Clinical trial results:
A Phase 3, Randomized, Open-Label, Active-Controlled Study of ALXN1210 Versus Eculizumab in Complement Inhibitor-Naïve Adult Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH)

Summary

EudraCT number	2016-002025-11
Trial protocol	GB DE SE BE CZ DK PT FI ES NL AT EE PL IT
Global end of trial date	

Results information

Result version number	v1
This version publication date	08 July 2020
First version publication date	08 July 2020

Trial information

Trial identification

Sponsor protocol code	ALXN1210-PNH-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02946463
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alexion Pharmaceuticals Inc.
Sponsor organisation address	121 Seaport Boulevard, Boston, MA, United States, 02210
Public contact	European Clinical Trial Information, Alexion Pharmaceuticals Inc., +33 147100606, clinicaltrials.eu@alexion.com
Scientific contact	European Clinical Trial Information, Alexion Pharmaceuticals Inc., +33 147100606, clinicaltrials.eu@alexion.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	Interim
Date of interim/final analysis	25 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 January 2018
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The primary purpose of this study was to assess the noninferiority of ravulizumab compared to eculizumab in adult participants with PNH who had never been treated with a complement inhibitor (treatment-naïve).

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the countries in which the study was conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 December 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	Estonia: 2
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Argentina: 4
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Brazil: 16
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Japan: 34
Country: Number of subjects enrolled	Malaysia: 30
Country: Number of subjects enrolled	Mexico: 2
Country: Number of subjects enrolled	Russian Federation: 41

Country: Number of subjects enrolled	Singapore: 2
Country: Number of subjects enrolled	Korea, Republic of: 40
Country: Number of subjects enrolled	Taiwan: 8
Country: Number of subjects enrolled	Thailand: 8
Country: Number of subjects enrolled	Turkey: 1
Country: Number of subjects enrolled	United States: 5
Worldwide total number of subjects	246
EEA total number of subjects	50

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)	212
From 65 to 84 years	33
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were stratified into 6 groups based on transfusion history and lactate dehydrogenase (LDH) screening levels. Stratified participants were then randomly assigned in a 1:1 ratio to receive either ravulizumab or eculizumab in the 26-week Primary Evaluation Period.

Period 1

Period 1 title	Primary Evaluation
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Ravulizumab: Primary Evaluation

Arm description:

Participants received weight-based doses of ravulizumab ranging from 2400 to 3000 milligrams (mg) on Day 1. Thereafter, weight-based doses of ravulizumab ranging from 3000 to 3600 mg were administered on Day 15 and every 8 weeks thereafter for 26 weeks.

Arm type	Experimental
Investigational medicinal product name	Ravulizumab
Investigational medicinal product code	
Other name	Ultomiris, ALXN1210
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received weight-based loading doses of ravulizumab ranging from 2400 to 3000 mg on Day 1. Thereafter, weight-based maintenance doses of ravulizumab ranging from 3000 to 3600 mg were administered on Day 15 and every 8 weeks thereafter for 26 weeks.

Arm title	Eculizumab: Primary Evaluation

Arm description:

Participants received 600 mg of eculizumab on Days 1, 8, 15, and 22, followed by 900 mg of eculizumab on Day 29 and every 2 weeks thereafter for 26 weeks.

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

Dosage and administration details:

Participants received 600-mg induction doses of eculizumab on Days 1, 8, 15, and 22, followed by 900-mg maintenance doses of eculizumab on Day 29 and every 2 weeks thereafter for 26 weeks.

Number of subjects in period 1	Ravulizumab: Primary Evaluation	Eculizumab: Primary Evaluation
Started	125	121
Received at Least 1 Dose of Study Drug	125	121
Completed	125	119
Not completed	0	2
Physician decision	-	1
Consent withdrawn by subject	-	1

Period 2

Period 2 title	Extension Period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Ravulizumab: Extension Period

Arm description:

After completion of the Primary Evaluation Period, all participants had the opportunity to enter the Extension Period, wherein participants will receive weight-based doses of ravulizumab for up to 5 years.

Arm type	Experimental
Investigational medicinal product name	Ravulizumab
Investigational medicinal product code	
Other name	Ultomiris, ALXN1210
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Weight-based maintenance doses of ravulizumab ranging from 3000 to 3600 mg were administered every 8 weeks for up to 5 years.

Arm title	Eculizumab/Ravulizumab: Extension Period

Arm description:

After completion of the Primary Evaluation Period, all participants had the opportunity to enter the Extension Period, wherein participants will receive weight-based doses of ravulizumab for up to 5 years.

Arm type	Experimental
Investigational medicinal product name	Ravulizumab
Investigational medicinal product code	
Other name	Ultomiris, ALXN1210
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received weight-based loading doses of ravulizumab ranging from 2400 to 3000 mg on Day 1. Thereafter, weight-based maintenance doses of ravulizumab ranging from 3000 to 3600 mg were administered on Day 15 and every 8 weeks thereafter for 5 years.

Number of subjects in period 2[1]	Ravulizumab: Extension Period	Eculizumab/Ravulizumab: Extension Period
Started	124	119
Received at Least 1 Dose of Study Drug	124	119
Completed	0	0
Not completed	124	119
Extension Period is ongoing	124	119

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: 1 participant did not enter the Extension Period.

Baseline characteristics

Reporting groups	
Reporting group title	Ravulizumab: Primary Evaluation
Reporting group description:	
Participants received weight-based doses of ravulizumab ranging from 2400 to 3000 milligrams (mg) on Day 1. Thereafter, weight-based doses of ravulizumab ranging from 3000 to 3600 mg were administered on Day 15 and every 8 weeks thereafter for 26 weeks.	
Reporting group title	Eculizumab: Primary Evaluation
Reporting group description:	
Participants received 600 mg of eculizumab on Days 1, 8, 15, and 22, followed by 900 mg of eculizumab on Day 29 and every 2 weeks thereafter for 26 weeks.	

Reporting group values	Ravulizumab: Primary Evaluation	Eculizumab: Primary Evaluation	Total
Number of subjects	125	121	246
Age categorical			
Measure Description: Age at first infusion of study drug			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	110	102	212
From 65-84 years	15	18	33
85 years and over	0	1	1
Age continuous			
Measure Description: Age at first infusion of study drug			
Units: years			
arithmetic mean	44.8	46.2	
standard deviation	± 15.16	± 16.24	-
Gender categorical			
Units: Subjects			
Female	60	52	112
Male	65	69	134
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	5	13	18
Not Hispanic or Latino	116	102	218
Unknown or Not Reported	4	6	10
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	1	1	2
Asian	72	57	129
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	4	6

White	43	51	94
More than one race	0	0	0
Unknown or Not Reported	7	8	15

End points

End points reporting groups

Reporting group title	Ravulizumab: Primary Evaluation
Reporting group description:	
Participants received weight-based doses of ravulizumab ranging from 2400 to 3000 milligrams (mg) on Day 1. Thereafter, weight-based doses of ravulizumab ranging from 3000 to 3600 mg were administered on Day 15 and every 8 weeks thereafter for 26 weeks.	
Reporting group title	Eculizumab: Primary Evaluation
Reporting group description:	
Participants received 600 mg of eculizumab on Days 1, 8, 15, and 22, followed by 900 mg of eculizumab on Day 29 and every 2 weeks thereafter for 26 weeks.	
Reporting group title	Ravulizumab: Extension Period
Reporting group description:	
After completion of the Primary Evaluation Period, all participants had the opportunity to enter the Extension Period, wherein participants will receive weight-based doses of ravulizumab for up to 5 years.	
Reporting group title	Eculizumab/Ravulizumab: Extension Period
Reporting group description:	
After completion of the Primary Evaluation Period, all participants had the opportunity to enter the Extension Period, wherein participants will receive weight-based doses of ravulizumab for up to 5 years.	

Primary: Proportion Of Participants With Normalization Of LDH Levels

End point title	Proportion Of Participants With Normalization Of LDH Levels
End point description:	
Lactate dehydrogenase is an indicator of intravascular hemolysis that occurs in participants with paroxysmal nocturnal hemoglobinuria (PNH). A decrease in LDH from above the upper limit of normal (ULN) to below the ULN indicates reduction (improvement) in hemolysis. Normalization of LDH levels (LDH-N) was LDH levels less than or equal to 1 x ULN, from Day 29 through Day 183. The ULN for LDH was 246 units/liter.	
End point type	Primary
End point timeframe:	
Day 29 through Day 183	

End point values	Ravulizumab: Primary Evaluation	Eculizumab: Primary Evaluation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	121		
Units: Proportion of Participants				
number (confidence interval 95%)	0.536 (0.459 to 0.612)	0.494 (0.417 to 0.570)		

Statistical analyses

Statistical analysis title	Analysis of Normalization Of LDH
Statistical analysis description:	
A minimum of 142 participants were estimated to provide 80% power to demonstrate noninferiority of	

ravulizumab to eculizumab.

Comparison groups	Ravulizumab: Primary Evaluation v Eculizumab: Primary Evaluation
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Odds ratio (OR)
Point estimate	1.187
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.796
upper limit	1.769

Notes:

[1] - LDH-N was analyzed using a generalized estimating equation approach. The model included the following terms: treatment group, history of transfusion (as a categorical variable based on the stratification factor levels), and baseline LDH level (as a continuous variable).

Noninferiority margin was based on the lower bound of the 95% confidence interval (CI) for the OR of ravulizumab versus eculizumab for LDH normalization being greater than an OR of 0.39.

Secondary: Percentage Of Participants Who Achieved Transfusion Avoidance

End point title	Percentage Of Participants Who Achieved Transfusion Avoidance

End point description:

The co-primary end point of transfusion avoidance (TA) was defined as the percentage of participants who remained transfusion free and did not require a transfusion per protocol-specified guidelines through Day 183.

End point type	Secondary

End point timeframe:

Baseline through Day 183

End point values	Ravulizumab: Primary Evaluation	Eculizumab: Primary Evaluation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	121		
Units: Percentage of Participants				
number (confidence interval 95%)	73.6 (65.87 to 81.33)	66.1 (57.68 to 74.55)		

Statistical analyses

Statistical analysis title	Analysis of TA

Statistical analysis description:

A minimum of 193 participants were estimated to provide 80% power to demonstrate noninferiority of ravulizumab to eculizumab. The difference of percentages were calculated using stratified Newcombe CI method. Stratification factors were: observed stratification groups of packed red blood cells (pRBC)/whole blood units transfused in the 1 year prior to first dose of study drug and screening LDH

Comparison groups	Ravulizumab: Primary Evaluation v Eculizumab: Primary Evaluation

Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Treatment difference
Point estimate	6.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.66
upper limit	18.14

Notes:

[2] - Noninferiority margin was based on the lower bound of the 95% CI. Noninferiority margin was -20%.

Secondary: Percentage Of Participants With Breakthrough Hemolysis

End point title	Percentage Of Participants With Breakthrough Hemolysis

End point description:

Breakthrough hemolysis (BTH) was defined as at least 1 new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin < 10 gram/deciliter (g/dL)], major adverse vascular event [including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2 × ULN, after prior LDH reduction to < 1.5 × ULN on therapy.

End point type	Secondary

End point timeframe:

Baseline through Day 183

End point values	Ravulizumab: Primary Evaluation	Eculizumab: Primary Evaluation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	121		
Units: Percentage Of Participants				
number (confidence interval 95%)	4.0 (0.56 to 7.44)	10.7 (5.23 to 16.26)		

Statistical analyses

Statistical analysis title	Analysis of BTH

Statistical analysis description:

The difference of percentages was calculated using stratified Newcombe CI method. The stratification factors were: observed stratification groups of pRBC units transfused in the 1 year prior to first dose of study drug and screening LDH levels.

Comparison groups	Ravulizumab: Primary Evaluation v Eculizumab: Primary Evaluation

Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Treatment Difference
Point estimate	-6.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.21
upper limit	0.18

Notes:

[3] - Noninferiority margin was based on the upper bound of the 95% CI. Noninferiority margin was 20%.

Secondary: Percent Change From Baseline In LDH Levels

End point title	Percent Change From Baseline In LDH Levels

End point description:

Baseline is defined as the average of all available assessments of LDH levels prior to first study drug dose. Estimates are based on mixed model for repeated measures (MMRM) that includes treatment group, history of transfusion (as a categorical variable based on the stratification factor levels) and baseline LDH level (as a continuous variable), study visit, and study visit by treatment group interaction. An unstructured covariance structure was used.

End point type	Secondary

End point timeframe:

Baseline, Day 183

End point values	Ravulizumab: Primary Evaluation	Eculizumab: Primary Evaluation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	121		
Units: Percent Change				
least squares mean (confidence interval 95%)	-76.84 (-79.96 to -73.73)	-76.02 (-79.20 to -72.83)		

Statistical analyses

Statistical analysis title	Analysis of LDH
Comparison groups	Ravulizumab: Primary Evaluation v Eculizumab: Primary Evaluation
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Parameter estimate	Treatment Difference
Point estimate	-0.83

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.21
upper limit	3.56

Notes:

[4] - Noninferiority margin was based on the upper bound of the 95% CI. Noninferiority margin was 20%.

Secondary: Change From Baseline In Quality Of Life As Assessed By The Functional Assessment Of Chronic Illness Therapy-Fatigue

End point title	Change From Baseline In Quality Of Life As Assessed By The Functional Assessment Of Chronic Illness Therapy-Fatigue

End point description:

The Functional Assessment Of Chronic Illness Therapy (FACIT)-Fatigue score ranges from 0 to 52, with a higher score indicating less fatigue. Baseline is defined as the last non-missing value prior to first dose of study drug. Estimates are based on MMRM that includes treatment group, the observed stratification randomization indicators (history of transfusion and LDH) and baseline FACIT-Fatigue level, study visit, and study visit by treatment group interaction. An unstructured covariance structure was used.

End point type	Secondary

End point timeframe:

Baseline, Day 183

End point values	Ravulizumab: Primary Evaluation	Eculizumab: Primary Evaluation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	121		
Units: Units On A Scale				
least squares mean (confidence interval 95%)	7.07 (5.55 to 8.60)	6.40 (4.85 to 7.96)		

Statistical analyses

Statistical analysis title	Analysis of FACIT-Fatigue
Comparison groups	Ravulizumab: Primary Evaluation v Eculizumab: Primary Evaluation
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Parameter estimate	Treatment Difference
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.21
upper limit	2.55

Notes:

[5] - Noninferiority margin was based on the lower bound of the 95% CI. Noninferiority margin was -5%.

Secondary: Percentage Of Participants With Stabilized Hemoglobin Levels

End point title	Percentage Of Participants With Stabilized Hemoglobin Levels

End point description:

Stabilized hemoglobin was defined as avoidance of a ≥ 2 g/dL decrease in hemoglobin level from baseline in the absence of transfusion through Day 183.

End point type	Secondary

End point timeframe:

Baseline through Day 183

End point values	Ravulizumab: Primary Evaluation	Eculizumab: Primary Evaluation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	121		
Units: Percentage of Participants				
number (confidence interval 95%)	68.0 (59.82 to 76.18)	64.5 (55.93 to 72.99)		

Statistical analyses

Statistical analysis title	Analysis of Stabilized Hemoglobin Levels

Statistical analysis description:

The difference of percentages was calculated using stratified Newcombe CI method. The stratification factors were: observed stratification groups of pRBC units transfused in the 1 year prior to first dose of study drug and screening LDH levels.

Comparison groups	Ravulizumab: Primary Evaluation v Eculizumab: Primary Evaluation
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Parameter estimate	Treatment Difference
Point estimate	2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.8
upper limit	14.64

Notes:

[6] - Noninferiority margin was based on the lower bound of the 95% CI. Noninferiority margin was -20%.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 (after first dose) through Day 183 (before dosing)

Adverse event reporting additional description:

Treatment-emergent adverse events reported below include those that occurred during the Primary Evaluation Period (during or after the first infusion of study treatment up to or before dosing on Day 183). Adverse events that occurred during or after dosing on Day 183 were considered as part of the Extension Period and were not reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Ravulizumab

Reporting group description:

Participants received weight-based doses of ravulizumab ranging from 2400 to 3000 mg on Day 1. Thereafter, weight-based doses of ravulizumab ranging from 3000 to 3600 mg were administered on Day 15 and every 8 weeks thereafter for 26 weeks.

Reporting group title	Eculizumab

Reporting group description:

Participants received 600 mg of eculizumab on Days 1, 8, 15, and 22, followed by 900 mg of eculizumab on Day 29 and every 2 weeks thereafter for 26 weeks.

Serious adverse events	Ravulizumab	Eculizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 125 (8.80%)	9 / 121 (7.44%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 125 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	0 / 125 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			

subjects affected / exposed[1]	1 / 60 (1.67%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Laceration			
subjects affected / exposed	1 / 125 (0.80%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 125 (0.80%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Left ventricular failure			
subjects affected / exposed	1 / 125 (0.80%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 125 (0.80%)	0 / 121 (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			
Anaemia			
subjects affected / exposed	1 / 125 (0.80%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aplastic anaemia			
subjects affected / exposed	1 / 125 (0.80%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	1 / 125 (0.80%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 125 (0.80%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 125 (0.80%)	2 / 121 (1.65%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	0 / 125 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	0 / 125 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Paroxysmal nocturnal haemoglobinuria			
subjects affected / exposed	0 / 125 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 125 (0.80%)	0 / 121 (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			
Abscess limb			

subjects affected / exposed	0 / 125 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 125 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 125 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leptospirosis			
subjects affected / exposed	1 / 125 (0.80%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 125 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic infection			
subjects affected / exposed	1 / 125 (0.80%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 125 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This is a sex-specific adverse event that only affected female participants.

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

Non-serious adverse events	Ravulizumab	Eculizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	109 / 125 (87.20%)	104 / 121 (85.95%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	9 / 125 (7.20%)	7 / 121 (5.79%)	
occurrences (all)	9	10	
Headache			
subjects affected / exposed	45 / 125 (36.00%)	40 / 121 (33.06%)	
occurrences (all)	70	72	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	6 / 125 (4.80%)	11 / 121 (9.09%)	
occurrences (all)	6	14	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	7 / 125 (5.60%)	7 / 121 (5.79%)	
occurrences (all)	7	7	
Diarrhoea			
subjects affected / exposed	10 / 125 (8.00%)	5 / 121 (4.13%)	
occurrences (all)	12	7	
Nausea			
subjects affected / exposed	11 / 125 (8.80%)	10 / 121 (8.26%)	
occurrences (all)	14	14	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 125 (3.20%)	8 / 121 (6.61%)	
occurrences (all)	4	11	
Oropharyngeal pain			
subjects affected / exposed	8 / 125 (6.40%)	6 / 121 (4.96%)	
occurrences (all)	10	6	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 125 (6.40%)	8 / 121 (6.61%)	
occurrences (all)	12	9	
Back pain			

subjects affected / exposed	7 / 125 (5.60%)	6 / 121 (4.96%)	
occurrences (all)	9	6	
Myalgia			
subjects affected / exposed	7 / 125 (5.60%)	9 / 121 (7.44%)	
occurrences (all)	8	12	
Pain in extremity			
subjects affected / exposed	9 / 125 (7.20%)	7 / 121 (5.79%)	
occurrences (all)	10	8	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	11 / 125 (8.80%)	18 / 121 (14.88%)	
occurrences (all)	14	20	
Upper respiratory tract infection			
subjects affected / exposed	13 / 125 (10.40%)	7 / 121 (5.79%)	
occurrences (all)	15	7	
Viral upper respiratory tract infection			
subjects affected / exposed	9 / 125 (7.20%)	9 / 121 (7.44%)	
occurrences (all)	10	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 September 2016	• Modified the weight-based dosing for ravulizumab. The initial dosing regimen was designed to achieve complete inhibition of terminal complement activity over the entire dosing interval in all participants. After discussion with the United States Food and Drug Administration, it was determined that these slightly lower dosing levels also met the initially established trough exposure levels to ensure complete inhibition of complement component 5 activity in all participants. Changes were as follows: – For participants weighing ≥ 40 to < 60 kilograms (kg): Loading dose changed from 2700 mg to 2400 mg and maintenance dose changed from 3300 mg to 3000 mg – For participants weighing ≥ 60 to < 100 kg: Loading dose changed from 3000 mg to 2700 mg and maintenance dose changed from 3600 mg to 3300 mg – For participants weighing ≥ 100 kg: Loading dose unchanged and maintenance dose changed from 3900 mg to 3600 mg • The Dosing Reference Chart for ravulizumab Dose Preparation also was modified accordingly.
25 January 2017	• Clarified that all safety data, including those in the Extension Period, would be reported. • Text added to address recommendations from regulatory authorities to incorporate a benefit-risk assessment summary in the study protocol. This included addition of a reference. • An additional secondary objective was added to gain an understanding of the benefit-risk of switching participants from eculizumab to ravulizumab. • Text was added as follows to minimize participant discomfort: To minimize needle sticks to the participant, the predose sample may be drawn through the venous access created for the dose infusion, prior to administration of the dose. • A study visit on Day 225 was added globally to the Extension Period for participants who received eculizumab during the Primary Evaluation Period, to allow for assessment 4 weeks after their first maintenance dose of ravulizumab. • Text added to ensure independent review of meningococcal infection cases.

23 October 2017	• Revised the statistical analysis description regarding control of Type I error when testing the primary and secondary end points for noninferiority and superiority. • Clarified that the last recorded study visit body weight should be used for determination of weight-based dose, and if study drug is prepared the night before a visit, the weight from the most recent study visit should be used. • Indicated the maximum permitted duration of an eculizumab infusion. • In order to reduce the incidence of ex vivo hemolyzed blood samples, it was specified that draws should not be made via a heparinized tube. • To reduce the participant data collection burden, removed the exploratory end points of Patient-Reported PNH Symptoms and Healthcare Resource Utilization, their description, and the questionnaires. • Clarified that transfusions administered in the inpatient or outpatient setting should not be captured as adverse events or serious adverse events unless identified as such by the Investigator.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30510080