Clinical trial results:
A Phase 3, Randomized, Parallel-Group, Multicenter, Open-Label, Pharmacokinetic, Noninferiority Study of Ravulizumab Administered Subcutaneously Versus Intravenously in Adult Patients With Paroxysmal Nocturnal Hemoglobinuria Currently Treated With Eculizumab

Summary

EudraCT number	2017-002370-39
Trial protocol	DE FR BE GB NL SE FI CZ ES AT IT
Global end of trial date	

Results information

Result version number	v1
This version publication date	25 August 2022
First version publication date	25 August 2022

Trial information

Trial identification

Sponsor protocol code	ALXN1210-PNH-303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03748823
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alexion Pharmaceuticals Inc.
Sponsor organisation address	121 Seaport Boulevard, Boston, United States, 02210
Public contact	European Clinical Trial Information, Alexion Europe SAS, +33 147100615, clinicaltrials.eu@alexion.com
Scientific contact	European Clinical Trial Information, Alexion Europe SAS, +33 147100615, 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	02 April 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate pharmacokinetics (PK) of ravulizumab administered subcutaneously via an on-body delivery system (OBDS) compared with intravenously administered ravulizumab in adult participants with Paroxysmal Nocturnal Hemoglobinuria (PNH) who are clinically stable on eculizumab for at least 6 months.

Protection of trial subjects:

This trial was conducted in compliance with Good Clinical Practice.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 March 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 9
Country: Number of subjects enrolled	Brazil: 25
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Russian Federation: 10
Country: Number of subjects enrolled	Turkey: 29
Country: Number of subjects enrolled	United States: 1
Worldwide total number of subjects	136
EEA total number of subjects	61

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)	123
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were stratified by weight group (≥40 to <60 kg and ≥60 to <100 kg) and then randomized in a 2:1 ratio to 2 treatment groups. This is an ongoing study and data presented are results from 10-week Randomized Treatment Period and data from the Extension Period through data cutoff date at 02 February 2021 (LSLV at Day 365).

Period 1

Period 1 title	Randomized Treatment Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Ravulizumab IV/SC Treatment Group

Arm description:

During the Randomized Treatment Period, participants received a weight-based single loading dose (2400 to 2700 milligrams [mg]) of ravulizumab IV on Day 1, followed by a maintenance weight-based dose (3000 to 3300 mg) of ravulizumab IV on Day 15. During the Extension Period (Day 71 up to Day 1275), participants received 490 mg of ravulizumab SC once every week (qw).

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

Dosage and administration details:

Participants received ALXN1210 at prespecified dose and timepoints.

Arm title	Ravulizumab SC/SC Treatment Group

Arm description:

During the Randomized Treatment Period, participants received a weight-based single loading dose (2400 to 2700 mg) of ravulizumab SC on Day 1, followed by maintenance weight-based doses (490 mg) of ravulizumab SC qw from Days 15 to 64. During the Extension Period (Day 71 up to Day 1275), participants received 490 mg of ravulizumab SC qw.

Arm type	Experimental
Investigational medicinal product name	Ravulizumab
Investigational medicinal product code	ALXN1210
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received ALXN1210 at prespecified dose and timepoints.

Number of subjects in period 1	Ravulizumab IV/SC Treatment Group	Ravulizumab SC/SC Treatment Group
Started	46	90
Received at least 1 dose of study drug	45	84 [1]
Treated and not included in analysis	1 [2]	6 [3]
Full Analysis Set	45	84 [4]
Safety Analysis Set	45	84 [5]
Completed	45	90
Not completed	1	0
Consent withdrawn by subject	1	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: 1 Participant in the SC treatment group withdrew the consent before entering the Extension Period.
[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: 1 Participant in the SC treatment group withdrew the consent before entering the Extension Period.
[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: 1 Participant in the SC treatment group withdrew the consent before entering the Extension Period.
[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: 1 Participant in the SC treatment group withdrew the consent before entering the Extension Period.
[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: 1 Participant in the SC treatment group withdrew the consent before entering the Extension Period.

Period 2

Period 2 title	Extension Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Ravulizumab IV/SC Treatment Group

Arm description:

During the Randomized Treatment Period, participants received a weight-based single loading dose (2400 to 2700 milligrams [mg]) of ravulizumab IV on Day 1, followed by a maintenance weight-based dose (3000 to 3300 mg) of ravulizumab IV on Day 15. During the Extension Period (Day 72 up to Day 1275), participants received 490 mg of ravulizumab SC once every week (qw).

Arm type	Experimental

Investigational medicinal product name	Ravulizumab
Investigational medicinal product code	
Other name	ALXN1210
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received ALXN1210 at prespecified dose and timepoints.

Arm title	Ravulizumab SC/SC Treatment Group

Arm description:

During the Randomized Treatment Period, participants received a weight-based single loading dose (2400 to 2700 mg) of ravulizumab SC on Day 1, followed by maintenance weight-based doses (490 mg) of ravulizumab SC qw from Days 15 to 64. During the Extension Period (Day 72 up to Day 1275), participants received 490 mg of ravulizumab SC qw.

Arm type	Experimental
Investigational medicinal product name	Ravulizumab
Investigational medicinal product code	
Other name	ALXN1210
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received ALXN1210 at prespecified dose and timepoints.

Number of subjects in period 2[6]	Ravulizumab IV/SC Treatment Group	Ravulizumab SC/SC Treatment Group
Started	45	89
Received at least 1 dose of study drug	45	89
Treated but not included in the analysis	1 [7]	6
Completed	2	2
Not completed	43	87
Adverse event, serious fatal	-	1
Consent withdrawn by subject	1	2
Ongoing in the Extension Period	41	84
Protocol deviation	1	-

Notes:

[6] - 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 in the SC treatment group withdrew the consent before entering the Extension Period.
[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: 1 Participant in the SC treatment group withdrew the consent before entering the Extension Period.

Baseline characteristics

Reporting groups	
Reporting group title	Ravulizumab IV/SC Treatment Group
Reporting group description:	
During the Randomized Treatment Period, participants received a weight-based single loading dose (2400 to 2700 milligrams [mg]) of ravulizumab IV on Day 1, followed by a maintenance weight-based dose (3000 to 3300 mg) of ravulizumab IV on Day 15. During the Extension Period (Day 71 up to Day 1275), participants received 490 mg of ravulizumab SC once every week (qw).	
Reporting group title	Ravulizumab SC/SC Treatment Group
Reporting group description:	
During the Randomized Treatment Period, participants received a weight-based single loading dose (2400 to 2700 mg) of ravulizumab SC on Day 1, followed by maintenance weight-based doses (490 mg) of ravulizumab SC qw from Days 15 to 64. During the Extension Period (Day 71 up to Day 1275), participants received 490 mg of ravulizumab SC qw.	

Reporting group values	Ravulizumab IV/SC Treatment Group	Ravulizumab SC/SC Treatment Group	Total
Number of subjects	46	90	136
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: years			
arithmetic mean	46.4	45.3	
standard deviation	± 13.22	± 14.47	-
Sex: Female, Male Units: participants			
Female	25	47	72
Male	21	43	64
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	7	19	26
Not Hispanic or Latino	29	53	82
Unknown or Not Reported	10	18	28
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	2	0	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	4	5	9

White	30	67	97
More than one race	2	4	6
Unknown or Not Reported	7	14	21

End points

End points reporting groups

Reporting group title	Ravulizumab IV/SC Treatment Group
Reporting group description:	
During the Randomized Treatment Period, participants received a weight-based single loading dose (2400 to 2700 milligrams [mg]) of ravulizumab IV on Day 1, followed by a maintenance weight-based dose (3000 to 3300 mg) of ravulizumab IV on Day 15. During the Extension Period (Day 71 up to Day 1275), participants received 490 mg of ravulizumab SC once every week (qw).	
Reporting group title	Ravulizumab SC/SC Treatment Group
Reporting group description:	
During the Randomized Treatment Period, participants received a weight-based single loading dose (2400 to 2700 mg) of ravulizumab SC on Day 1, followed by maintenance weight-based doses (490 mg) of ravulizumab SC qw from Days 15 to 64. During the Extension Period (Day 71 up to Day 1275), participants received 490 mg of ravulizumab SC qw.	
Reporting group title	Ravulizumab IV/SC Treatment Group
Reporting group description:	
During the Randomized Treatment Period, participants received a weight-based single loading dose (2400 to 2700 milligrams [mg]) of ravulizumab IV on Day 1, followed by a maintenance weight-based dose (3000 to 3300 mg) of ravulizumab IV on Day 15. During the Extension Period (Day 72 up to Day 1275), participants received 490 mg of ravulizumab SC once every week (qw).	
Reporting group title	Ravulizumab SC/SC Treatment Group
Reporting group description:	
During the Randomized Treatment Period, participants received a weight-based single loading dose (2400 to 2700 mg) of ravulizumab SC on Day 1, followed by maintenance weight-based doses (490 mg) of ravulizumab SC qw from Days 15 to 64. During the Extension Period (Day 72 up to Day 1275), participants received 490 mg of ravulizumab SC qw.	

Primary: Ctrough Serum Concentration of Ravulizumab

End point title	Ctrough Serum Concentration of Ravulizumab
End point description:	
Pharmacokinetic (PK) analysis set included all participants who had evaluable PK data.	
End point type	Primary
End point timeframe:	
Predose at Day 71	

End point values	Ravulizumab IV/SC Treatment Group	Ravulizumab SC/SC Treatment Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	70		
Units: microgram/milliliter (µg/mL)				
arithmetic mean (standard deviation)	457.58 (± 108.491)	578.70 (± 140.819)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Ravulizumab IV/SC Treatment Group v Ravulizumab SC/SC Treatment Group
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [1]
Method	ANOVA
Parameter estimate	Ratio of Geometric Least Squares Mean
Point estimate	1.257
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.16
upper limit	1.361

Notes:

[1] - Analysis of variance (ANOVA) was performed on log-transformed Ctrough and included treatment and stratified weight group as fixed effects.

Secondary: Ctrough Serum Concentration of Ravulizumab at Day 351

End point title	Ctrough Serum Concentration of Ravulizumab at Day 351

End point description:

SC treated full analysis set included all participants who had signed informed consent, were randomized, received at least 1 dose of ravulizumab SC, and were not excluded from analysis. Here, Number of Participants Analyzed signifies those participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Predose at Day 351

End point values	Ravulizumab IV/SC Treatment Group	Ravulizumab SC/SC Treatment Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	74		
Units: µg/mL				
arithmetic mean (standard deviation)	712.79 (± 203.180)	737.65 (± 208.894)		

Statistical analyses

No statistical analyses for this end point

Secondary: Free Serum Complement Component 5 (C5) Concentrations at Day 71

End point title	Free Serum Complement Component 5 (C5) Concentrations at Day 71

End point description:

Pharmacodynamic (PD) analysis set included all participants who received at least 1 dose of ravulizumab and who had evaluable PD data. Here, Number of Participants Analyzed signifies those participants who

were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Predose at Day 71

End point values	Ravulizumab IV/SC Treatment Group	Ravulizumab SC/SC Treatment Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	83		
Units: µg/mL				
arithmetic mean (standard deviation)	0.072193 (± 0.0245225)	0.059458 (± 0.0182180)		

Statistical analyses

No statistical analyses for this end point

Secondary: Free Serum Complement Component 5 (C5) Concentrations at Day 351

End point title	Free Serum Complement Component 5 (C5) Concentrations at Day 351

End point description:

SC treated full analysis set included all participants who had signed informed consent, were randomized, received at least 1 dose of ravulizumab SC, and were not excluded from analysis. Here, Number of Participants Analyzed signifies those participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Predose at Day 351

End point values	Ravulizumab IV/SC Treatment Group	Ravulizumab SC/SC Treatment Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	73		
Units: µg/mL				
arithmetic mean (standard deviation)	0.071627 (± 0.0227980)	0.069711 (± 0.0208784)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Lactate Dehydrogenase (LDH) Levels at Day 71

End point title	Percent Change From Baseline in Lactate Dehydrogenase (LDH) Levels at Day 71

End point description:

Baseline was defined as the last assessment prior to first study drug dose. Lactate dehydrogenase samples impacted by tabletop hemolysis were excluded from the analysis. Full analysis set included all participants who had signed informed consent, were randomized, received at least 1 dose of ravulizumab, and were not excluded from analysis. Here, Number of Participants Analyzed signifies those participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Day 71

End point values	Ravulizumab IV/SC Treatment Group	Ravulizumab SC/SC Treatment Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	82		
Units: percent change				
arithmetic mean (standard deviation)	5.73 (± 29.716)	2.57 (± 33.883)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Lactate Dehydrogenase Levels at Day 351

End point title	Percent Change From Baseline in Lactate Dehydrogenase Levels at Day 351

End point description:

Subcutaneous baseline was defined as the last assessment prior to first dose of subcutaneous treatment. Lactate dehydrogenase samples impacted by tabletop hemolysis were excluded from the analysis. SC treated full analysis set included all participants who had signed informed consent, were randomized, received at least 1 dose of ravulizumab SC, and were not excluded from analysis. Here, Number of Participants Analyzed signifies those participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Day 351

End point values	Ravulizumab IV/SC Treatment Group	Ravulizumab SC/SC Treatment Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	73		
Units: percent change				
arithmetic mean (standard deviation)	-0.83 (± 17.225)	1.74 (± 21.905)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Subscale Version 4 Score at Day 71

End point title	Change From Baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Subscale Version 4 Score at Day 71

End point description:

FACIT-fatigue subscale is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function over the preceding 7 days; total scores range from 0 to 52 with higher score indicating better health-related quality of life. Baseline was defined as the last non-missing value prior to the first dose of study drug. Full analysis set included all participants who had signed informed consent, were randomized, received at least 1 dose of ravulizumab, and were not excluded from analysis. Here, Number of Participants Analyzed signifies those participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Day 71

End point values	Ravulizumab IV/SC Treatment Group	Ravulizumab SC/SC Treatment Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	80		
Units: units on a scale				
arithmetic mean (standard deviation)	-0.83 (± 7.378)	1.21 (± 7.882)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue Scale Version 4 Score at Day 351

End point title	Change From Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue Scale Version 4 Score at Day 351[2]

End point description:

FACIT-fatigue scale is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function over the preceding 7 days; total scores range from 0 to 52 with higher score indicating better health-related quality of life. Baseline was defined as the last non-missing value prior to the first dose of subcutaneous treatment. SC treated full analysis set included all participants who had signed informed consent, were randomized, received at least 1 dose of ravulizumab SC, and were not excluded from analysis. Here, Number of Participants Analyzed signifies those participants who were evaluable for this outcome measure. This outcome measure was planned to be reported for ravulizumab SC/SC treatment group only.

End point type	Secondary

End point timeframe:

Baseline, Day 351

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive analysis was planned to be reported for this endpoint.

End point values	Ravulizumab SC/SC Treatment Group			
Subject group type	Reporting group			
Number of subjects analysed	70			
Units: units on a scale				
arithmetic mean (standard deviation)	2.57 (± 7.178)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Treatment Administration Satisfaction Questionnaire (TASQ) Score at Day 71

End point title	Change From Baseline in Treatment Administration Satisfaction Questionnaire (TASQ) Score at Day 71

End point description:

TASQ is a validated questionnaire that assesses participants' perceptions and satisfaction with ravulizumab treatment administration routes, which included 5 domains: physical impact, psychological impact, impact on activities of daily living, convenience, and satisfaction. Each domain offers up to 5 response options with lower scores indicating a more positive response; scoring is completed by summing each of the 5 domains. Baseline was defined as the last non-missing value prior to the first dose of study drug. Full analysis set included all participants who had signed informed consent, were randomized, received at least 1 dose of ravulizumab, and were not excluded from analysis. Here, Number of Participants Analyzed signifies those participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Day 71

End point values	Ravulizumab IV/SC Treatment Group	Ravulizumab SC/SC Treatment Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	78		
Units: units on a scale				
arithmetic mean (standard deviation)	-7.00 (± 34.581)	-70.54 (± 70.522)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Treatment Administration Satisfaction Questionnaire (TASQ) Score at Day 351

End point title	Change From Baseline in Treatment Administration Satisfaction Questionnaire (TASQ) Score at Day 351[3]

End point description:

TASQ is a validated questionnaire that assesses participants' perceptions and satisfaction with ravulizumab treatment administration routes, which included 5 domains: physical impact, psychological impact, impact on activities of daily living, convenience, and satisfaction. Each domain offers up to 5 response options with lower scores indicating a more positive response; scoring is completed by summing each of the 5 domains. Baseline was defined as the last non-missing value prior to the first dose of subcutaneous treatment. SC treated full analysis set included all participants who had signed informed consent, were randomized, received at least 1 dose of ravulizumab SC, and were not excluded from analysis. Here, Number of Participants analyzed signifies those participants who were evaluable for this outcome measure. This outcome measure was planned to be reported for ravulizumab SC/SC treatment group only.

End point type	Secondary

End point timeframe:

Baseline, Day 351

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive analysis was planned to be reported for this endpoint.

End point values	Ravulizumab SC/SC Treatment Group			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: units on a scale				
arithmetic mean (standard deviation)	-69.29 (± 80.068)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Experienced Breakthrough Hemolysis up

to Day 71

End point title	Percentage of Participants Who Experienced Breakthrough Hemolysis up to Day 71

End point description:

Breakthrough hemolysis was defined as at least one new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin <10 grams/deciliter (g/dL)], major adverse vascular event [MAVE, including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥2*upper limit of normal (ULN). Denominator for a percentage was participants with at least one post-baseline data for the period. For Through Day 71, only visits with data were used to assess breakthrough hemolysis. Full analysis set included all participants who had signed informed consent, were randomized, received at least 1 dose of ravulizumab, and were not excluded from analysis.

End point type	Secondary

End point timeframe:

Baseline up to Day 71

End point values	Ravulizumab IV/SC Treatment Group	Ravulizumab SC/SC Treatment Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	84		
Units: percentage of participants				
number (confidence interval 95%)	2.2 (0.06 to 11.77)	1.2 (0.03 to 6.46)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Experienced Breakthrough Hemolysis up to Day 351

End point title	Percentage of Participants Who Experienced Breakthrough Hemolysis up to Day 351

End point description:

Breakthrough hemolysis was defined as at least one new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin <10 g/dL], major adverse vascular event [MAVE, including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥2*ULN. Denominator for a percentage was participants with at least one post-baseline data for the period. SC treated full analysis set included all participants who had signed informed consent, were randomized, received at least 1 dose of ravulizumab SC, and were not excluded from analysis. Here, Number of Participants Analyzed signifies those participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline up to Day 351

End point values	Ravulizumab IV/SC Treatment Group	Ravulizumab SC/SC Treatment Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	84		
Units: percentage of participants				
number (confidence interval 95%)	4.5 (0.56 to 15.47)	3.6 (0.74 to 10.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Achieved Transfusion Avoidance up to Day 71

End point title	Percentage of Participants Who Achieved Transfusion Avoidance up to Day 71

End point description:

Transfusion Avoidance was defined as participants who remained transfusion free and did not require a transfusion after the first dose of study drug through the period of interest. Percentages are based on participants with any post-baseline data for the period. For Through Day 71, only visits with data were used to assess Transfusion Avoidance. Full analysis set included all participants who had signed informed consent, were randomized, received at least 1 dose of ravulizumab, and were not excluded from analysis.

End point type	Secondary

End point timeframe:

Baseline up to Day 71

End point values	Ravulizumab IV/SC Treatment Group	Ravulizumab SC/SC Treatment Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	84		
Units: percentage of participants				
number (confidence interval 95%)	86.7 (73.21 to 94.95)	94.0 (86.65 to 98.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Achieved Transfusion Avoidance up to Day 351

End point title	Percentage of Participants Who Achieved Transfusion Avoidance up to Day 351

End point description:

Transfusion Avoidance was defined as participants who remained transfusion free and did not require a

transfusion after the first dose of study drug through the period of interest. Denominator for a percentage was participants with at least one post-baseline data for the period. SC treated full analysis set included all participants who had signed informed consent, were randomized, received at least 1 dose of ravulizumab SC, and were not excluded from analysis. Here, Number of Participants Analyzed signifies those participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline up to Day 351

End point values	Ravulizumab IV/SC Treatment Group	Ravulizumab SC/SC Treatment Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	84		
Units: percentage of participants				
number (confidence interval 95%)	79.5 (64.70 to 90.20)	85.7 (76.38 to 92.39)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Maintained Stabilized Hemoglobin up to Day 71

End point title	Percentage of Participants Who Maintained Stabilized Hemoglobin up to Day 71

End point description:

Stabilized hemoglobin (SHg) was defined as the avoidance of a ≥2 g/dL decrease in hemoglobin level from Baseline (defined as the last assessment prior to the first dose of the study drug) in the absence of transfusion to the end of the period of interest. Percentages were based on participants with at least one post-baseline data for the period. For Through Day 71, only visits with data were used to assess SHg. Full analysis set included all participants who had signed informed consent, were randomized, received at least 1 dose of ravulizumab, and were not excluded from analysis. Here, Number of Participants Analyzed signifies those participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline up to Day 71

End point values	Ravulizumab IV/SC Treatment Group	Ravulizumab SC/SC Treatment Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	78		
Units: percentage of participants				
number (confidence interval 95%)	81.8 (67.29 to 91.81)	93.6 (85.67 to 97.89)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Maintained Stabilized Hemoglobin up to Day 351

End point title	Percentage of Participants Who Maintained Stabilized Hemoglobin up to Day 351

End point description:

SHg was defined as the avoidance of a ≥2 g/dL decrease in hemoglobin level from SC Baseline (defined as the last assessment prior to the first dose of SC treatment) in the absence of transfusion to the end of the period of interest. Denominator for a percentage was participants with at least one post-baseline data for the period. Visits were based on the number of days since first dose of SC treatment. SC treated full analysis set included all participants who had signed informed consent, were randomized, received at least 1 dose of ravulizumab SC, and were not excluded from analysis. Here, Number of Participants analyzed signifies those participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline up to Day 351

End point values	Ravulizumab IV/SC Treatment Group	Ravulizumab SC/SC Treatment Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	79		
Units: percentage of participants				
number (confidence interval 95%)	72.7 (57.21 to 85.04)	83.5 (73.51 to 90.94)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Day 365 (data cutoff date)

Adverse event reporting additional description:

Safety analysis set included all participants who received at least 1 dose of ravulizumab and were not excluded from analysis. Adverse events (AEs) are reported for the entire study period by the participant's randomized treatment group during the controlled portion of the study. AEs are reported through the 52 week data cutoff date.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Ravulizumab SC/SC Treatment Group

Reporting group description:

During the Randomized Treatment Period, participants received a weight-based single loading dose (2400 to 2700 mg) of ravulizumab SC on Day 1, followed by maintenance weight-based doses (490 mg) of ravulizumab SC qw from Days 15 to 64. During the Extension Period (Day 71 up to Day 1275), participants received 490 mg of ravulizumab SC qw.

Reporting group title	Ravulizumab IV/SC Treatment Group

Reporting group description:

During the Randomized Treatment Period, participants received a weight-based single loading dose (2400 to 2700 mg) of ravulizumab IV on Day 1, followed by a maintenance weight-based dose (3000 to 3300 mg) of ravulizumab IV on Day 15. During the Extension Period (Day 71 up to Day 1275), participants received 490 mg of ravulizumab SC qw.

Serious adverse events	Ravulizumab SC/SC Treatment Group	Ravulizumab IV/SC Treatment Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 84 (21.43%)	11 / 45 (24.44%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 84 (1.19%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon adenoma			
subjects affected / exposed	0 / 84 (0.00%)	1 / 45 (2.22%)	
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 / 84 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Procedural hypotension			
subjects affected / exposed	1 / 84 (1.19%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfusion reaction			
subjects affected / exposed	1 / 84 (1.19%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cervicobrachial syndrome			
subjects affected / exposed	1 / 84 (1.19%)	0 / 45 (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 / 84 (1.19%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolysis			
subjects affected / exposed	1 / 84 (1.19%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 84 (1.19%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aplastic anaemia			
subjects affected / exposed	1 / 84 (1.19%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haemolytic anaemia			
subjects affected / exposed	1 / 84 (1.19%)	0 / 45 (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 / 84 (1.19%)	0 / 45 (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 / 84 (1.19%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Application site induration			
subjects affected / exposed	1 / 84 (1.19%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest Pain			
subjects affected / exposed	1 / 84 (1.19%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Lens dislocation			
subjects affected / exposed	1 / 84 (1.19%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	0 / 84 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Adnexal torsion			

subjects affected / exposed[1]	1 / 44 (2.27%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 84 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 84 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 84 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 84 (1.19%)	0 / 45 (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			
Urinary retention			
subjects affected / exposed	1 / 84 (1.19%)	0 / 45 (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			
COVID-19			
subjects affected / exposed	4 / 84 (4.76%)	2 / 45 (4.44%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bacterial infection			

subjects affected / exposed	1 / 84 (1.19%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	0 / 84 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	1 / 84 (1.19%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 84 (1.19%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis viral			
subjects affected / exposed	1 / 84 (1.19%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
subjects affected / exposed	0 / 84 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 84 (1.19%)	0 / 45 (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	0 / 84 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubo-ovarian abscess			

subjects affected / exposed[2]	1 / 44 (2.27%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
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: The Adverse event is gender specific. Hence, the number of participants at risk are female participants only.
[2] - 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: The Adverse event is gender specific. Hence, the number of participants at risk are female participants only.

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

Non-serious adverse events	Ravulizumab SC/SC Treatment Group	Ravulizumab IV/SC Treatment Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	74 / 84 (88.10%)	43 / 45 (95.56%)	
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 84 (15.48%)	10 / 45 (22.22%)	
occurrences (all)	21	12	
Dizziness			
subjects affected / exposed	5 / 84 (5.95%)	3 / 45 (6.67%)	
occurrences (all)	5	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 84 (8.33%)	2 / 45 (4.44%)	
occurrences (all)	9	4	
Haemolysis			
subjects affected / exposed	4 / 84 (4.76%)	4 / 45 (8.89%)	
occurrences (all)	8	4	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	10 / 84 (11.90%)	3 / 45 (6.67%)	
occurrences (all)	12	7	
Asthenia			
subjects affected / exposed	10 / 84 (11.90%)	2 / 45 (4.44%)	
occurrences (all)	11	2	
Influenza like illness			

subjects affected / exposed	6 / 84 (7.14%)	0 / 45 (0.00%)	
occurrences (all)	6	0	
Injection site erythema			
subjects affected / exposed	5 / 84 (5.95%)	1 / 45 (2.22%)	
occurrences (all)	19	2	
Injection site reaction			
subjects affected / exposed	5 / 84 (5.95%)	1 / 45 (2.22%)	
occurrences (all)	23	8	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	13 / 84 (15.48%)	3 / 45 (6.67%)	
occurrences (all)	14	3	
Abdominal pain			
subjects affected / exposed	8 / 84 (9.52%)	5 / 45 (11.11%)	
occurrences (all)	12	6	
Nausea			
subjects affected / exposed	6 / 84 (7.14%)	4 / 45 (8.89%)	
occurrences (all)	7	5	
Vomiting			
subjects affected / exposed	6 / 84 (7.14%)	2 / 45 (4.44%)	
occurrences (all)	6	2	
Constipation			
subjects affected / exposed	5 / 84 (5.95%)	0 / 45 (0.00%)	
occurrences (all)	6	0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	2 / 84 (2.38%)	3 / 45 (6.67%)	
occurrences (all)	3	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 84 (2.38%)	6 / 45 (13.33%)	
occurrences (all)	2	8	
Oropharyngeal pain			
subjects affected / exposed	3 / 84 (3.57%)	3 / 45 (6.67%)	
occurrences (all)	3	3	
Dyspnoea			

subjects affected / exposed	1 / 84 (1.19%)	3 / 45 (6.67%)	
occurrences (all)	1	3	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	9 / 84 (10.71%)	3 / 45 (6.67%)	
occurrences (all)	12	4	
Pain in extremity			
subjects affected / exposed	5 / 84 (5.95%)	2 / 45 (4.44%)	
occurrences (all)	6	2	
Arthralgia			
subjects affected / exposed	5 / 84 (5.95%)	2 / 45 (4.44%)	
occurrences (all)	5	5	
Myalgia			
subjects affected / exposed	5 / 84 (5.95%)	0 / 45 (0.00%)	
occurrences (all)	5	0	
Infections and infestations			
COVID-19			
subjects affected / exposed	9 / 84 (10.71%)	6 / 45 (13.33%)	
occurrences (all)	10	6	
Nasopharyngitis			
subjects affected / exposed	8 / 84 (9.52%)	6 / 45 (13.33%)	
occurrences (all)	10	6	
Upper respiratory tract infection			
subjects affected / exposed	4 / 84 (4.76%)	3 / 45 (6.67%)	
occurrences (all)	4	3	
Urinary tract infection			
subjects affected / exposed	6 / 84 (7.14%)	1 / 45 (2.22%)	
occurrences (all)	8	1	
Influenza			
subjects affected / exposed	2 / 84 (2.38%)	4 / 45 (8.89%)	
occurrences (all)	2	4	
Product issues			
Device delivery system issue	Additional description: Adverse Events relating to drug delivery were coded to the MedDRA SOC of "Product Issues", including missing dose (ie, no dose) and partial dose (ie, less than full volume of dose administered) medication errors occurring with use of device.		
subjects affected / exposed	36 / 84 (42.86%)	22 / 45 (48.89%)	
occurrences (all)	76	45	

Incorrect dose administered by device	Additional description: Adverse Events relating to drug delivery were coded to the MedDRA SOC of "Product Issues", including missing dose (ie, no dose) and partial dose (ie, less than full volume of dose administered) medication errors occurring with use of device.		
subjects affected / exposed	30 / 84 (35.71%)	17 / 45 (37.78%)	
occurrences (all)	59	39	
Drug dose omission by device	Additional description: Adverse Events relating to drug delivery were coded to the MedDRA SOC of "Product Issues", including missing dose (ie, no dose) and partial dose (ie, less than full volume of dose administered) medication errors occurring with use of device.		
subjects affected / exposed	7 / 84 (8.33%)	6 / 45 (13.33%)	
occurrences (all)	13	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 August 2018	• Removed free hemoglobin testing • Added restriction on ova donation for female subjects.
20 September 2018	• Modified the criteria for the assessment of causality of AEs by the Investigator • Added data collection for the documentation of medication errors occurring with the use of ravulizumab on-body delivery system (OBDS) as adverse device effect (ADEs).
17 May 2019	• Removed 3 in-clinic study visits for participants in the ravulizumab SC treatment group during the Randomized Treatment Period and replaced with self-administration of ravulizumab SC by the participant in the home setting to reduce the participants burden • Provided additional information required by International Organization for Standardization (ISO) guidelines for investigational devices • Decreased length of time on eculizumab prior to study entry from 6 months to 3 months • Decreased the period in which participant may have experienced LDH values > 2 × upper limit of normal (ULN) from 6 months to 3 months • Clarified that the quality of life (QoL) instruments will be administered and recorded on paper rather than using an e-diary.
19 November 2019	• Increased the total study treatment duration to up to 3.5 years (182 weeks) • Revised the definition for the PK analysis set based on an assessment of compliance with the dosing and PK sampling windows specified in the Schedule of Activities and on PK simulations conducted to confirm permitted dosing and sampling windows • Clarified the timing of doses and PK/PD sample collection after Day 1 • Updated definitions of overdose for ravulizumab administered via IV infusion and via the ravulizumab OBDS • Clarified the definition of ADE.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Efficacy data are reported up to SC Day 351 and safety data up to 1 year data cut (LSLV Day 365). To ensure quality of results, all 7 participants from a noncompliant site were excluded from all analysis sets due to source documentation deviations.

Notes: