ITT set included all randomized subjects.

End point type	Secondary

End point timeframe:

Day 1 to Week 16

End point values	RCP: Pegcetacoplan	RCP: Eculizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	39		
Units: Percentage of subjects				
number (not applicable)	85.4	15.4		

Statistical analyses

Statistical analysis title	Pegcetacoplan Versus Eculizumab

Statistical analysis description:

Analysis was based on prespecified non-inferiority margins (NIM) and non-inferiority was achieved if the lower confidence limit or upper confidence limit of the 95% CI of the treatment difference met the prespecified NIM of -20%. Stratified Cochran-Mantel Haenszel (CMH) chi-square test was used for treatment comparison and the 95% CI for difference in percentage between treatments is constructed using the stratified (Miettinen-Nurminen) method.

Comparison groups	RCP: Pegcetacoplan v RCP: Eculizumab
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	< 0.0001
Method	Miettinen-Nurminen
Parameter estimate	Risk difference (RD)
Point estimate	0.6253
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.483
upper limit	0.7677

Notes:

[2] - Non-inferiority was tested at the 2.5% level.

Secondary: LS Mean Change From Baseline to Week 16 in Absolute Reticulocyte Count (ARC) During the RCP

End point title	LS Mean Change From Baseline to Week 16 in Absolute Reticulocyte Count (ARC) During the RCP

End point description:

Baseline was the average of available measurements recorded from central laboratory before taking the first dose of pegcetacoplan. Analysis excluded data before the RCP and was censored for transfusions. The ITT set included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	RCP: Pegcetacoplan	RCP: Eculizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	39		
Units: 10^9cells/ liter (L)				
least squares mean (standard error)	-135.82 (± 6.543)	27.79 (± 11.859)		

Statistical analyses

Statistical analysis title	Pegcetacoplan Versus Eculizumab

Statistical analysis description:

Analysis was based on prespecified NIM and non-inferiority was achieved if the lower confidence limit or upper confidence limit of the 95% CI of the treatment difference met the prespecified NIM of 10.

Comparison groups	RCP: Pegcetacoplan v RCP: Eculizumab
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	< 0.0001
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-163.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-189.91
upper limit	-137.3

Notes:

[3] - Non-inferiority was tested at the 2.5% level. MMRM includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of randomization stratification factors.

Secondary: LS Mean Change From Baseline to Week 16 in Lactate Dehydrogenase (LDH) Level During the RCP

End point title	LS Mean Change From Baseline to Week 16 in Lactate Dehydrogenase (LDH) Level During the RCP

End point description:

Baseline was the average of available measurements recorded from central laboratory before taking the first dose of pegcetacoplan. Analysis excluded data before the RCP and was censored for transfusions. The ITT set included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	RCP: Pegcetacoplan	RCP: Eculizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	39		
Units: Units (U)/L				
least squares mean (standard error)	-14.76 (± 42.708)	-10.12 (± 71.025)		

Statistical analyses

Statistical analysis title	Pegcetacoplan Versus Eculizumab

Statistical analysis description:

Analysis was based on prespecified NIM and non-inferiority was achieved if the lower confidence limit or upper confidence limit of the 95% CI of the treatment difference met the prespecified NIM of 20.

Comparison groups	RCP: Pegcetacoplan v RCP: Eculizumab
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
P-value	= 0.9557
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-4.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-181.3
upper limit	172.04

Notes:

[4] - Non-inferiority was tested at the 2.5% level. MMRM includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of randomization stratification factors.

Secondary: LS Mean Change From Baseline to Week 16 in Functional Assessment of Chronic Illness Therapy (FACIT) - Fatigue Scale Score During the RCP

End point title	LS Mean Change From Baseline to Week 16 in Functional Assessment of Chronic Illness Therapy (FACIT) - Fatigue Scale Score During the RCP

End point description:

The FACIT-fatigue scale version 4 is a 13-item Likert scaled instrument where the subject was presented with 13 statements and asked to indicate their response as it applied to the past 7 days. The 5 possible responses were 'Not at all' (0), 'A little bit (1), 'Somewhat' (2), 'Quite a bit' (3) and 'Very much' (4). With 13 statements the total score had a range of 0 to 52. A higher score corresponds to a higher quality of life (QoL). Baseline was the last available, nonmissing observation before taking the first dose of pegcetacoplan. Data collected after transfusion is excluded from analysis. The ITT set included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	RCP: Pegcetacoplan	RCP: Eculizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	39		
Units: Score on a scale				
least squares mean (standard error)	9.22 (± 1.607)	-2.65 (± 2.821)		

Statistical analyses

Statistical analysis title	Pegcetacoplan Versus Eculizumab

Statistical analysis description:

Non-inferiority was not assessed because of the prespecified hierarchical testing. Analysis was a between-treatment-group comparison using an MMRM. The difference between pegcetacoplan and eculizumab LS mean changes from Baseline at Week 16 was calculated along with its 2-sided 95% CI and associated P-value from the MMRM model for the ITT set, censored for transfusions.

Comparison groups	RCP: Pegcetacoplan v RCP: Eculizumab
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.0005
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	11.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.49
upper limit	18.25

Notes:

[5] - MRMM includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of randomization stratification factors.

Secondary: Percentage of Subjects Who Achieved a Hb Response in the Absence of Transfusions at Week 16

End point title	Percentage of Subjects Who Achieved a Hb Response in the Absence of Transfusions at Week 16

End point description:

Hb response was defined as an increase of at least 1 g/dL in Hb from Baseline at Week 16. Baseline was the average of measurements recorded before taking the first dose of pegcetacoplan, which included local and central laboratory values during the screening period. Analysis excluded data before the RCP and was censored for transfusions. The ITT set included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	RCP: Pegcetacoplan	RCP: Eculizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	39		
Units: Percentage of subjects				
number (not applicable)	75.6	0.0		

Statistical analyses

Statistical analysis title	Pegcetacoplan Versus Eculizumab
Statistical analysis description:	
Stratified CMH chi-square test was used for treatment comparison and the 95% CI for difference in percentage between treatments is constructed using the stratified Miettinen-Nurminen method.	
Comparison groups	RCP: Pegcetacoplan v RCP: Eculizumab
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in percentage]
Point estimate	0.6745
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5452
upper limit	0.8039

Secondary: Percentage of Subjects Who Achieved Reticulocyte Normalization in the Absence of Transfusions at Week 16

End point title	Percentage of Subjects Who Achieved Reticulocyte Normalization in the Absence of Transfusions at Week 16
End point description:	
Reticulocyte normalization was defined as the ARC being below the upper limit of the gender-specific normal range at Week 16, censored for transfusions. Subjects who received a transfusion between Day 1 and Week 16 or withdrew without providing efficacy data at Week 16 were classified as nonresponders. The ITT set includes all randomized subjects.	
End point type	Secondary
End point timeframe:	
Week 16	

End point values	RCP: Pegcetacoplan	RCP: Eculizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	39		
Units: Percentage of subjects				
number (not applicable)	78.0	2.6		

Statistical analyses

Statistical analysis title	Pegcetacoplan Versus Eculizumab
Statistical analysis description:	
Stratified CMH chi-square test was used for treatment comparison and the 95% CI for difference in percentage between treatments is constructed using the stratified Miettinen-Nurminen method.	
Comparison groups	RCP: Pegcetacoplan v RCP: Eculizumab
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in percentage
Point estimate	0.6639
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5309
upper limit	0.7968

Secondary: Percentage of Subjects Who Achieved Hb Normalization in the Absence of Transfusions at Week 16

End point title	Percentage of Subjects Who Achieved Hb Normalization in the Absence of Transfusions at Week 16
End point description:	
Hb normalization was defined as the Hb level being above the lower limit of the normal range at Week 16, censored for transfusions. Subjects who received a transfusion between Day 1 and Week 16 or withdrew without providing efficacy data at Week 16 are classified as nonnormalization. The ITT set included all randomized subjects.	
End point type	Secondary
End point timeframe:	
Week 16	

End point values	RCP: Pegcetacoplan	RCP: Eculizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	39		
Units: Percentage of subjects				
number (not applicable)	34.1	0.0		

Statistical analyses

Statistical analysis title	Pegcetacoplan Versus Eculizumab

Statistical analysis description:

Stratified CMH chi-square test was used for treatment comparison and the 95% CI for difference in percentage between treatments is constructed using the stratified Miettinen-Nurminen method.

Comparison groups	RCP: Pegcetacoplan v RCP: Eculizumab
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in percentage
Point estimate	0.3043
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1493
upper limit	0.4593

Secondary: LS Mean Change From Baseline to Week 16 in Indirect Bilirubin Level During the RCP

End point title	LS Mean Change From Baseline to Week 16 in Indirect Bilirubin Level During the RCP

End point description:

Baseline was the average of available measurements recorded from central laboratory before taking the first dose of pegcetacoplan. Analysis excluded data before the RCP and was censored for transfusions. The ITT set included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	RCP: Pegcetacoplan	RCP: Eculizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	39		
Units: Micromole (µmol)/L				
least squares mean (standard error)	-17.78 (± 2.727)	4.15 (± 4.477)		

Statistical analyses

Statistical analysis title	Pegcetacoplan Versus Eculizumab

Statistical analysis description:

Analysis was a between-treatment-group comparison using an MMRM. The difference between pegcetacoplan and eculizumab LS mean changes from Baseline at Week 16 was calculated along with its 2-sided 95% CI and associated P-value from the MMRM model for the ITT set, censored for transfusions.

Comparison groups	RCP: Pegcetacoplan v RCP: Eculizumab

Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.0002
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-21.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.49
upper limit	-11.36

Notes:

[6] - MRMM includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of randomization stratification factors.

Secondary: LS Mean Change From Baseline to Week 16 in Haptoglobin Level During the RCP

End point title	LS Mean Change From Baseline to Week 16 in Haptoglobin Level During the RCP

End point description:

Baseline was the average of available measurements recorded from central laboratory before taking the first dose of pegcetacoplan. Analysis excluded data before the RCP and was censored for transfusions. The ITT set included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	RCP: Pegcetacoplan	RCP: Eculizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	39		
Units: g/L				
least squares mean (standard error)	-0.02 (± 0.033)	0.12 (± 0.063)		

Statistical analyses

Statistical analysis title	Pegcetacoplan Versus Eculizumab

Statistical analysis description:

Analysis was a between-treatment-group comparison using an MMRM. The difference between pegcetacoplan and eculizumab LS mean changes from Baseline at Week 16 was calculated along with its 2-sided 95% CI and associated P-value from the MMRM model for the ITT set, censored for transfusions.

Comparison groups	RCP: Pegcetacoplan v RCP: Eculizumab

Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.0369
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	-0.01

Notes:

[7] - MRMM includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of randomization stratification factors.

Secondary: LS Mean Change From Baseline to Week 16 in Linear Analog Scale Assessment (LASA) Scores During the RCP

End point title	LS Mean Change From Baseline to Week 16 in Linear Analog Scale Assessment (LASA) Scores During the RCP

End point description:

The LASA consists of 3 items, where the respondents were asked to rate their perceived level of functioning. Specific domains included activity level, ability to carry out daily activities, and an item for overall QoL. Their level of functioning was reported on a 0 to 100 scale with 0 indicates "As low as could be" and 100 indicates "As high as could be". The combined score ranged from 0 to 300, with higher scores corresponding to a higher QoL. The ITT set included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	RCP: Pegcetacoplan	RCP: Eculizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	39		
Units: Score on a scale				
least squares mean (standard error)	49.38 (± 10.189)	-9.72 (± 18.988)		

Statistical analyses

Statistical analysis title	Pegcetacoplan Versus Eculizumab

Statistical analysis description:

Analysis was a between-treatment-group comparison using an MMRM. The difference between pegcetacoplan and eculizumab LS mean changes from Baseline at Week 16 was calculated along with its 2-sided 95% CI and associated P-value from the MMRM model for the ITT set, censored for transfusions.

Comparison groups	RCP: Pegcetacoplan v RCP: Eculizumab

Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.0069
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	59.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.88
upper limit	101.32

Notes:

[8] - MRMM includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of randomization stratification factors.

Secondary: LS Mean Change From Baseline to Week 16 in European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire - Core 30 Scale (QLQ-C30) Scores During the RCP

End point title	LS Mean Change From Baseline to Week 16 in European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire - Core 30 Scale (QLQ-C30) Scores During the RCP

End point description:

The EORTC QLQ-C30 questionnaire (version 3.0) consists of 30 questions comprised of both multi-item scales and single-item measures to assess overall QoL in subjects. Questions are designated by functional scales, symptom scales, and global subject QoL/overall perceived health status. For the first 28 questions the 4 possible responses are 'Not at all' (1), 'A little' (2), 'Quite a bit' (3) and 'Very much' (4). For the remaining 2 questions the response is requested on a 7-point scale from 1 ('Very poor') to 7 ('Excellent'). The raw scale scores were linear transformed, producing scale scores that ranged from 0% to 100%. A high scale score represents a higher response level. Hence for the functional scales and the global health status a higher score indicates a better QoL, whilst for the symptom scale scores this is implied by a lower score. The ITT set included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	RCP: Pegcetacoplan	RCP: Eculizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	39		
Units: Score on a scale				
least squares mean (standard error)				
Global Health Status/QoL	15.91 (± 3.635)	-2.71 (± 8.515)		
Functional Scales - Physical functioning	16.92 (± 2.081)	4.06 (± 3.605)		
Functional Scales - Role functioning	15.39 (± 3.930)	-9.04 (± 6.954)		
Functional Scales - Emotional functioning	7.98 (± 3.366)	3.86 (± 7.237)		
Functional Scales - Cognitive functioning	5.76 (± 3.258)	-3.80 (± 6.420)		
Functional Scales - Social functioning	15.08 (± 2.946)	3.82 (± 6.349)		

Symptom Scales - Fatigue	-22.93 (± 3.321)	-2.18 (± 6.644)		
Symptom Scales - Nausea and vomiting	-0.34 (± 1.632)	-0.33 (± 3.876)		
Symptom Scales - Pain	-0.74 (± 4.323)	2.01 (± 7.841)		
Symptom Scales - Dyspnoea	-20.12 (± 3.488)	-5.55 (± 7.019)		
Symptom Scales - Insomnia	-9.18 (± 3.955)	-9.50 (± 7.090)		
Symptom Scales - Appetite loss	-3.76 (± 3.357)	4.19 (± 7.009)		
Symptom Scales - Constipation	2.98 (± 3.248)	1.19 (± 8.129)		
Symptom Scales - Diarrhoea	0.31 (± 3.711)	1.68 (± 8.204)		
Symptom Scales - Financial difficulties	-6.82 (± 3.853)	0.58 (± 6.297)		

Statistical analyses

Statistical analysis title	Global Health Status/QoL

Statistical analysis description:

Analysis was a between-treatment-group comparison using an MMRM. The difference between pegcetacoplan and eculizumab LS mean changes from Baseline at Week 16 was calculated along with its 2-sided 95% CI and associated P-value from the MMRM model for the ITT set, censored for transfusions.

Comparison groups	RCP: Pegcetacoplan v RCP: Eculizumab
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.0486
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	18.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	37.13

Notes:

[9] - MRMM includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of randomization stratification factors.

Statistical analysis title	Functional Scales - Physical functioning

Statistical analysis description:

Analysis was a between-treatment-group comparison using an MMRM. The difference between pegcetacoplan and eculizumab LS mean changes from Baseline at Week 16 was calculated along with its 2-sided 95% CI and associated P-value from the MMRM model for the ITT set, censored for transfusions.

Comparison groups	RCP: Pegcetacoplan v RCP: Eculizumab

Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.0023
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	12.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.86
upper limit	20.86

Notes:

[10] - MRMM includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of randomization stratification factors.

Statistical analysis title	Functional Scales - Role functioning

Statistical analysis description:

Analysis was a between-treatment-group comparison using an MMRM. The difference between pegcetacoplan and eculizumab LS mean changes from Baseline at Week 16 was calculated along with its 2-sided 95% CI and associated P-value from the MMRM model for the ITT set, censored for transfusions.

Comparison groups	RCP: Eculizumab v RCP: Pegcetacoplan
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.0027
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	24.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.84
upper limit	40.01

Notes:

[11] - MRMM includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of randomization stratification factors.

Statistical analysis title	Functional Scales - Emotional functioning

Statistical analysis description:

Analysis was a between-treatment-group comparison using an MMRM. The difference between pegcetacoplan and eculizumab LS mean changes from Baseline at Week 16 was calculated along with its 2-sided 95% CI and associated P-value from the MMRM model for the ITT set, censored for transfusions.

Comparison groups	RCP: Pegcetacoplan v RCP: Eculizumab
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.6013
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	4.11

Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.58
upper limit	19.8

Notes:

[12] - MRMM includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of randomization stratification factors.

Statistical analysis title	Functional Scales - Cognitive functioning

Statistical analysis description:

Analysis was a between-treatment-group comparison using an MMRM. The difference between pegcetacoplan and eculizumab LS mean changes from Baseline at Week 16 was calculated along with its 2-sided 95% CI and associated P-value from the MMRM model for the ITT set, censored for transfusions.

Comparison groups	RCP: Pegcetacoplan v RCP: Eculizumab
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.1792
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	9.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.52
upper limit	23.64

Notes:

[13] - MRMM includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of randomization stratification factors.

Statistical analysis title	Functional Scales - Social functioning

Statistical analysis description:

Analysis was a between-treatment-group comparison using an MMRM. The difference between pegcetacoplan and eculizumab LS mean changes from Baseline at Week 16 was calculated along with its 2-sided 95% CI and associated P-value from the MMRM model for the ITT set, censored for transfusions.

Comparison groups	RCP: Pegcetacoplan v RCP: Eculizumab
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	= 0.1039
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	11.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.38
upper limit	24.92

Notes:

[14] - MRMM includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of randomization stratification factors.

Statistical analysis title	Symptom Scales - Fatigue

Statistical analysis description:

Analysis was a between-treatment-group comparison using an MMRM. The difference between pegcetacoplan and eculizumab LS mean changes from Baseline at Week 16 was calculated along with its 2-sided 95% CI and associated P-value from the MMRM model for the ITT set, censored for transfusions.

Comparison groups	RCP: Pegcetacoplan v RCP: Eculizumab
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.0062
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-20.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-35.29
upper limit	-6.19

Notes:

[15] - MRMM includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of randomization stratification factors.

Statistical analysis title	Symptom Scales - Nausea and vomiting

Statistical analysis description:

Analysis was a between-treatment-group comparison using an MMRM. The difference between pegcetacoplan and eculizumab LS mean changes from Baseline at Week 16 was calculated along with its 2-sided 95% CI and associated P-value from the MMRM model for the ITT set, censored for transfusions.

Comparison groups	RCP: Pegcetacoplan v RCP: Eculizumab
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	= 0.9975
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.38
upper limit	8.35

Notes:

[16] - MRMM includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of randomization stratification factors.

Statistical analysis title	Symptom Scales - Pain

Statistical analysis description:

Analysis was a between-treatment-group comparison using an MMRM. The difference between pegcetacoplan and eculizumab LS mean changes from Baseline at Week 16 was calculated along with its 2-sided 95% CI and associated P-value from the MMRM model for the ITT set, censored for transfusions.

Comparison groups	RCP: Pegcetacoplan v RCP: Eculizumab

Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	= 0.7554
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-2.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.36
upper limit	14.85

Notes:

[17] - MRMM includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of randomization stratification factors.

Statistical analysis title	Symptom Scales - Dyspnoea

Statistical analysis description:

Analysis was a between-treatment-group comparison using an MMRM. The difference between pegcetacoplan and eculizumab LS mean changes from Baseline at Week 16 was calculated along with its 2-sided 95% CI and associated P-value from the MMRM model for the ITT set, censored for transfusions.

Comparison groups	RCP: Pegcetacoplan v RCP: Eculizumab
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	= 0.062
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-14.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.9
upper limit	0.76

Notes:

[18] - MRMM includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of randomization stratification factors.

Statistical analysis title	Symptom Scales - Insomnia

Statistical analysis description:

Analysis was a between-treatment-group comparison using an MMRM. The difference between pegcetacoplan and eculizumab LS mean changes from Baseline at Week 16 was calculated along with its 2-sided 95% CI and associated P-value from the MMRM model for the ITT set, censored for transfusions.

Comparison groups	RCP: Pegcetacoplan v RCP: Eculizumab
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.9686
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.32

Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.67
upper limit	16.3

Notes:

[19] - MRMM includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of randomization stratification factors.

Statistical analysis title	Symptom Scales - Appetite loss

Statistical analysis description:

Analysis was a between-treatment-group comparison using an MMRM. The difference between pegcetacoplan and eculizumab LS mean changes from Baseline at Week 16 was calculated along with its 2-sided 95% CI and associated P-value from the MMRM model for the ITT set, censored for transfusions.

Comparison groups	RCP: Pegcetacoplan v RCP: Eculizumab
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other[20]
P-value	= 0.3002
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-7.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.23
upper limit	7.33

Notes:

[20] - MRMM includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of randomization stratification factors.

Statistical analysis title	Symptom Scales - Constipation

Statistical analysis description:

Analysis was a between-treatment-group comparison using an MMRM. The difference between pegcetacoplan and eculizumab LS mean changes from Baseline at Week 16 was calculated along with its 2-sided 95% CI and associated P-value from the MMRM model for the ITT set, censored for transfusions.

Comparison groups	RCP: Pegcetacoplan v RCP: Eculizumab
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other[21]
P-value	= 0.8374
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	1.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.7
upper limit	19.29

Notes:

[21] - MRMM includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of randomization stratification factors.

Statistical analysis title	Symptom Scales - Diarrhoea

Statistical analysis description:

Analysis was a between-treatment-group comparison using an MMRM. The difference between pegcetacoplan and eculizumab LS mean changes from Baseline at Week 16 was calculated along with its 2-sided 95% CI and associated P-value from the MMRM model for the ITT set, censored for transfusions.

Comparison groups	RCP: Pegcetacoplan v RCP: Eculizumab
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other[22]
P-value	= 0.8775
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-1.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.28
upper limit	16.52

Notes:

[22] - MRMM includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of randomization stratification factors.

Statistical analysis title	Symptom Scales - Financial difficulties

Statistical analysis description:

Analysis was a between-treatment-group comparison using an MMRM. The difference between pegcetacoplan and eculizumab LS mean changes from Baseline at Week 16 was calculated along with its 2-sided 95% CI and associated P-value from the MMRM model for the ITT set, censored for transfusions.

Comparison groups	RCP: Pegcetacoplan v RCP: Eculizumab
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	= 0.3066
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-7.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.76
upper limit	6.95

Notes:

[23] - MRMM includes treatment + baseline value + analysis visit + strata + analysis visit × treatment, where strata is the combination of randomization stratification factors.

Secondary: Total Number of PRBC Units Transfused During the RCP

End point title	Total Number of PRBC Units Transfused During the RCP

End point description:

Subjects who withdrew during the RCP before Week 16 will have their number of units of PRBC estimated from the duration they were in the study. The ITT set included all randomized subjects.

End point type	Secondary

End point timeframe:

Day 1 to Week 16

End point values	RCP: Pegcetacoplan	RCP: Eculizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	39		
Units: PRBC Units				
number (not applicable)	26	198		

Statistical analyses

Statistical analysis title	Pegcetacoplan versus Eculizumab
Statistical analysis description:	
Wilcoxon rank-sum test P-value for the comparison between treatments is based on median using stratified non-parametric analysis. The 95% CI is constructed using Hodges-Lehmann Estimation of Location Shift.	
Comparison groups	RCP: Pegcetacoplan v RCP: Eculizumab
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Wilcoxon rank-sum test
Parameter estimate	Median difference (final values)
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	2
upper limit	4

Secondary: Mean Change From Baseline to Week 48 in Hb Level During the Treatment Period

End point title	Mean Change From Baseline to Week 48 in Hb Level During the Treatment Period
End point description:	
Baseline was the average of measurements recorded before taking the first dose of pegcetacoplan, which included local and central laboratory values during the screening period. Analysis excluded data before the RCP and was censored for transfusions. The ITT set included all randomized subjects.	
End point type	Secondary
End point timeframe:	
Baseline and Week 48	

End point values	Treatment Period: Pegcetacoplan	Treatment Period: Eculizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	33	30		
Units: g/dL				
arithmetic mean (standard deviation)	2.47 (± 1.72)	2.93 (± 2.09)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Week 17 to Week 48 in Hb Level During the Open-label Period

End point title	Mean Change From Week 17 to Week 48 in Hb Level During the Open-label Period

End point description:

Baseline was the average of measurements recorded before taking the first dose of pegcetacoplan, which included local and central laboratory values during the screening period. Analysis excluded data before the RCP and was censored for transfusions. The ITT set included all randomized subjects.

End point type	Secondary

End point timeframe:

Week 17 and Week 48

End point values	Open-label Period: Continue Pegcetacoplan	Open-label Period: Crossover to Pegcetacoplan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	29		
Units: g/dL				
arithmetic mean (standard deviation)	-0.16 (± 1.154)	2.89 (± 2.078)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline to Week 48 in ARC During the Treatment Period

End point title	Mean Change From Baseline to Week 48 in ARC During the Treatment Period

End point description:

Baseline was the average of available measurements recorded from central laboratory before taking the first dose of pegcetacoplan. Analysis excluded data before the RCP and was censored for transfusions. The ITT set included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline and Week 48

End point values	Treatment Period: Pegcetacoplan	Treatment Period: Eculizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	29		
Units: 10^9 cells/L				
arithmetic mean (standard deviation)	-135.64 (± 67.90)	-128.22 (± 59.60)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Week 17 to Week 48 in ARC During the Open-label Period

End point title	Mean Change From Week 17 to Week 48 in ARC During the Open-label Period

End point description:

Baseline was the average of available measurements recorded from central laboratory before taking the first dose of pegcetacoplan. Analysis excluded data before the RCP and was censored for transfusions. The ITT set included all randomized subjects.

End point type	Secondary

End point timeframe:

Week 17 and Week 48

End point values	Open-label Period: Continue Pegcetacoplan	Open-label Period: Crossover to Pegcetacoplan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	29		
Units: 10^9 cells/L				
arithmetic mean (standard deviation)	-6.50 (± 26.471)	-121.15 (± 70.969)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline to Week 48 in LDH Level During the Treatment Period

End point title	Mean Change From Baseline to Week 48 in LDH Level During the Treatment Period

End point description:

Baseline was the average of available measurements recorded from central laboratory before taking the first dose of pegcetacoplan. Analysis excluded data before the RCP and was censored for transfusions. The ITT set included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline and Week 48

End point values	Treatment Period: Pegcetacoplan	Treatment Period: Eculizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	33	30		
Units: U/L				
arithmetic mean (standard deviation)	-41.53 (± 153.68)	-105.27 (± 315.59)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Week 17 to Week 48 in LDH Level During the Open-label Period

End point title	Mean Change From Week 17 to Week 48 in LDH Level During the Open-label Period

End point description:

Baseline was the average of available measurements recorded from central laboratory before taking the first dose of pegcetacoplan. Analysis excluded data before the RCP and was censored for transfusions. The ITT set included all randomized subjects.

End point type	Secondary

End point timeframe:

Week 17 and Week 48

End point values	Open-label Period: Continue Pegcetacoplan	Open-label Period: Crossover to Pegcetacoplan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	28		
Units: U/L				
arithmetic mean (standard deviation)	8.03 (± 129.285)	-46.84 (± 292.607)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline to Week 48 in FACIT-fatigue Scale Score During the Treatment Period

End point title	Mean Change From Baseline to Week 48 in FACIT-fatigue Scale Score During the Treatment Period

End point description:

The FACIT-fatigue scale version 4 is a 13-item Likert scaled instrument where the subject was presented with 13 statements and asked to indicate their response as it applied to the past 7 days. The 5 possible responses were 'Not at all' (0), 'A little bit (1), 'Somewhat' (2), 'Quite a bit' (3) and 'Very much' (4). With 13 statements the total score had a range of 0 to 52. A higher score corresponds to a higher QoL. Baseline was the last available, nonmissing observation before taking the first dose of pegcetacoplan. Data collected after transfusion is excluded from analysis. The ITT set included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline and Week 48

End point values	Treatment Period: Pegcetacoplan	Treatment Period: Eculizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	29		
Units: Score on a scale				
arithmetic mean (standard deviation)	10.14 (± 9.06)	9.62 (± 10.34)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Week 17 to Week 48 in FACIT-fatigue Scale Score During the Open-label Period

End point title	Mean Change From Week 17 to Week 48 in FACIT-fatigue Scale Score During the Open-label Period

End point description:

The FACIT-fatigue scale is a 13 item Likert scaled instrument where the subject was presented with 13 statements and asked to indicate their response as it applied to the past 7 days. The 5 possible responses were 'Not at all' (0), 'A little bit (1), 'Somewhat' (2), 'Quite a bit' (3) and 'Very much' (4). With 13 statements the total score had a range of 0 to 52. Higher score corresponds to a higher QoL. The ITT set included all randomized subjects.

End point type	Secondary

End point timeframe:

Week 17 and Week 48

End point values	Open-label Period: Continue Pegcetacoplan	Open-label Period: Crossover to Pegcetacoplan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	26		
Units: Score on a scale				
arithmetic mean (standard deviation)	1.28 (± 7.805)	10.19 (± 10.973)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline to Week 48 in LASA Scores During the Treatment Period

End point title	Mean Change From Baseline to Week 48 in LASA Scores During the Treatment Period

End point description:

The LASA consists of 3 items, where the respondents were asked to rate their perceived level of functioning. Specific domains included activity level, ability to carry out daily activities, and an item for overall QoL. Their level of functioning was reported on a 0 to 100 scale with 0 indicates "As low as could be" and 100 indicates "As high as could be". The combined score ranged from 0 to 300, with higher scores corresponding to a higher QoL. The ITT set included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline and Week 48

End point values	Treatment Period: Pegcetacoplan	Treatment Period: Eculizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	29	29		
Units: Score on a scale				
arithmetic mean (standard deviation)	58.66 (± 51.16)	56.52 (± 65.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Week 17 to Week 48 in LASA Scores During the Open-label Period

End point title	Mean Change From Week 17 to Week 48 in LASA Scores During the Open-label Period

End point description:

The FACIT-fatigue scale is a 13 item Likert scaled instrument where the subject was presented with 13 statements and asked to indicate their response as it applied to the past 7 days. The 5 possible responses were 'Not at all' (0), 'A little bit (1), 'Somewhat' (2), 'Quite a bit' (3) and 'Very much' (4).

With 13 statements the total score had a range of 0 to 52. Higher score corresponds to a higher QoL. The ITT set included all randomized subjects.

End point type	Secondary

End point timeframe:

Week 17 and Week 48

End point values	Open-label Period: Continue Pegcetacoplan	Open-label Period: Crossover to Pegcetacoplan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	26		
Units: Score on a scale				
arithmetic mean (standard deviation)	13.13 (± 46.296)	62.92 (± 60.053)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline to Week 48 in QLQ-C30 Scores During the Treatment Period

End point title	Mean Change From Baseline to Week 48 in QLQ-C30 Scores During the Treatment Period

End point description:

The EORTC QLQ-C30 questionnaire (version 3.0) consists of 30 questions comprised of both multi-item scales and single-item measures to assess overall QoL in subjects. Questions are designated by functional scales, symptom scales, and global subject QoL/overall perceived health status. For the first 28 questions the 4 possible responses are 'Not at all' (1), 'A little' (2), 'Quite a bit' (3) and 'Very much' (4). For the remaining 2 questions the response is requested on a 7-point scale from 1 ('Very poor') to 7 ('Excellent'). The raw scale scores were linear transformed, producing scale scores that ranged from 0% to 100%. A high scale score represents a higher response level. Hence for the functional scales and the global health status a higher score indicates a better QoL, whilst for the symptom scale scores this is implied by a lower score. The ITT set included all randomized subjects.

End point type	Secondary

End point timeframe:

Baseline and Week 48

End point values	Treatment Period: Pegcetacoplan	Treatment Period: Eculizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	28		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Global Health Status/QoL	18.89 (± 17.635)	13.99 (± 22.912)		
Functional Scales - Physical functioning	15.33 (± 15.278)	10.80 (± 17.765)		

Functional Scales - Role functioning	16.67 (± 27.334)	20.11 (± 27.595)		
Functional Scales - Emotional functioning	10.28 (± 18.657)	5.36 (± 17.005)		
Functional Scales - Cognitive functioning	7.78 (± 23.462)	0.00 (± 18.703)		
Functional Scales - Social functioning	16.11 (± 24.166)	14.88 (± 22.379)		
Symptom Scales - Fatigue	-21.48 (± 26.733)	-23.75 (± 29.506)		
Symptom Scales - Nausea and vomiting	-2.22 (± 11.357)	0.00 (± 4.454)		
Symptom Scales - Pain	0.56 (± 27.849)	3.45 (± 20.596)		
Symptom Scales - Dyspnoea	-17.78 (± 29.985)	-27.59 (± 33.415)		
Symptom Scales - Insomnia	-6.67 (± 25.371)	0.00 (± 28.172)		
Symptom Scales - Appetite loss	-7.78 (± 14.339)	-3.45 (± 22.440)		
Symptom Scales - Constipation	-1.11 (± 22.289)	-2.38 (± 8.742)		
Symptom Scales - Diarrhoea	1.11 (± 29.664)	5.95 (± 15.853)		
Symptom Scales - Financial difficulties	-15.56 (± 24.343)	-8.33 (± 19.510)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Week 17 to Week 48 in QLQ-C30 Scores During the Open-label Period

End point title	Mean Change From Week 17 to Week 48 in QLQ-C30 Scores During the Open-label Period

End point description:

The EORTC QLQ-C30 questionnaire (version 3.0) consists of 30 questions comprised of both multi-item scales and single-item measures to assess overall QoL in subjects. Questions are designated by functional scales, symptom scales, and global subject QoL/overall perceived health status. For the first 28 questions the 4 possible responses are 'Not at all' (1), 'A little' (2), 'Quite a bit' (3) and 'Very much' (4). For the remaining 2 questions the response is requested on a 7-point scale from 1 ('Very poor') to 7 ('Excellent'). The raw scale scores were linear transformed, producing scale scores that ranged from 0% to 100%. A high scale score represents a higher response level. Hence for the functional scales and the global health status a higher score indicates a better QoL, whilst for the symptom scale scores this is implied by a lower score. The ITT set included all randomized subjects.

End point type	Secondary

End point timeframe:

Week 17 and Week 48

End point values	Open-label Period: Continue Pegcetacoplan	Open-label Period: Crossover to Pegcetacoplan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	26		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Global Health Status/QoL	7.22 (± 19.664)	23.08 (± 22.149)		
Functional Scales - Physical functioning	0.89 (± 10.168)	11.03 (± 17.173)		
Functional Scales - Role functioning	5.00 (± 20.599)	19.87 (± 22.617)		
Functional Scales - Emotional functioning	-2.22 (± 27.328)	1.92 (± 13.806)		
Functional Scales - Cognitive functioning	-2.78 (± 16.999)	2.56 (± 24.355)		
Functional Scales - Social functioning	3.89 (± 18.919)	12.18 (± 23.361)		
Symptom Scales - Fatigue	-2.96 (± 20.824)	-23.08 (± 28.790)		
Symptom Scales - Nausea and vomiting	-2.22 (± 5.762)	-4.49 (± 12.072)		
Symptom Scales - Pain	-2.78 (± 23.195)	-5.77 (± 21.051)		
Symptom Scales - Dyspnoea	3.33 (± 25.295)	-19.23 (± 28.555)		
Symptom Scales - Insomnia	8.89 (± 23.050)	-5.13 (± 27.797)		
Symptom Scales - Appetite loss	-8.89 (± 26.164)	-5.13 (± 22.494)		
Symptom Scales - Constipation	-1.11 (± 20.498)	-1.28 (± 11.473)		
Symptom Scales - Diarrhoea	-4.44 (± 28.679)	3.85 (± 27.206)		
Symptom Scales - Financial difficulties	-2.22 (± 12.172)	-2.56 (± 16.119)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total Number of PRBC Units Transfused During the Open-Label Period

End point title	Total Number of PRBC Units Transfused During the Open-Label Period

End point description:

Number of units of PRBC transfused to subjects in the open-label period are reported. The ITT set included all randomized subjects.

End point type	Secondary

End point timeframe:

Week 17 to Week 48

End point values	Open-label Period: Continue Pegcetacoplan	Open-label Period: Crossover to Pegcetacoplan	Open-label Run-in Period: Crossover to Pegcetacoplan	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	38	39	38	
Units: PRBC Units				
number (not applicable)	68	110	14	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day -28 to Week 54, a maximum of approximately 58 weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	Run-in Periods: Pegcetacoplan + Eculizumab
Reporting group description:	
During the 4-week run-in period (Day –28 to ≤Day 1) all subjects received twice-weekly SC doses of pegcetacoplan 1080 mg in addition to their current dosage of eculizumab treatment. During the 4-week open-label run-in period (Week 17 to Week 20) subjects randomized to receive monotherapy with their pre-screening stable dose of eculizumab via intravenous infusion every 2 weeks during the RCP also received twice-weekly SC doses of pegcetacoplan 1080 mg.	
Reporting group title	Open-label Period: Pegcetacoplan
Reporting group description:	
The subjects who were randomized to receive monotherapy with SC infusions of pegcetacoplan 1080 mg twice-weekly or every 3 days during the RCP continued to receive monotherapy with pegcetacoplan until the end of the open-label period (Week 17 to Week 48). Subjects randomized to receive monotherapy with their pre-screening stable dose of eculizumab via intravenous infusion every 2 weeks during the RCP received monotherapy with SC infusions of pegcetacoplan 1080 mg twice-weekly or every 3 days after the open-label run-in period, up to the end of the open-label period (Week 20 to Week 48).	
Reporting group title	RCP: Eculizumab
Reporting group description:	
Subjects randomized to receive monotherapy with their pre-screening stable dose of eculizumab via intravenous infusion every 2 weeks during the RCP.	
Reporting group title	RCP: Pegcetacoplan
Reporting group description:	
Subjects randomized to receive monotherapy with SC infusions of pegcetacoplan 1080 mg twice-weekly or every 3 days during the RCP.	

Serious adverse events	Run-in Periods: Pegcetacoplan + Eculizumab	Open-label Period: Pegcetacoplan	RCP: Eculizumab
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 80 (5.00%)	18 / 77 (23.38%)	5 / 39 (12.82%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 80 (0.00%)	1 / 77 (1.30%)	0 / 39 (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
Diffuse large B-cell lymphoma			

subjects affected / exposed	0 / 80 (0.00%)	1 / 77 (1.30%)	0 / 39 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 80 (0.00%)	1 / 77 (1.30%)	0 / 39 (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
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 80 (0.00%)	0 / 77 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperthermia			
subjects affected / exposed	0 / 80 (0.00%)	0 / 77 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Allergy to immunoglobulin therapy			
subjects affected / exposed	0 / 80 (0.00%)	1 / 77 (1.30%)	0 / 39 (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
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 80 (0.00%)	1 / 77 (1.30%)	0 / 39 (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
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 80 (0.00%)	0 / 77 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			

subjects affected / exposed	0 / 80 (0.00%)	1 / 77 (1.30%)	0 / 39 (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
Hypersensitivity pneumonitis			
subjects affected / exposed	0 / 80 (0.00%)	1 / 77 (1.30%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 80 (0.00%)	0 / 77 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Facial paralysis			
subjects affected / exposed	0 / 80 (0.00%)	0 / 77 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Haemolysis			
subjects affected / exposed	1 / 80 (1.25%)	5 / 77 (6.49%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytopenia			
subjects affected / exposed	0 / 80 (0.00%)	1 / 77 (1.30%)	0 / 39 (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
Haemolytic anaemia			
subjects affected / exposed	0 / 80 (0.00%)	1 / 77 (1.30%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 80 (0.00%)	1 / 77 (1.30%)	0 / 39 (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

Anaemia			
subjects affected / exposed	0 / 80 (0.00%)	0 / 77 (0.00%)	2 / 39 (5.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 80 (0.00%)	1 / 77 (1.30%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal ischaemia			
subjects affected / exposed	0 / 80 (0.00%)	1 / 77 (1.30%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedematous pancreatitis			
subjects affected / exposed	0 / 80 (0.00%)	1 / 77 (1.30%)	0 / 39 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 80 (0.00%)	1 / 77 (1.30%)	0 / 39 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 80 (0.00%)	1 / 77 (1.30%)	0 / 39 (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
Hepatocellular injury			
subjects affected / exposed	0 / 80 (0.00%)	0 / 77 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 80 (0.00%)	0 / 77 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Jaundice			
subjects affected / exposed	0 / 80 (0.00%)	0 / 77 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 80 (0.00%)	1 / 77 (1.30%)	0 / 39 (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
Musculoskeletal and connective tissue disorders			
Haematoma muscle			
subjects affected / exposed	0 / 80 (0.00%)	1 / 77 (1.30%)	0 / 39 (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	0 / 80 (0.00%)	1 / 77 (1.30%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 80 (0.00%)	2 / 77 (2.60%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial infection			
subjects affected / exposed	0 / 80 (0.00%)	0 / 77 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary sepsis			
subjects affected / exposed	0 / 80 (0.00%)	1 / 77 (1.30%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			

subjects affected / exposed	0 / 80 (0.00%)	1 / 77 (1.30%)	0 / 39 (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
Post procedural sepsis			
subjects affected / exposed	0 / 80 (0.00%)	1 / 77 (1.30%)	0 / 39 (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
Sepsis			
subjects affected / exposed	2 / 80 (2.50%)	1 / 77 (1.30%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 80 (0.00%)	1 / 77 (1.30%)	0 / 39 (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
Nasopharyngitis			
subjects affected / exposed	1 / 80 (1.25%)	0 / 77 (0.00%)	0 / 39 (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

Serious adverse events	RCP: Pegcetacoplan		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 41 (17.07%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diffuse large B-cell lymphoma			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperthermia			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Allergy to immunoglobulin therapy			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypersensitivity pneumonitis			

subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Facial paralysis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Haemolysis			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cytopenia			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemolytic anaemia			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anaemia			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intestinal ischaemia			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oedematous pancreatitis			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatocellular injury			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperbilirubinaemia			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Jaundice			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Haematoma muscle			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bacterial infection			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Biliary sepsis			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Post procedural sepsis			

subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nasopharyngitis			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Run-in Periods: Pegcetacoplan + Eculizumab	Open-label Period: Pegcetacoplan	RCP: Eculizumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	71 / 80 (88.75%)	71 / 77 (92.21%)	36 / 39 (92.31%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 80 (0.00%)	3 / 77 (3.90%)	1 / 39 (2.56%)
occurrences (all)	0	4	1
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	33 / 80 (41.25%)	9 / 77 (11.69%)	0 / 39 (0.00%)
occurrences (all)	75	127	0
Fatigue			
subjects affected / exposed	5 / 80 (6.25%)	8 / 77 (10.39%)	6 / 39 (15.38%)
occurrences (all)	5	11	7
Pyrexia			

subjects affected / exposed	6 / 80 (7.50%)	6 / 77 (7.79%)	1 / 39 (2.56%)
occurrences (all)	6	9	1
Injection site pruritus			
subjects affected / exposed	12 / 80 (15.00%)	5 / 77 (6.49%)	0 / 39 (0.00%)
occurrences (all)	14	7	0
Asthenia			
subjects affected / exposed	1 / 80 (1.25%)	4 / 77 (5.19%)	5 / 39 (12.82%)
occurrences (all)	1	4	7
Injection site bruising			
subjects affected / exposed	2 / 80 (2.50%)	3 / 77 (3.90%)	0 / 39 (0.00%)
occurrences (all)	3	7	0
Injection site induration			
subjects affected / exposed	5 / 80 (6.25%)	5 / 77 (6.49%)	0 / 39 (0.00%)
occurrences (all)	12	27	0
Injection site reaction			
subjects affected / exposed	8 / 80 (10.00%)	2 / 77 (2.60%)	0 / 39 (0.00%)
occurrences (all)	26	8	0
Injection site swelling			
subjects affected / exposed	10 / 80 (12.50%)	1 / 77 (1.30%)	0 / 39 (0.00%)
occurrences (all)	18	4	0
Injection site pain			
subjects affected / exposed	6 / 80 (7.50%)	4 / 77 (5.19%)	0 / 39 (0.00%)
occurrences (all)	13	68	0
Vaccination site pain			
subjects affected / exposed	3 / 80 (3.75%)	0 / 77 (0.00%)	2 / 39 (5.13%)
occurrences (all)	3	0	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 80 (2.50%)	9 / 77 (11.69%)	1 / 39 (2.56%)
occurrences (all)	2	9	1
Oropharyngeal pain			
subjects affected / exposed	0 / 80 (0.00%)	6 / 77 (7.79%)	3 / 39 (7.69%)
occurrences (all)	0	7	3
Dyspnoea			

subjects affected / exposed	4 / 80 (5.00%)	2 / 77 (2.60%)	3 / 39 (7.69%)
occurrences (all)	4	2	4
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 80 (2.50%)	4 / 77 (5.19%)	2 / 39 (5.13%)
occurrences (all)	2	5	2
Insomnia			
subjects affected / exposed	0 / 80 (0.00%)	1 / 77 (1.30%)	2 / 39 (5.13%)
occurrences (all)	0	1	2
Injury, poisoning and procedural complications			
Vaccination complication			
subjects affected / exposed	2 / 80 (2.50%)	2 / 77 (2.60%)	0 / 39 (0.00%)
occurrences (all)	3	2	0
Contusion			
subjects affected / exposed	3 / 80 (3.75%)	4 / 77 (5.19%)	0 / 39 (0.00%)
occurrences (all)	3	4	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 80 (1.25%)	1 / 77 (1.30%)	2 / 39 (5.13%)
occurrences (all)	2	1	2
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 80 (12.50%)	8 / 77 (10.39%)	9 / 39 (23.08%)
occurrences (all)	12	13	10
Dizziness			
subjects affected / exposed	3 / 80 (3.75%)	3 / 77 (3.90%)	5 / 39 (12.82%)
occurrences (all)	3	3	5
Lethargy			
subjects affected / exposed	0 / 80 (0.00%)	0 / 77 (0.00%)	2 / 39 (5.13%)
occurrences (all)	0	0	2
Blood and lymphatic system disorders			
Haemolysis			
subjects affected / exposed	1 / 80 (1.25%)	13 / 77 (16.88%)	9 / 39 (23.08%)
occurrences (all)	1	14	14
Thrombocytopenia			

subjects affected / exposed	2 / 80 (2.50%)	3 / 77 (3.90%)	0 / 39 (0.00%)
occurrences (all)	2	5	0
Anaemia			
subjects affected / exposed	1 / 80 (1.25%)	2 / 77 (2.60%)	5 / 39 (12.82%)
occurrences (all)	1	2	5
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	10 / 80 (12.50%)	11 / 77 (14.29%)	2 / 39 (5.13%)
occurrences (all)	11	15	2
Abdominal pain			
subjects affected / exposed	2 / 80 (2.50%)	3 / 77 (3.90%)	3 / 39 (7.69%)
occurrences (all)	2	3	3
Abdominal distension			
subjects affected / exposed	1 / 80 (1.25%)	4 / 77 (5.19%)	1 / 39 (2.56%)
occurrences (all)	1	4	1
Nausea			
subjects affected / exposed	7 / 80 (8.75%)	2 / 77 (2.60%)	2 / 39 (5.13%)
occurrences (all)	8	4	2
Vomiting			
subjects affected / exposed	1 / 80 (1.25%)	3 / 77 (3.90%)	4 / 39 (10.26%)
occurrences (all)	1	3	4
Abdominal discomfort			
subjects affected / exposed	2 / 80 (2.50%)	0 / 77 (0.00%)	2 / 39 (5.13%)
occurrences (all)	2	0	2
Constipation			
subjects affected / exposed	1 / 80 (1.25%)	2 / 77 (2.60%)	3 / 39 (7.69%)
occurrences (all)	1	2	3
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 80 (0.00%)	3 / 77 (3.90%)	2 / 39 (5.13%)
occurrences (all)	0	3	2
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 80 (0.00%)	3 / 77 (3.90%)	0 / 39 (0.00%)
occurrences (all)	0	3	0
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	0 / 80 (0.00%)	4 / 77 (5.19%)	0 / 39 (0.00%)
occurrences (all)	0	4	0
Chromaturia			
subjects affected / exposed	3 / 80 (3.75%)	2 / 77 (2.60%)	2 / 39 (5.13%)
occurrences (all)	3	2	3
Haemoglobinuria			
subjects affected / exposed	0 / 80 (0.00%)	1 / 77 (1.30%)	2 / 39 (5.13%)
occurrences (all)	0	1	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 80 (2.50%)	6 / 77 (7.79%)	2 / 39 (5.13%)
occurrences (all)	2	7	2
Pain in extremity			
subjects affected / exposed	3 / 80 (3.75%)	5 / 77 (6.49%)	2 / 39 (5.13%)
occurrences (all)	3	6	2
Back pain			
subjects affected / exposed	3 / 80 (3.75%)	2 / 77 (2.60%)	4 / 39 (10.26%)
occurrences (all)	3	2	4
Myalgia			
subjects affected / exposed	3 / 80 (3.75%)	4 / 77 (5.19%)	1 / 39 (2.56%)
occurrences (all)	3	4	3
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 80 (5.00%)	12 / 77 (15.58%)	2 / 39 (5.13%)
occurrences (all)	5	13	2
Upper respiratory tract infection			
subjects affected / exposed	0 / 80 (0.00%)	7 / 77 (9.09%)	1 / 39 (2.56%)
occurrences (all)	0	8	1
Urinary tract infection			
subjects affected / exposed	1 / 80 (1.25%)	7 / 77 (9.09%)	2 / 39 (5.13%)
occurrences (all)	1	7	2
Oral herpes			
subjects affected / exposed	1 / 80 (1.25%)	6 / 77 (7.79%)	0 / 39 (0.00%)
occurrences (all)	1	7	0
Sinusitis			

subjects affected / exposed	1 / 80 (1.25%)	3 / 77 (3.90%)	2 / 39 (5.13%)
occurrences (all)	1	3	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 80 (0.00%)	2 / 77 (2.60%)	2 / 39 (5.13%)
occurrences (all)	0	2	2

Non-serious adverse events	RCP: Pegcetacoplan		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 41 (87.80%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	7 / 41 (17.07%)		
occurrences (all)	44		
Fatigue			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Injection site pruritus			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Asthenia			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Injection site bruising			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Injection site induration			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	8		
Injection site reaction			

subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	56		
Injection site swelling			
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	6		
Injection site pain			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	9		
Vaccination site pain			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Dyspnoea			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Vaccination complication			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Contusion			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Cardiac disorders			

Palpitations			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Dizziness			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Lethargy			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Haemolysis			
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	4		
Thrombocytopenia			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Anaemia			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 41 (21.95%)		
occurrences (all)	9		
Abdominal pain			
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	4		
Abdominal distension			
subjects affected / exposed	0 / 41 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Vomiting			

subjects affected / exposed occurrences (all) Abdominal discomfort subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0 2 / 41 (4.88%) 2 0 / 41 (0.00%) 0		
Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1		
Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all)	2 / 41 (4.88%) 2		
Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all) Chromaturia subjects affected / exposed occurrences (all) Haemoglobinuria subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0 0 / 41 (0.00%) 0 0 / 41 (0.00%) 0		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all)	2 / 41 (4.88%) 2 2 / 41 (4.88%) 5 3 / 41 (7.32%) 4		

Myalgia subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Oral herpes subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all)	 3 / 41 (7.32%) 3 1 / 41 (2.44%) 1 0 / 41 (0.00%) 0 2 / 41 (4.88%) 2 1 / 41 (2.44%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 0 / 41 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 August 2018	Protocol amendment 1 included the following changes: - Allowed subjects to proceed to Visit 2 at any time (rather than waiting at least 2 weeks) after confirmation of study eligibility. - Clarified the appropriate 6-hour postdose pharmacokinetics sample window: ±30 minutes. - End of trial was defined as follows: The end of the trial is defined as when the last subject either completes their Week 48 visit and enrolls in the long-term safety extension (LTSE) study, or, should a subject elect not to enter the LTSE study, when the last subject completes their exit visit at Week 60. - Clarified that during the 4-week run-in period (Week - 4 to Day -1), Visit 5 (Day 1), and through the course of the study, pegcetacoplan administration and study visits should be conducted and scheduled independently of each subject's regular eculizumab administration schedule. - Inclusion Criterion #13: added to require that subjects have a body mass index (BMI) ≤40 in order to qualify for study entry. - Inclusion Criterion #5: updated eligibility of ARC >1.0× upper limit of normal (ULN) at screening visit (from previous requirement of >1.5× ULN). - LDH isoenzymes and erythropoietin were added to the serum chemistry panel.
13 December 2018	Protocol amendment 2 included the following changes: - Screening window extended to up to 8 weeks (Week - 12) - Clarified that use of silica reagents in coagulation panels was to be avoided. - Added emphasis that subjects should be instructed to take pegcetacoplan treatment as prescribed and should contact the investigator immediately for guidance in the event of any missed doses. - Allowed administration of eculizumab at home. - Clarified that there was no requirement for eculizumab to be administered on the day of a study visit. - Clarified that subjects administer pegcetacoplan at the study site through the run-in period and on Day 1. After that, every effort should be made to ensure that the subject's pegcetacoplan dosing schedule aligned with study visit days. If not possible, dosing should occur according to the dosing schedule and not the visit schedule, as there was no requirement for subjects to administer pegcetacoplan at the study site. - Noted that if a screening visit was more than 28 days before dosing, the hematology panel should be repeated.
08 February 2019	Protocol amendment 3 included the following changes: - Re-arranged secondary endpoints into key secondary and secondary endpoints. The classification of "tertiary endpoints" was removed and former tertiary endpoints were reclassified as secondary endpoints. The duration of when the endpoint was being assessed was specified within some endpoint descriptions for clarity. - Modified randomization stratification factors as follows: 1. Number of PRBC transfusions within the 12 months prior to Day -28 (<4; ≥4) 2. Platelet count at screening (<100,000; ≥100,000). - The study diagram and descriptions of the study were modified to remove references to the wash-out period. - Modified Inclusion Criterion #13: excluded subjects with Class 2 or greater obesity (subjects with a BMI ≥35.0 kg/m^2).

16 August 2019	Protocol amendment 4 included the following changes: - Clarified S. pneumoniae vaccination requirements. - Clarified that during the screening period (from up to Week -12 to Week -4), clinical laboratory tests (eg, hematology, coagulation, serum chemistry, flow cytometry, urinalysis) could be repeated with written approval from the sponsor (including the assigned medical monitor), with no requirement to designate the subject as a screen failure. - Dose adjustment was updated to mandate dose escalation to 1080 mg every third day upon the first instance of LDH >2× ULN, rather than requiring LDH to be elevated on 2 consecutive occasions at least 1 week apart. - Clarified subject transfusion history collection requirements.
06 May 2020	As a result of the COVID-19 global pandemic, Apellis issued an Urgent Safety Measure to safeguard the rights, welfare, and safety of APL2-302 study subjects and investigative site staff. Protocol amendment 5 included the following changes: - Added clarifying language to indicate that a dose adjustment can occur for subjects receiving pegcetacoplan monotherapy if LDH is >2 × ULN "on 1 occasion.". - Terminology updated to reflect current language regarding antidrug antibody assessments, pegcetacoplan peptide antibodies, or anti-pegcetacoplan antibodies. - The "Unknown" category of relationship between adverse events and serious adverse events to study treatment was removed. - Severity of events definitions were updated. - Appendix 6 added to reflect changes made as a result of the COVID-19 pandemic.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported