Clinical trial results:
A Phase 3, Randomized, Multicenter, Open-Label, Controlled Study to Evaluate the Efficacy and Safety of APL-2 in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH)

Summary

EudraCT number	2018-004220-11
Trial protocol	PL
Global end of trial date	23 June 2021

Results information

Result version number	v1 (current)
This version publication date	14 August 2022
First version publication date	14 August 2022

Trial information

Trial identification

Sponsor protocol code	APL2-308

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04085601
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Apellis Pharmaceuticals, Inc
Sponsor organisation address	100 5th Avenue, Waltham, Massachusetts, United States, 02451
Public contact	Apellis Pharmaceuticals, Inc,, Apellis Clinical Trial Information Line, 1 833-284-6361, clinicaltrials@apellis.com
Scientific contact	Apellis Pharmaceuticals, Inc,, Apellis Clinical Trial Information Line, 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	23 June 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of pegcetacoplan (APL-2), compared to standard of care (SoC) (excluding complement inhibitors), in subjects with paroxysmal nocturnal hemoglobinuria (PNH), as assessed by:
• Hemoglobin (Hb) stabilization, defined as avoidance of a > 1 gram per deciliter (g/dL) decrease in Hb levels from Baseline in the absence of transfusion through Week 26 (Yes/No)
AND
• Reduction in lactate dehydrogenase (LDH) level from Baseline to Week 26

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 safety and tolerability data of the study periodically.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 August 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Thailand: 13
Country: Number of subjects enrolled	Malaysia: 7
Country: Number of subjects enrolled	Hong Kong: 4
Country: Number of subjects enrolled	Mexico: 2
Country: Number of subjects enrolled	Singapore: 3
Country: Number of subjects enrolled	Philippines: 12
Country: Number of subjects enrolled	Peru: 9
Country: Number of subjects enrolled	Colombia: 3
Worldwide total number of subjects	53
EEA total number of subjects	0

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)	47
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted in subjects with PNH at 22 investigational sites. The study consisted of a screening period (up to 4 weeks), followed by a randomized controlled period (RCP) (26 weeks). All subjects who completed RCP rolled over into a separate open-label, long-term extension study (APL2-307) or completed the safety follow-up (34 weeks).

Pre-assignment

Screening details:

A total of 68 subjects were screened. Of which, 53 subjects with PNH who met all of the inclusion criteria and none of the exclusion criteria were randomized in a 2:1 ratio either to receive pegcetacoplan or to remain on their current SoC in RCP.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Pegcetacoplan

Arm description:

Subjects were received subcutaneous (SC) infusion of pegcetacoplan 1080 milligram (mg) twice weekly or every 3 days up to end of the RCP (Week 26). Subjects were not allowed to receive treatment with other complement inhibitors.

Arm type	Experimental
Investigational medicinal product name	Pegcetacoplan
Investigational medicinal product code	APL-2
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Pegcetacoplan was administered as a 20 milliliter SC infusion. The preferred site of infusion was the abdomen.

Arm title	Standard of Care

Arm description:

Subjects continued to receive SoC treatment but were not allowed to receive treatment with a complement inhibitor unless they qualified for pegcetacoplan escape therapy.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Pegcetacoplan	Standard of Care
Started	35	18
SoC to Pegcetacoplan (Escape therapy)	0 [1]	11 [2]
Completed	33	17
Not completed	2	1
Death	1	1

Lost to follow-up	1	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Subjects assigned to the SoC reporting group were commenced escape pegcetacoplan therapy if they were classified as a failure for the first coprimary endpoint.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Subjects assigned to the SoC reporting group were commenced escape pegcetacoplan therapy if they were classified as a failure for the first coprimary endpoint.

Baseline characteristics

Reporting groups	
Reporting group title	Pegcetacoplan
Reporting group description:	
Subjects were received subcutaneous (SC) infusion of pegcetacoplan 1080 milligram (mg) twice weekly or every 3 days up to end of the RCP (Week 26). Subjects were not allowed to receive treatment with other complement inhibitors.	
Reporting group title	Standard of Care
Reporting group description:	
Subjects continued to receive SoC treatment but were not allowed to receive treatment with a complement inhibitor unless they qualified for pegcetacoplan escape therapy.	

Reporting group values	Pegcetacoplan	Standard of Care	Total
Number of subjects	35	18	53
Age categorical Units: Subjects			
<65 years	33	14	47
>= 65 and < 75 years	2	4	6
Age continuous Units: years			
arithmetic mean	42.2	49.1	
standard deviation	± 12.70	± 15.64	-
Gender categorical Units: Subjects			
Female	16	8	24
Male	19	10	29
Race Units: Subjects			
Black or African American	2	0	2
American Indian or Alaska Native	9	2	11
Asian	23	16	39
Other	1	0	1
Ethnicity Units: Subjects			
Hispanic or Latino	12	2	14
Not Hispanic or Latino	23	16	39

End points

End points reporting groups

Reporting group title	Pegcetacoplan
Reporting group description:	
Subjects were received subcutaneous (SC) infusion of pegcetacoplan 1080 milligram (mg) twice weekly or every 3 days up to end of the RCP (Week 26). Subjects were not allowed to receive treatment with other complement inhibitors.	
Reporting group title	Standard of Care
Reporting group description:	
Subjects continued to receive SoC treatment but were not allowed to receive treatment with a complement inhibitor unless they qualified for pegcetacoplan escape therapy.	

Primary: Number of Subjects who Achieved Hb Stabilization

End point title	Number of Subjects who Achieved Hb Stabilization
End point description:	
The Hb stabilization was defined as avoidance of a >1 g/dL decrease in Hb concentration from Baseline in the absence of transfusion through Week 26. The intent-to-treat (ITT) set included all subjects assigned to treatment.	
End point type	Primary
End point timeframe:	
From Baseline (Day 1) up to Week 26	

End point values	Pegcetacoplan	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	18		
Units: subjects				
number (not applicable)	30	0		

Statistical analyses

Statistical analysis title	Treatment difference in Hb Stabilization
Comparison groups	Pegcetacoplan v Standard of Care
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	0.7311

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.572
upper limit	0.8902

Notes:

[1] - Cochran-Mantel-Haenszel test is stratified by number of packed red blood cell (PRBC) within 12 months prior to screening (<4, ≥ 4) reported in electronic data capture (EDC) data.

Primary: Change From Baseline in LDH Concentration At Week 26

End point title	Change From Baseline in LDH Concentration At Week 26

End point description:

The LDH concentration was analyzed using an analysis of covariance (ANCOVA) model with a last observation carried forward (LOCF) and a baseline observation carried forward (BOCF) approach for handling missing data. Baseline was defined as average of measurements prior to first dose of pegcetacoplan or on or prior to randomization of SoC. Post baseline missing values are imputed using multiple imputation method with Markov Chain Mont Carlo method. The ITT set included all subjects assigned to treatment.

End point type	Primary

End point timeframe:

Baseline (Day 1) and Week 26

End point values	Pegcetacoplan	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	18		
Units: Units/Liter (U/L)				
least squares mean (standard error)	-1870.47 (± 100.971)	-400.09 (± 312.988)		

Statistical analyses

Statistical analysis title	Treatment difference in LDH level
Comparison groups	Pegcetacoplan v Standard of Care
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-1470.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2113.44
upper limit	-827.32

Notes:

[2] - P-value for Baseline, strata and treatment is from least square (LS) mean of proc mixed and proc mianalyze based on parameter estimates.

Secondary: Number of Subjects with an Hb Response in the Absence of Transfusions

End point title	Number of Subjects with an Hb Response in the Absence of Transfusions

End point description:

An Hb response was defined as a =>1 g/dL increase in Hb from baseline at Week 26. The ITT set included all subjects assigned to treatment.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Pegcetacoplan	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	18		
Units: subjects				
number (not applicable)	25	1		

Statistical analyses

Statistical analysis title	Hb Response in the absence of transfusion
Comparison groups	Pegcetacoplan v Standard of Care
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	0.5411
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.339
upper limit	0.7431

Notes:

[3] - Cochran-Mantel-Haenszel test is stratified by number of PRBC within 12 months prior to screening (<4, ≥ 4) reported in EDC data.

Secondary: Change From Baseline in Absolute Reticulocyte Count (ARC) at Week 26

End point title	Change From Baseline in Absolute Reticulocyte Count (ARC) at Week 26

End point description:

Blood samples were collected via direct venipuncture at the specific time points to determine ARC. Baseline was defined as average of measurements prior to first dose of pegcetacoplan or on or prior to randomization of SoC. Post baseline missing values are imputed using multiple imputation method with Markov Chain Mont Carlo method. The ITT set included all subjects assigned to treatment.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Pegcetacoplan	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	18		
Units: 10^9/L				
least squares mean (standard error)	-123.26 (± 9.164)	-19.44 (± 25.209)		

Statistical analyses

Statistical analysis title	ARC during RCP
Comparison groups	Pegcetacoplan v Standard of Care
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [4]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-103.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-158.9
upper limit	-48.74

Notes:

[4] - P-value for Baseline, strata and treatment is from LS mean of proc mixed and proc mianalyze based on parameter estimates.

Secondary: Change From Baseline in Hb Concentration at Week 26

End point title	Change From Baseline in Hb Concentration at Week 26

End point description:

Baseline was defined as average of measurements prior to first dose of pegcetacoplan or on or prior to randomization of SoC. Post baseline missing values are imputed using multiple imputation method with Markov Chain Mont Carlo method. The ITT set included all subjects assigned to treatment.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Pegcetacoplan	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	18		
Units: g/dL				
least squares mean (standard error)	2.94 (± 0.383)	0.27 (± 0.759)		

Statistical analyses

Statistical analysis title	Hb change from Baseline
Comparison groups	Pegcetacoplan v Standard of Care
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0019 [5]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	2.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	4.35

Notes:

[5] - P-value for baseline, strata and treatment is from LS mean of proc mixed and proc mianalyze based on parameter estimates.

Secondary: Percentage of Subjects Who Received Transfusion or Decrease of Hb >2 g/dL From Baseline

End point title	Percentage of Subjects Who Received Transfusion or Decrease of Hb >2 g/dL From Baseline

End point description:

Transfusion refers to any transfusion of packed red blood cell (PRBC), leukocyte-depleted red blood cells (LDPRC), leukocyte poor packed red blood cell (LPRC), leukocyte poor blood (LPB) or whole blood. The ITT set included all subjects assigned to treatment.

End point type	Secondary

End point timeframe:

At Week 26

End point values	Pegcetacoplan	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	18		
Units: percentage of subjects				
number (not applicable)	11.4	100		

Statistical analyses

Statistical analysis title	Transfusions or decrease of Hb
Comparison groups	Pegcetacoplan v Standard of Care
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	-0.7505
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9041
upper limit	-0.5969

Notes:

[6] - Cochran-Mantel-Haenszel test is stratified by number of PRBC within 12 months prior to screening (<4, ≥4) reported in EDC data.

Secondary: Percentage of Subjects with Transfusion Avoidance

End point title	Percentage of Subjects with Transfusion Avoidance

End point description:

Transfusion avoidance was defined as the percentage of subjects who did not require a transfusion during the RCP. Transfusion refers to any transfusion of PRBC, LDPRC, LPRC, LPB or whole blood. The ITT set included all subjects assigned to treatment.

End point type	Secondary

End point timeframe:

At Week 26

End point values	Pegcetacoplan	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	18		
Units: percentage of subjects				
number (not applicable)	91.4	5.6		

Statistical analyses

Statistical analysis title	Treatment difference in transfusions avoidance
Comparison groups	Pegcetacoplan v Standard of Care

Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	0.7241
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5583
upper limit	0.8899

Notes:

[7] - Cochran-Mantel-Haenszel test is stratified by number of PRBC within 12 months prior to screening (<4, ≥4) reported in EDC data.

Secondary: Number of PRBC Units Transfused from Baseline Through Week 26

End point title	Number of PRBC Units Transfused from Baseline Through Week 26

End point description:

The number of units of PRBC transfusions was estimated. In one transfusion subjects received one or more units. The ITT set included all subjects assigned to treatment.

End point type	Secondary

End point timeframe:

Up to Week 26

End point values	Pegcetacoplan	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	18		
Units: PRBC transfusions				
median (full range (min-max))	0.0 (0 to 19)	3.0 (0 to 13)		

Statistical analyses

Statistical analysis title	Treatment difference in PRBC transfusion units
Comparison groups	Pegcetacoplan v Standard of Care
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	Wilcoxon Rank-Sum Test
Parameter estimate	Median difference (net)
Point estimate	3

Confidence interval	
level	95 %
sides	2-sided
lower limit	2
upper limit	4

Notes:

[8] - 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.

Secondary: Change From Baseline in Functional Assessment of Chronic Illness Therapy- (FACIT-Fatigue) Scale score at Week 26

End point title	Change From Baseline in Functional Assessment of Chronic Illness Therapy- (FACIT-Fatigue) Scale score at Week 26

End point description:

The FACIT-Fatigue Scale is a 13-item Likert scaled instrument that is self-administered by the subjects during clinic visits. Subjects were presented with 13 statements and asked to indicate their responses as it applied to the past 7 days. The 5 possible responses are "Not at all" (0), "A little bit" (1), "Somewhat" (2), "Quite a bit" (3), and "Very much" (4). With 13 statements, the total score has a range of 0 to 52. The higher score corresponded to a higher quality of life. Baseline is defined as average of measurements prior to first dose of pegcetacoplan or on or prior to randomization of SoC. Post baseline missing values are imputed using multiple imputation method with Markov Chain Mont Carlo method. The ITT set included all subjects assigned to treatment.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Pegcetacoplan	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	18		
Units: scores on a scale				
least squares mean (standard error)	7.78 (± 1.210)	3.26 (± 2.113)		

Statistical analyses

Statistical analysis title	Treatment difference in FACIT-Fatigue Scale Scores
Comparison groups	Pegcetacoplan v Standard of Care
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.061 [9]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	4.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	9.24

Notes:

[9] - P-value for baseline, strata and treatment is from LS mean of proc mixed and proc mianalyze based on parameter estimates.

Secondary: Percentage of Subjects with Hb Normalization levels at Week 26

End point title	Percentage of Subjects with Hb Normalization levels at Week 26

End point description:

Normalization of Hb levels defined as >= 1xlower limit of normal (LLN) at Week 26 in the absence of transfusion. Transfusion refers to any transfusion of PRBC, LDPRC, LPRC, LPB or whole blood. The ITT set included all subjects assigned to treatment.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Pegcetacoplan	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	18		
Units: percentage of subjects				
number (not applicable)	45.7	0		

Statistical analyses

Statistical analysis title	Hb normalization
Comparison groups	Pegcetacoplan v Standard of Care
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	0.3645
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1648
upper limit	0.5642

Secondary: Percentage of Subjects With LDH Normalization at Week 26

End point title	Percentage of Subjects With LDH Normalization at Week 26

End point description:

The LDH normalization was defined as LDH <= 1xULN of normal range at week 26 in the absence of transfusion. Transfusion refers to any transfusion of PRBC, LDPRC, LPPRC, LPRC, LPB or whole blood. The ITT set included all subjects assigned to treatment.

End point type	Secondary

End point timeframe:

At Week 26

End point values	Pegcetacoplan	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	18		
Units: percentage of subjects				
number (not applicable)	65.7	0		

Statistical analyses

Statistical analysis title	LDH Normalization at Week 26
Comparison groups	Pegcetacoplan v Standard of Care
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	0.5592
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3682
upper limit	0.7502

Secondary: Change From Baseline in European Organization for Research and Treatment of Cancer (EORTC) 30-item Core Quality of Life Questionnaire (QLQ-C30) scores at Week 26

End point title	Change From Baseline in European Organization for Research and Treatment of Cancer (EORTC) 30-item Core Quality of Life Questionnaire (QLQ-C30) scores at Week 26

End point description:

The EORTC QLQ-C30 questionnaire (version 3.0) consisted of 30 questions comprised of both multi-item scales and single-item measures to assess overall quality of life in subjects. Questions were 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'). Each scale has a range of 0% - 100%. A high scale score represents a higher response level. Baseline is defined as average of measurements prior to first dose of pegcetacoplan or on or prior to randomization of SoC. Post baseline missing values are imputed using multiple imputation method with Markov Chain Mont Carlo method. The ITT set included all subjects assigned to treatment.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Pegcetacoplan	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	18		
Units: scores on a scale				
least squares mean (standard error)	18.90 (± 2.909)	-2.85 (± 5.703)		

Statistical analyses

Statistical analysis title	Treatment difference in EORTC QLC-C30 score
Comparison groups	Pegcetacoplan v Standard of Care
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006 [10]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	21.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.35
upper limit	34.16

Notes:

[10] - P-value for baseline, strata and treatment is from LS mean of proc mixed and proc mianalyze based on parameter estimates.

Secondary: Change From Baseline in Linear Analog Assessment (LASA) Scales Score at Week 26

End point title	Change From Baseline in Linear Analog Assessment (LASA) Scales Score at Week 26

End point description:

The LASA consisted of 3 items asking respondents to rate their perceived level of functioning. Specific domains include activity level, ability to carry out daily activities, and an item for overall QOL. Their level of functioning was reported on a 0-100 scale with 0 representing "As low as could be" and 100 representing "As high as could be". The ITT set included all subjects assigned to treatment.

End point type	Secondary

End point timeframe:

Baseline and Week 26

End point values	Pegcetacoplan	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	18		
Units: scores on scale				
least squares mean (standard error)	50.39 (± 9.062)	-5.39 (± 17.689)		

Statistical analyses

Statistical analysis title	LASA Scores
Comparison groups	Pegcetacoplan v Standard of Care
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005 [11]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	55.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.83
upper limit	94.74

Notes:

[11] - P-value for baseline, strata and treatment is from LS mean of proc mixed and proc mianalyze based on parameter estimates.

Secondary: Percentage of Subjects with ARC Normalization

End point title	Percentage of Subjects with ARC Normalization

End point description:

Absolute reticulocyte count normalization is defined as ARC < 1xupper limit of normal (ULN) of the gender-specific normal range at week 26 in the absence of transfusion. Subjects who received a transfusion or withdraw from study or escaped from SoC to pegcetacoplan treatment group or lost to follow up without providing efficacy data at Week 26 were classified as non-responders. Transfusion refers to any transfusion of PRBC, LDPRC, LPRC, LPB or whole blood. The ITT set included all subjects assigned to treatment.

End point type	Secondary

End point timeframe:

At Week 26

End point values	Pegcetacoplan	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	18		
Units: percentage of subjects				
number (not applicable)	60.0	5.6		

Statistical analyses

Statistical analysis title	Treatment difference in ARC Normalization
Comparison groups	Pegcetacoplan v Standard of Care
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference
Point estimate	0.4639
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2529
upper limit	0.675

Notes:

[12] - Cochran-Mantel-Haenszel test is stratified by number of PRBC within 12 months prior to screening (<4, ≥ 4) reported in EDC data.

Secondary: Number of Subjects with Failure of Hb Stabilization

End point title	Number of Subjects with Failure of Hb Stabilization

End point description:

Hb stabilization is defined as avoidance of a >1 g/dL decrease in Hb levels from baseline through Week 26 in the absence of transfusion. Transfusion refers to any transfusion of PRBC, LDPRC, LPRC, LPB or whole blood. The ITT set included all subjects assigned to treatment.

End point type	Secondary

End point timeframe:

Up to Week 26

End point values	Pegcetacoplan	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	18		
Units: subjects				
number (not applicable)	4	18		

Statistical analyses

Statistical analysis title	Treatment difference in Hb stabilization failure
Comparison groups	Pegcetacoplan v Standard of Care

Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [13]
Method	Stratified Wilcoxon
Parameter estimate	Stratified Hazard Ratio
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.004
upper limit	0.091

Notes:

[13] - Hazard ratio is based on cox proportional hazards model.

Secondary: Time to First PRBC Transfusion

End point title	Time to First PRBC Transfusion

End point description:

Time to first-on-study PRBC transfusions during RCP were reported. Here 9999 indicates not estimable. The ITT set included all subjects assigned to treatment.

End point type	Secondary

End point timeframe:

Up to Week 26

End point values	Pegcetacoplan	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	18		
Units: weeks				
median (confidence interval 95%)	9999 (9999 to 9999)	7.000 (4.143 to 10.286)		

Statistical analyses

Statistical analysis title	Time to First PRBC Transfusion
Comparison groups	Pegcetacoplan v Standard of Care
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Stratified Wilcoxon
Parameter estimate	Stratified Hazard Ratio
Point estimate	0.025

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.005
upper limit	0.121

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events were reported from the first dose of study medication and for up to 8 weeks after the last dose of study medication, approximately 34 weeks.

Adverse event reporting additional description:

The safety set included all subjects who received at least 1 dose of pegcetacoplan and all subjects who were randomized to SoC. Overall Pegcetacoplan included 11 subjects who escaped from the SoC group to pegcetacoplan group.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Overall Pegcetacoplan

Reporting group description:

Subjects were received SC infusion of pegcetacoplan 1080 mg twice weekly or every 3 days up to end of the RCP (Week 26). Subjects were not allowed to receive treatment with other complement inhibitors. During the study, any subject assigned to the SoC reporting group (excluding complement inhibitors) who had an Hb concentration >=2 g/dL below baseline or who presented with a qualifying thromboembolic event secondary to PNH was offered early escape therapy with pegcetacoplan.

Reporting group title	Standard of Care

Reporting group description:

Subjects continued to receive SoC treatment but were not allowed to receive treatment with a complement inhibitor unless they qualified for pegcetacoplan escape therapy.

Serious adverse events	Overall Pegcetacoplan	Standard of Care	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 46 (13.04%)	3 / 18 (16.67%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	1	1	
Congenital, familial and genetic disorders			
Dermoid cyst			
subjects affected / exposed	1 / 46 (2.17%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 46 (2.17%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neutropenia			

subjects affected / exposed	1 / 46 (2.17%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 46 (2.17%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	0 / 46 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 46 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemolysis			
subjects affected / exposed	1 / 46 (2.17%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 46 (2.17%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 46 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 46 (2.17%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 46 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 46 (2.17%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Herpes virus infection			
subjects affected / exposed	0 / 46 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary tract infection			
subjects affected / exposed	0 / 46 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Metabolic acidosis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Overall Pegcetacoplan	Standard of Care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 46 (76.09%)	12 / 18 (66.67%)	
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	4 / 46 (8.70%)	0 / 18 (0.00%)	
occurrences (all)	4	0	
Fatigue			
subjects affected / exposed	1 / 46 (2.17%)	1 / 18 (5.56%)	
occurrences (all)	1	2	
Malaise			
subjects affected / exposed	0 / 46 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 46 (6.52%)	0 / 18 (0.00%)	
occurrences (all)	3	0	
Epistaxis			
subjects affected / exposed	3 / 46 (6.52%)	0 / 18 (0.00%)	
occurrences (all)	3	0	
Dyspnoea			
subjects affected / exposed	1 / 46 (2.17%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Oropharyngeal discomfort			
subjects affected / exposed	1 / 46 (2.17%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Rhinitis allergic			
subjects affected / exposed	1 / 46 (2.17%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 46 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Investigations			
Blood creatinine increased			
subjects affected / exposed	3 / 46 (6.52%)	0 / 18 (0.00%)	
occurrences (all)	3	0	
Injury, poisoning and procedural complications			
Skin abrasion			

subjects affected / exposed	0 / 46 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 46 (10.87%)	0 / 18 (0.00%)	
occurrences (all)	10	0	
Headache			
subjects affected / exposed	4 / 46 (8.70%)	0 / 18 (0.00%)	
occurrences (all)	9	0	
Somnolence			
subjects affected / exposed	3 / 46 (6.52%)	0 / 18 (0.00%)	
occurrences (all)	3	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 46 (6.52%)	1 / 18 (5.56%)	
occurrences (all)	3	1	
Haemolysis			
subjects affected / exposed	3 / 46 (6.52%)	0 / 18 (0.00%)	
occurrences (all)	3	0	
Thrombocytopenia			
subjects affected / exposed	3 / 46 (6.52%)	0 / 18 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 46 (6.52%)	0 / 18 (0.00%)	
occurrences (all)	3	0	
Abdominal pain upper			
subjects affected / exposed	3 / 46 (6.52%)	1 / 18 (5.56%)	
occurrences (all)	4	1	
Dyspepsia			
subjects affected / exposed	1 / 46 (2.17%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	3 / 46 (6.52%)	0 / 18 (0.00%)	
occurrences (all)	4	0	
Erythema			

subjects affected / exposed	3 / 46 (6.52%)	0 / 18 (0.00%)	
occurrences (all)	4	0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 46 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	6 / 46 (13.04%)	0 / 18 (0.00%)	
occurrences (all)	8	0	
Arthralgia			
subjects affected / exposed	5 / 46 (10.87%)	0 / 18 (0.00%)	
occurrences (all)	9	0	
Musculoskeletal pain			
subjects affected / exposed	3 / 46 (6.52%)	0 / 18 (0.00%)	
occurrences (all)	5	0	
Plantar fasciitis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Infections and infestations			
Viral infection			
subjects affected / exposed	3 / 46 (6.52%)	0 / 18 (0.00%)	
occurrences (all)	3	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 46 (2.17%)	2 / 18 (11.11%)	
occurrences (all)	1	2	
Influenza			
subjects affected / exposed	0 / 46 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	0 / 46 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	6 / 46 (13.04%)	2 / 18 (11.11%)	
occurrences (all)	7	2	

Hyperuricaemia			
subjects affected / exposed	1 / 46 (2.17%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Dehydration			
subjects affected / exposed	0 / 46 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 March 2019	Amended to update throughout to mandate prophylactic antibiotic therapy for 14 days post vaccination. Definitions of coprimary objectives/endpoints were clarified. Secondary objectives were re-ordered. The following secondary objective was added: Normalization of Hb levels (defined as ≥1x ULN) from Baseline at Week 26 in the absence of transfusions (Yes/No). The following safety objective was added to correct an error of omission: Incidence of anti-APL2 antibodies. To ensure equal distribution of baseline characteristics across treatment groups, stratification at randomization was clarified: Randomization were stratified by the following values: number of PRBC transfusions within the 12 months prior to screening (≤4; >4) (ie, number of transfusion events regardless of PRBC units transfused). The following inclusion criterion was modified to exclude subjects with Class 2 or greater obesity from enrolling in the study (subjects with a body mass index ≥35.0 kilogram per square meter, as defined by the US Centers for Disease Control and Prevention's criteria [CDC 2016]). The criteria for escape therapy was clarified as follows: Following Visit 2 (Week 0), subjects assigned to the SoC (excluding complement inhibitors) treatment arm who have an Hb level measured by the central laboratory that is ≥2 g/dL below the Baseline value will be offered the opportunity to receive escape therapy with APL-2. Pharmacokinetic (PK) assessment was changed to Weeks 0, 4, 8, 12, 20, 26, and 30. Complement profile assessment (total hemolytic complement activity assay, alternative pathway hemolytic complement activity assay) was changed to Weeks 0, 4, 8, 12, 20, 26, and 30. The C3 assessment was separated out from complement profile and changed to every clinic visit except screening and APL-2 Initiation Visit.
20 May 2020	Added coronavirus disease 2019 (COVID-19) pandemic-related information. The PK sample collection and complement profile sample collection timepoints shown on the schedule of events were updated to accurately reflect changes made in Amendment 1. The Week 2 draw was removed and a Week 8 draw was added for both PK and complement sample collection. Added benefit/risk information regarding pegcetacoplan use and the potential risks/complications with COVID-19. Deleted the following as a secondary objective: Change from Baseline to Week 26 in Hb level. Added information related to an altitude correction factor for Hb in subjects living at altitudes ≥1000 meters above sea level. A typo in the PRBC transfusion stratification categories (was changed from [≤4; >4] to [<4, ≥4]) was corrected. The statement regarding scheduling of data monitoring committee meetings was removed to allow scheduling flexibility. The LDH criterion for dose increase was changed in order to allow consideration of more frequent dosing to occur after 1 instance of an LDH result of ≥2 x ULN, instead of 2 consecutive occasions at least one week apart. It was clarified that serious adverse event not considered related to study drug, or in subjects randomized to the SoC, do not have to be reported to regulatory authorities.

10 August 2020	Removed language regarding an altitude correction factor for Hb because no subjects enrolled in the study live at altitudes ≥1000 meters above sea level. Added a section regarding the collection of COVID-19 test results. Added a new section, regarding drug abuse, misuse, overdose, and medication error.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported