



Clinical trial results:

A Phase 3, Randomized, Open-Label, Active-Controlled Study of ALXN1210 Versus Eculizumab in Adult Patients With Paroxysmal Nocturnal Hemoglobinuria (PNH) Currently Treated With Eculizumab Summary

EudraCT number	2016-002026-36
Trial protocol	GB DE ES NL 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-302
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03056040
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	08 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 March 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 were clinically stable after having been treated with eculizumab for at least 6 months.

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	05 June 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 11
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	United Kingdom: 44
Country: Number of subjects enrolled	France: 29
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Australia: 10
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	Italy: 15
Country: Number of subjects enrolled	Japan: 13
Country: Number of subjects enrolled	Korea, Republic of: 20
Country: Number of subjects enrolled	United States: 14
Worldwide total number of subjects	195
EEA total number of subjects	128

Notes:

Subjects enrolled per age group

In utero	0
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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)	165
From 65 to 84 years	30
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were stratified into 1 of 2 groups based on their transfusion history. Stratified participants were randomly assigned in a 1:1 ratio to receive ravulizumab or eculizumab.

Period 1

Period 1 title	Primary Evaluation Period
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 Period

Arm description:

On Day 1, participants received weight-based doses of ravulizumab ranging from 2400 to 3000 milligrams (mg). Thereafter, weight-based doses of ravulizumab ranging from 3000 to 3600 mg were administered on Days 15, 71, and 127.

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:

On Day 1, participants received weight-based loading doses of ravulizumab ranging from 2400 to 3000 mg. Thereafter, weight-based maintenance doses of ravulizumab ranging from 3000 to 3600 mg were administered on Days 15, 71, and 127.

Arm title	Eculizumab: Primary Evaluation Period
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Arm description:

Participants received 900 mg of eculizumab every 2 weeks (q2w) 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 continued to receive the approved dose of eculizumab for the treatment of PNH: 900 mg of eculizumab q2w for 26 weeks.

Number of subjects in period 1	Ravulizumab: Primary Evaluation Period	Ecuzumab: Primary Evaluation Period
Started	97	98
Received at Least 1 Dose of Study Drug	97	98
Completed	96	95
Not completed	1	3
Consent withdrawn by subject	1	1
Pregnancy	-	1
Lack of efficacy	-	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 26-week Primary Evaluation Period, participants had the opportunity to enter the Extension Period, wherein participants will receive weight-based doses of ravulizumab for up to 3 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 for up to 3 years.

Arm title	Ecuzumab: Extension Period
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Arm description:

After completion of the 26-week Primary Evaluation Period, participants had the opportunity to enter the Extension Period, wherein participants will receive weight-based doses of ravulizumab for up to 3 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. Thereafter, weight-based maintenance doses of ravulizumab ranging from 3000 to 3600 mg were administered for up to 3 years.

Number of subjects in period 2	Ravulizumab: Extension Period	Eculizumab: Extension Period
Started	96	95
Received at Least 1 Dose of Ravulizumab	96	95
Completed	0	0
Not completed	96	95
Extension Period is ongoing	96	95

Baseline characteristics

Reporting groups

Reporting group title	Ravulizumab: Primary Evaluation Period
Reporting group description:	
On Day 1, participants received weight-based doses of ravulizumab ranging from 2400 to 3000 milligrams (mg). Thereafter, weight-based doses of ravulizumab ranging from 3000 to 3600 mg were administered on Days 15, 71, and 127.	
Reporting group title	Eculizumab: Primary Evaluation Period
Reporting group description:	
Participants received 900 mg of eculizumab every 2 weeks (q2w) for 26 weeks.	

Reporting group values	Ravulizumab: Primary Evaluation Period	Eculizumab: Primary Evaluation Period	Total
Number of subjects	97	98	195
Age categorical			
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)	84	81	165
From 65-84 years	13	17	30
85 years and over	0	0	0
Age continuous			
Measure Description: Age at first infusion of study drug			
Units: years			
arithmetic mean	46.6	48.8	
standard deviation	± 14.41	± 13.97	-
Gender categorical			
Units: Subjects			
Female	47	50	97
Male	50	48	98
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	3	4	7
Not Hispanic or Latino	76	77	153
Unknown or Not Reported	18	17	35
Race/Ethnicity, Customized			
Units: Subjects			
White	50	61	111
Asian	23	19	42
Not Reported	13	13	26
Black or African American	5	3	8
Unknown	3	1	4
Other	2	1	3

Multiple	1	0	1
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End points

End points reporting groups

Reporting group title	Ravulizumab: Primary Evaluation Period
Reporting group description: On Day 1, participants received weight-based doses of ravulizumab ranging from 2400 to 3000 milligrams (mg). Thereafter, weight-based doses of ravulizumab ranging from 3000 to 3600 mg were administered on Days 15, 71, and 127.	
Reporting group title	Eculizumab: Primary Evaluation Period
Reporting group description: Participants received 900 mg of eculizumab every 2 weeks (q2w) for 26 weeks.	
Reporting group title	Ravulizumab: Extension Period
Reporting group description: After completion of the 26-week Primary Evaluation Period, participants had the opportunity to enter the Extension Period, wherein participants will receive weight-based doses of ravulizumab for up to 3 years.	
Reporting group title	Eculizumab: Extension Period
Reporting group description: After completion of the 26-week Primary Evaluation Period, participants had the opportunity to enter the Extension Period, wherein participants will receive weight-based doses of ravulizumab for up to 3 years.	

Primary: Percent Change In Lactate Dehydrogenase Levels From Baseline To Day 183

End point title	Percent Change In Lactate Dehydrogenase Levels From Baseline To Day 183
End point description: Lactate dehydrogenase (LDH) is an indicator of intravascular hemolysis that occurs in participants with paroxysmal nocturnal hemoglobinuria. A decrease in LDH indicates reduction (improvement) in hemolysis. Baseline was defined as the average of all available on-study assessments prior to the first study drug infusion. The percent change in LDH was analyzed using a mixed-effect model for repeated measures (MMRM) with the fixed, categorical effects of treatment, study visit, and study visit by treatment group interaction, as well as the continuous, fixed covariate of baseline LDH and the stratification randomization indicator of packed red blood cells transfusion history (yes/no within 12 months prior to Day 1).	
End point type	Primary
End point timeframe: Baseline, Day 183	

End point values	Ravulizumab: Primary Evaluation Period	Eculizumab: Primary Evaluation Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	98		
Units: Percent Change				
least squares mean (confidence interval 95%)	-0.82 (-7.75 to 6.11)	8.39 (1.47 to 15.32)		

Statistical analyses

Statistical analysis title	Analysis of LDH Levels
Statistical analysis description: Adjusting for a possible 10% dropout rate, a minimum of 192 participants were estimated to provide 90% power to demonstrate noninferiority of ravulizumab to eculizumab.	
Comparison groups	Ravulizumab: Primary Evaluation Period v Eculizumab: Primary Evaluation Period
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
Parameter estimate	Treatment Difference
Point estimate	-9.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.84
upper limit	0.42

Notes:

[1] - A difference in percent change in LDH between the ravulizumab and eculizumab treatment groups at Day 183 along with a 2-sided 95% confidence interval (CI) was calculated. The upper bound of the 95% CI was used for the determination of noninferiority. Noninferiority margin (NIM) was 15%.

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 one new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, dyspnea, anemia [hemoglobin < 10 grams (g)/deciliter (dL)], major adverse vascular event [including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH \geq 2 times the upper limit of normal.	
End point type	Secondary
End point timeframe: Baseline through Day 183	

End point values	Ravulizumab: Primary Evaluation Period	Eculizumab: Primary Evaluation Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	98		
Units: Percentage of Participants				
number (confidence interval 95%)	0.0 (0.00 to 3.73)	5.1 (1.68 to 11.51)		

Statistical analyses

Statistical analysis title	Analysis of BTH
Statistical analysis description: A difference in the percentages of participants with BTH was calculated between the ravulizumab and eculizumab treatment groups, along with a 95% CI for the difference using the stratified Newcombe CI method. The stratification factor observed was transfusion history within 1 year prior to first dose of	

study drug.

Comparison groups	Ecuzumab: Primary Evaluation Period v Ravuzumab: Primary Evaluation Period
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[2]
Parameter estimate	Treatment Difference
Point estimate	-5.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.99
upper limit	8.89

Notes:

[2] - The upper bound of the 95% CI was used for the determination of noninferiority. NIM was 20%.

Secondary: Change From Baseline To Day 183 In Functional Assessment Of Chronic Illness Therapy (FACIT)-Fatigue Scores

End point title	Change From Baseline To Day 183 In Functional Assessment Of Chronic Illness Therapy (FACIT)-Fatigue Scores
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End point description:

The FACIT-Fatigue score ranges from 0 to 52, with a higher score indicating less fatigue. Baseline was defined as the last non-missing assessment value prior to first study drug dose. Change in FACIT-Fatigue score from Baseline to Day 183 was analyzed using an MMRM with the fixed, categorical effects of treatment, the stratification randomization indicator of packed red blood cells transfusion history (yes/no within 12 months prior to Day 1), study visit, and study visit by treatment group interaction, as well as the continuous fixed covariate of Baseline FACIT-Fatigue score.

End point type	Secondary
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End point timeframe:

Baseline, Day 183

End point values	Ravuzumab: Primary Evaluation Period	Ecuzumab: Primary Evaluation Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	98		
Units: Units on a Scale				
least squares mean (confidence interval 95%)	2.01 (0.64 to 3.39)	0.54 (-0.84 to 1.93)		

Statistical analyses

Statistical analysis title	Analysis of FACIT-Fatigue Scores
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Statistical analysis description:

The lower bound of the 95% CI was used for the determination of noninferiority. NIM margin was -3.

Comparison groups	Ravuzumab: Primary Evaluation Period v Ecuzumab: Primary Evaluation Period
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Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Treatment Difference
Point estimate	1.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	3.15

Secondary: Percentage Of Participants Who Achieved Transfusion Avoidance

End point title	Percentage Of Participants Who Achieved Transfusion Avoidance
End point description:	
Transfusion avoidance (TA) was defined as the percentage of participants who remained transfusion free and did not require a transfusion per protocol-specified guidelines (hemoglobin value of ≤ 9 g/dL with signs or symptoms of sufficient severity to warrant a transfusion, or a hemoglobin value of ≤ 7 g/dL regardless of presence of clinical signs or symptoms) through Day 183.	
End point type	Secondary
End point timeframe:	
Baseline through Day 183	

End point values	Ravulizumab: Primary Evaluation Period	Eculizumab: Primary Evaluation Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	98		
Units: Percentage of Participants				
number (confidence interval 95%)	87.6 (81.08 to 94.18)	82.7 (75.16 to 90.15)		

Statistical analyses

Statistical analysis title	Analysis Of TA
Statistical analysis description:	
A difference in the percentages of participants achieving transfusion avoidance was calculated between the ravulizumab and eculizumab treatment groups, along with a 95% CI for the difference using the stratified Newcombe CI method. The stratification factor observed was transfusion history within 1 year prior to first dose of study drug.	
Comparison groups	Ravulizumab: Primary Evaluation Period v Eculizumab: Primary Evaluation Period

Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[3]
Parameter estimate	Treatment Difference
Point estimate	5.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.27
upper limit	15.68

Notes:

[3] - The lower bound of the 95% CI was used for the determination of noninferiority. NIM was -20%.

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 Period	Eculizumab: Primary Evaluation Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	98		
Units: Percentage of Participants				
number (confidence interval 95%)	76.3 (67.82 to 84.75)	75.5 (67.00 to 84.02)		

Statistical analyses

Statistical analysis title	Analysis Of Stabilized Hemoglobin Levels
Statistical analysis description:	A difference in the percentages of participants with stabilized hemoglobin was calculated between the ravulizumab and eculizumab treatment groups, along with a 95% CI for the difference using the stratified Newcombe CI method. The stratification factor observed was transfusion history within 1 year prior to first dose of study drug.
Comparison groups	Ravulizumab: Primary Evaluation Period v Eculizumab: Primary Evaluation Period
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[4]
Parameter estimate	Treatment Difference
Point estimate	1.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.41
upper limit	13.31

Notes:

[4] - The lower bound of the 95% CI was used for the determination of noninferiority. NIM was -20%.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline (after first dose) to Day 183 (before dosing)

Adverse event reporting additional description:

Treatment-emergent adverse events reported 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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	Ravulizumab
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Reporting group description:

On Day 1, participants received weight-based doses of ravulizumab ranging from 2400 to 3000 mg. Thereafter, weight-based doses of ravulizumab ranging from 3000 to 3600 mg were administered on Days 15, 71, and 127.

Reporting group title	Eculizumab
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Reporting group description:

Participants received 900 mg of eculizumab q2w for 26 weeks.

Serious adverse events	Ravulizumab	Eculizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 97 (4.12%)	8 / 98 (8.16%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 97 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 97 (1.03%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Haemolysis			

subjects affected / exposed	0 / 97 (0.00%)	2 / 98 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Hyperthermia			
subjects affected / exposed	1 / 97 (1.03%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 97 (0.00%)	3 / 98 (3.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 97 (1.03%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 97 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 97 (1.03%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Influenza			
subjects affected / exposed	1 / 97 (1.03%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			

subjects affected / exposed	1 / 97 (1.03%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 97 (0.00%)	1 / 98 (1.02%)	
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	Ravulizumab	Eculizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	84 / 97 (86.60%)	85 / 98 (86.73%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 97 (3.09%)	7 / 98 (7.14%)	
occurrences (all)	3	8	
Headache			
subjects affected / exposed	26 / 97 (26.80%)	17 / 98 (17.35%)	
occurrences (all)	31	26	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 97 (6.19%)	3 / 98 (3.06%)	
occurrences (all)	7	4	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	3 / 97 (3.09%)	9 / 98 (9.18%)	
occurrences (all)	5	12	
Fatigue			
subjects affected / exposed	6 / 97 (6.19%)	6 / 98 (6.12%)	
occurrences (all)	8	8	
Influenza like illness			
subjects affected / exposed	7 / 97 (7.22%)	8 / 98 (8.16%)	
occurrences (all)	8	10	
Pyrexia			

subjects affected / exposed occurrences (all)	9 / 97 (9.28%) 11	2 / 98 (2.04%) 4	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 97 (6.19%)	9 / 98 (9.18%)	
occurrences (all)	9	9	
Constipation			
subjects affected / exposed	7 / 97 (7.22%)	5 / 98 (5.10%)	
occurrences (all)	7	6	
Diarrhoea			
subjects affected / exposed	9 / 97 (9.28%)	7 / 98 (7.14%)	
occurrences (all)	10	7	
Nausea			
subjects affected / exposed	8 / 97 (8.25%)	9 / 98 (9.18%)	
occurrences (all)	9	9	
Vomiting			
subjects affected / exposed	6 / 97 (6.19%)	4 / 98 (4.08%)	
occurrences (all)	6	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 97 (5.15%)	10 / 98 (10.20%)	
occurrences (all)	5	11	
Dyspnoea			
subjects affected / exposed	0 / 97 (0.00%)	6 / 98 (6.12%)	
occurrences (all)	0	8	
Oropharyngeal pain			
subjects affected / exposed	4 / 97 (4.12%)	9 / 98 (9.18%)	
occurrences (all)	4	9	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	2 / 97 (2.06%)	5 / 98 (5.10%)	
occurrences (all)	2	5	
Pain in extremity			
subjects affected / exposed	5 / 97 (5.15%)	4 / 98 (4.08%)	
occurrences (all)	5	6	
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	21 / 97 (21.65%)	20 / 98 (20.41%)	
occurrences (all)	26	21	
Rhinitis			
subjects affected / exposed	5 / 97 (5.15%)	4 / 98 (4.08%)	
occurrences (all)	7	5	
Upper respiratory tract infection			
subjects affected / exposed	18 / 97 (18.56%)	10 / 98 (10.20%)	
occurrences (all)	22	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 October 2017	<ul style="list-style-type: none">- 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 participants who have home visits during the extension phase must return to the study site for any visit at which an abbreviated physical examination is required, as specified in the Schedule of Assessments.

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/30510079>