



## 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	08 April 2022

#### Results information

Result version number	v2
This version publication date	30 March 2023
First version publication date	08 July 2020
Version creation reason	

#### Trial information

##### Trial identification

Sponsor protocol code	ALXN1210 PNH 302
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##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	Alexion Pharmaceuticals Inc.
Sponsor organisation address	100 College Street, New Haven, CT, United States, 06510
Public contact	lexion Europe SAS European Clinical Trial Information, Alexion Pharmaceuticals Inc., +33 7 87148158, clinicaltrials.eu@alexion.com
Scientific contact	Alexion Europe SAS European Clinical Trial Information, Alexion Pharmaceuticals Inc., +33 7 87148158, 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	Final
Date of interim/final analysis	31 March 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2022
Global end of trial reached?	Yes
Global end of trial date	08 April 2022
Was the trial ended prematurely?	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 patients with PNH who were clinically stable after having been treated with eculizumab for at least the past 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	4 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 10
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	France: 29
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Italy: 15
Country: Number of subjects enrolled	Japan: 13
Country: Number of subjects enrolled	Netherlands: 11
Country: Number of subjects enrolled	Korea, Republic of: 20
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	United Kingdom: 44
Country: Number of subjects enrolled	United States: 14
Worldwide total number of subjects	195
EEA total number of subjects	84

Notes:

<b>Subjects enrolled per age group</b>	
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)	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. Participants in the full analysis set (FAS) were also reported.

### 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
<b>Arm title</b>	Ravulizumab/Ravulizumab

Arm 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. After completion of the 26-week Primary Evaluation Period, participants had the opportunity to enter the Extension Period, wherein participants received weight-based doses of ravulizumab for up to 4 years.

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

Dosage and administration details:

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. After completion of the 26-week Primary Evaluation Period, participants had the opportunity to enter the Extension Period, wherein participants received weight-based doses of ravulizumab for up to 4 years.

<b>Arm title</b>	Eculizumab/Ravulizumab
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Arm description:

Participants received 900 mg of eculizumab every 2 weeks (q2w) for 26 weeks. After completion of the 26-week Primary Evaluation Period, participants had the opportunity to enter the Extension Period, wherein participants received weight-based doses of ravulizumab for up to 4 years.

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

Dosage and administration details:

Participants received 900 mg of eculizumab every 2 weeks (q2w) for 26 weeks. After completion of the 26-week Primary Evaluation Period, participants had the opportunity to enter the Extension Period, wherein participants received weight-based doses of ravulizumab for up to 4 years.

Number of subjects in period 1	Ravulizumab/Ravulizumab	Ecilizumab/Ravulizumab
Started	97	98
Received at least 1 dose of study drug	97	98
Participants in the FAS	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
<b>Arm title</b>	Ravulizumab/Ravulizumab

### Arm 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. After completion of the 26-week Primary Evaluation Period, participants had the opportunity to enter the Extension Period, wherein participants received weight-based doses of ravulizumab for up to 4 years.

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

### Dosage and administration details:

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. After completion of the 26-week Primary Evaluation Period, participants had the opportunity to enter the Extension Period, wherein participants received weight-based doses of ravulizumab for up to 4 years.

<b>Arm title</b>	Ecilizumab/Ravulizumab
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### Arm description:

Participants received 900 mg of ecilizumab every 2 weeks (q2w) for 26 weeks. After completion of the 26-week Primary Evaluation Period, participants had the opportunity to enter the Extension Period, wherein participants received weight-based doses of ravulizumab for up to 4 years.

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

Dosage and administration details:

Participants received 900 mg of eculizumab every 2 weeks (q2w) for 26 weeks. After completion of the 26- week Primary Evaluation Period, participants had the opportunity to enter the Extension Period, wherein participants received weight-based doses of ravulizumab for up to 4 years.

<b>Number of subjects in period 2</b>	Ravulizumab/Ravulizumab	Eculizumab/Ravulizumab
Started	96	95
Completed	92	88
Not completed	4	7
Adverse event, serious fatal	-	3
Physician decision	3	3
Consent withdrawn by subject	1	-
Lost to follow-up	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	Ravulizumab/Ravulizumab
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. After completion of the 26-week Primary Evaluation Period, participants had the opportunity to enter the Extension Period, wherein participants received weight-based doses of ravulizumab for up to 4 years.	
Reporting group title	Eculizumab/Ravulizumab
Reporting group description:	
Participants received 900 mg of eculizumab every 2 weeks (q2w) for 26 weeks. After completion of the 26-week Primary Evaluation Period, participants had the opportunity to enter the Extension Period, wherein participants received weight-based doses of ravulizumab for up to 4 years.	

Reporting group values	Ravulizumab/Ravulizumab	Eculizumab/Ravulizumab	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			
Age at first infusion of study drug			
Units: years			
arithmetic mean	46.6	48.8	
standard deviation	± 14.41	± 13.97	-
Sex: Female, Male			
Units: participants			
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



## End points

### End points reporting groups

Reporting group title	Ravulizumab/Ravulizumab
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. After completion of the 26-week Primary Evaluation Period, participants had the opportunity to enter the Extension Period, wherein participants received weight-based doses of ravulizumab for up to 4 years.	
Reporting group title	Eculizumab/Ravulizumab
Reporting group description: Participants received 900 mg of eculizumab every 2 weeks (q2w) for 26 weeks. After completion of the 26-week Primary Evaluation Period, participants had the opportunity to enter the Extension Period, wherein participants received weight-based doses of ravulizumab for up to 4 years.	
Reporting group title	Ravulizumab/Ravulizumab
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. After completion of the 26-week Primary Evaluation Period, participants had the opportunity to enter the Extension Period, wherein participants received weight-based doses of ravulizumab for up to 4 years.	
Reporting group title	Eculizumab/Ravulizumab
Reporting group description: Participants received 900 mg of eculizumab every 2 weeks (q2w) for 26 weeks. After completion of the 26-week Primary Evaluation Period, participants had the opportunity to enter the Extension Period, wherein participants received weight-based doses of ravulizumab for up to 4 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/Ravulizumab	Eculizumab/Ravulizumab		
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

<b>Statistical analysis title</b>	Percent Change In Lactate Dehydrogenase Level
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/Ravulizumab v Eculizumab/Ravulizumab
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Treatment Difference
Point estimate	-9.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.84
upper limit	0.42

## Secondary: Number Of Participants With Breakthrough Hemolysis Through Day 183

End point title	Number Of Participants With Breakthrough Hemolysis Through Day 183
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 (ULN).	
End point type	Secondary
End point timeframe: Baseline through Day 183	

<b>End point values</b>	Ravulizumab/Ravulizumab	Eculizumab/Ravulizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	98		
Units: number of participants				
number (confidence interval 95%)	0 (0.00 to 3.73)	5 (1.68 to 11.51)		

## Statistical analyses

<b>Statistical analysis title</b>	Number of Participants with Breakthrough Hemolysis
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	Ravulizumab/Ravulizumab v Eculizumab/Ravulizumab
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Treatment Difference
Point estimate	-5.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.99
upper limit	8.89

### 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:

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

<b>End point values</b>	Ravulizumab/Ravulizumab	Eculizumab/Ravulizumab		
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

<b>Statistical analysis title</b>	Change from Baseline in FACIT-Fatigue Scores
Comparison groups	Ravulizumab/Ravulizumab v Eculizumab/Ravulizumab

Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	
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 Through Day 183

End point title	Percentage Of Participants Who Achieved Transfusion Avoidance Through Day 183
End point description:	
Transfusion avoidance was defined as the percentage of participants who remained transfusion free and did not require a transfusion per protocol-specified guidelines (hemoglobin value of $\leq 9$ g/dL with signs or symptoms of sufficient severity to warrant a transfusion, or a hemoglobin value of $\leq 7$ 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/Ravulizumab	Ecuzumab/Ravulizumab		
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	Participants with Transfusion Avoidance
Statistical analysis description:	
A difference in the percentages of participants achieving transfusion avoidance was calculated between the ravulizumab and ecuzumab 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/Ravulizumab v Ecuzumab/Ravulizumab

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

## Secondary: Percentage Of Participants With Stabilized Hemoglobin Levels Through Day 183

End point title	Percentage Of Participants With Stabilized Hemoglobin Levels Through Day 183
End point description:	Stabilized hemoglobin was defined as avoidance of a $\geq 2$ 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/Ravulizumab	Ecuzumab/Ravulizumab		
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	Participants with Stabilized Hemoglobin Levels
Statistical analysis description:	A difference in the percentages of participants with stabilized hemoglobin was calculated between the ravulizumab and ecuzumab 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/Ravulizumab v Ecuzumab/Ravulizumab
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Treatment Difference
Point estimate	1.4

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

### Secondary: Number Of Participants With Breakthrough Hemolysis Through End of Study

End point title	Number Of Participants With Breakthrough Hemolysis Through End of Study
End point description:	
BTH was defined as at least one new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, dyspnea, anemia [hemoglobin <10 g/dL], major adverse vascular event [including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH $\geq 2$ times the ULN.	
End point type	Secondary
End point timeframe:	
Baseline through end of study (up to 5 years)	

End point values	Ravulizumab/Ravulizumab	Eculizumab/Ravulizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	95		
Units: number of participants				
number (confidence interval 95%)	9 (4.38 to 17.05)	6 (2.35 to 13.24)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline To End of Study In FACIT-Fatigue Scores Through End of Study

End point title	Change From Baseline To End of Study In FACIT-Fatigue Scores Through End of Study
End point description:	
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
End point timeframe:	
Baseline, End of Study (up to 5 years)	

End point values	Ravulizumab/Ravulizumab	Ecuzumab/Ravulizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	13		
Units: units on a scale				
arithmetic mean (standard deviation)	-1.43 ( $\pm$ 5.694)	0.00 ( $\pm$ 5.944)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage Of Participants Who Achieved Transfusion Avoidance Through End of Study

End point title	Percentage Of Participants Who Achieved Transfusion Avoidance Through End of Study
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End point description:

Transfusion avoidance was defined as the percentage of participants who remained transfusion free and did not require a transfusion per protocol-specified guidelines (hemoglobin value of  $\leq 9$  g/dL with signs or symptoms of sufficient severity to warrant a transfusion, or a hemoglobin value of  $\leq 7$  g/dL regardless of presence of clinical signs or symptoms) through the end of study.

End point type	Secondary
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End point timeframe:

Baseline through end of study (up to 5 years)

End point values	Ravulizumab/Ravulizumab	Ecuzumab/Ravulizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	95		
Units: percentage of participants				
number (confidence interval 95%)	70.83 (60.67 to 79.67)	70.53 (60.29 to 79.44)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage Of Participants With Stabilized Hemoglobin Levels Through End of Study

End point title	Percentage Of Participants With Stabilized Hemoglobin Levels Through End of Study
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End point description:

Stabilized hemoglobin was defined as avoidance of a  $\geq 2$  g/dL decrease in hemoglobin level from

Baseline in the absence of transfusion through end of study.

End point type	Secondary
End point timeframe:	
Baseline through end of study (up to 5 years)	

<b>End point values</b>	Ravulizumab/Ravulizumab	Eculizumab/Ravulizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	95		
Units: percentage of participants				
number (confidence interval 95%)	58.33 (47.82 to 68.32)	67.37 (59.68 to 76.64)		

### Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From Baseline (after first dose) to end of study (up to 5 years)

Adverse event reporting additional description:

Ravulizumab arm: data for All-Cause Mortality, Serious Adverse Events, and Other Adverse Events are for participants in the Ravulizumab-Treated Set. Eculizumab arm: data for All-Cause Mortality, Serious Adverse Events, and Other Adverse Events are for the participants in the Safety Set.

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. After completion of the 26-week Primary Evaluation Period, participants had the opportunity to enter the Extension Period, wherein participants received weight-based doses of ravulizumab for up to 4 years.

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	60 / 192 (31.25%)	8 / 98 (8.16%)	
number of deaths (all causes)	3	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung cancer metastatic			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Endometrial cancer			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			

subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seborrhoeic keratosis			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer metastatic			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Invasive papillary breast carcinoma			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (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 / 192 (0.52%)	0 / 98 (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	5 / 192 (2.60%)	3 / 98 (3.06%)	
occurrences causally related to treatment / all	2 / 6	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			

subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Liver function test increased			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament injury			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Tibia fracture			
subjects affected / exposed	1 / 192 (0.52%)	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 limb fracture			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfusion reaction			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 192 (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 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrospinal fluid retention			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (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			
Haemolysis			

subjects affected / exposed	5 / 192 (2.60%)	2 / 98 (2.04%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Aplastic anaemia</b>			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Anaemia</b>			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Haemolytic anaemia</b>			
subjects affected / exposed	3 / 192 (1.56%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Bone marrow failure</b>			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Breakthrough haemolysis</b>			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Gastrointestinal disorders</b>			
<b>Colitis</b>			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Toothache</b>			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Pneumoperitoneum</b>			

subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 192 (0.52%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	2 / 192 (1.04%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary colic			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver disorder			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermal cyst			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Ureterolithiasis			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc degeneration			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dupuytren's contracture			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot deformity			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (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			
Pyelonephritis acute			
subjects affected / exposed	0 / 192 (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	
Influenza			
subjects affected / exposed	5 / 192 (2.60%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lower respiratory tract infection subjects affected / exposed	3 / 192 (1.56%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 subjects affected / exposed	2 / 192 (1.04%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bacteraemia subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia subjects affected / exposed	2 / 192 (1.04%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection subjects affected / exposed	2 / 192 (1.04%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			



subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal infection			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suspected COVID-19			
subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	1 / 192 (0.52%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Ravulizumab	Eculizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	175 / 192 (91.15%)	85 / 98 (86.73%)	
Cardiac disorders			
Palpitations			
subjects affected / exposed	10 / 192 (5.21%)	0 / 98 (0.00%)	
occurrences (all)	12	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	26 / 192 (13.54%)	7 / 98 (7.14%)	
occurrences (all)	30	8	
Headache			
subjects affected / exposed	60 / 192 (31.25%)	17 / 98 (17.35%)	
occurrences (all)	94	26	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	16 / 192 (8.33%)	3 / 98 (3.06%)	
occurrences (all)	22	4	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	12 / 192 (6.25%)	9 / 98 (9.18%)	
occurrences (all)	15	12	
Fatigue			
subjects affected / exposed	41 / 192 (21.35%)	6 / 98 (6.12%)	
occurrences (all)	87	8	
Pyrexia			
subjects affected / exposed	40 / 192 (20.83%)	2 / 98 (2.04%)	
occurrences (all)	61	4	
Influenza like illness			

subjects affected / exposed occurrences (all)	21 / 192 (10.94%) 45	8 / 98 (8.16%) 10	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	15 / 192 (7.81%)	4 / 98 (4.08%)	
occurrences (all)	18	4	
Nausea			
subjects affected / exposed	35 / 192 (18.23%)	9 / 98 (9.18%)	
occurrences (all)	43	9	
Diarrhoea			
subjects affected / exposed	36 / 192 (18.75%)	7 / 98 (7.14%)	
occurrences (all)	50	7	
Constipation			
subjects affected / exposed	13 / 192 (6.77%)	5 / 98 (5.10%)	
occurrences (all)	14	6	
Abdominal pain			
subjects affected / exposed	29 / 192 (15.10%)	9 / 98 (9.18%)	
occurrences (all)	41	9	
Abdominal pain upper			
subjects affected / exposed	16 / 192 (8.33%)	0 / 98 (0.00%)	
occurrences (all)	19	0	
Dysphagia			
subjects affected / exposed	11 / 192 (5.73%)	0 / 98 (0.00%)	
occurrences (all)	12	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	32 / 192 (16.67%)	10 / 98 (10.20%)	
occurrences (all)	43	11	
Dyspnoea			
subjects affected / exposed	16 / 192 (8.33%)	6 / 98 (6.12%)	
occurrences (all)	26	8	
Oropharyngeal pain			
subjects affected / exposed	20 / 192 (10.42%)	9 / 98 (9.18%)	
occurrences (all)	25	9	
Skin and subcutaneous tissue disorders			

Pruritus			
subjects affected / exposed	10 / 192 (5.21%)	0 / 98 (0.00%)	
occurrences (all)	12	0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	0 / 192 (0.00%)	5 / 98 (5.10%)	
occurrences (all)	0	5	
Pain in extremity			
subjects affected / exposed	24 / 192 (12.50%)	4 / 98 (4.08%)	
occurrences (all)	28	6	
Back pain			
subjects affected / exposed	26 / 192 (13.54%)	0 / 98 (0.00%)	
occurrences (all)	34	0	
Arthralgia			
subjects affected / exposed	22 / 192 (11.46%)	0 / 98 (0.00%)	
occurrences (all)	26	0	
Myalgia			
subjects affected / exposed	10 / 192 (5.21%)	0 / 98 (0.00%)	
occurrences (all)	17	0	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	53 / 192 (27.60%)	10 / 98 (10.20%)	
occurrences (all)	79	13	
Rhinitis			
subjects affected / exposed	19 / 192 (9.90%)	4 / 98 (4.08%)	
occurrences (all)	32	5	
Nasopharyngitis			
subjects affected / exposed	58 / 192 (30.21%)	20 / 98 (20.41%)	
occurrences (all)	96	21	
Gastroenteritis			
subjects affected / exposed	11 / 192 (5.73%)	0 / 98 (0.00%)	
occurrences (all)	15	0	
Influenza			
subjects affected / exposed	14 / 192 (7.29%)	0 / 98 (0.00%)	
occurrences (all)	15	0	
Urinary tract infection			

subjects affected / exposed	16 / 192 (8.33%)	0 / 98 (0.00%)	
occurrences (all)	31	0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
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 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.
01 March 2019	• Prolonged Extension Period from 2 years to 3 years and revised Schedule of Assessments.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported