Clinical trial results:
A Phase 2, Open-Label, Multiple Ascending Dose Study to Evaluate the Efficacy, Safety, Tolerability, Immunogenicity, Pharmacokinetics, and Pharmacodynamics of ALXN1210 Administered Intravenously to Patients with Paroxysmal Nocturnal Hemoglobinuria

Summary

EudraCT number	2015-002674-20
Trial protocol	DE GB SE ES
Global end of trial date	

Results information

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

Trial information

Trial identification

Sponsor protocol code	ALXN1210-PNH-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02605993
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alexion Pharmaceuticals Inc.
Sponsor organisation address	121 Seaport Boulevard, Boston, MA, United States, 02210
Public contact	European Clinical Trial Information, Alexion Pharmaceuticals Inc., +33 147100606, clinicaltrials.eu@alexion.com
Scientific contact	European Clinical Trial Information, Alexion Pharmaceuticals Inc., +33 147100606, clinicaltrials.eu@alexion.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	23 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 February 2017
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The primary purpose of this study was to evaluate the safety, tolerability, and efficacy of multiple intravenous (IV) doses of ravulizumab administered to complement inhibitor treatment-naïve participants with paroxysmal nocturnal hemoglobinuria (PNH).

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 country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 January 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 6
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 7
Worldwide total number of subjects	26
EEA total number of subjects	17

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)	23
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study consisted of a screening period of up to 30 days and a Treatment Period of up to 253 days for Cohorts 1-3 and 281 days for Cohort 4. After completion of the Treatment Period, all participants had the opportunity to enter the Extension Period, wherein participants continue to receive ravulizumab for up to 5 years.

Period 1

Period 1 title	Treatment Period
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: Treatment Period

Arm description:

During the Treatment Period, participants were administered ravulizumab 1400 milligram (mg) on Day 1, ravulizumab 1000 mg on Day 15 and Day 29, and then ravulizumab 1000 mg every 4 weeks for 7 doses.

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

Dosage and administration details:

During the Treatment Period, participants were administered ravulizumab 1400 mg on Day 1, ravulizumab 1000 mg on Day 15 and Day 29, and then ravulizumab 1000 mg every 4 weeks for 7 doses. Ravulizumab was formulated at pH 7.0 and was to be supplied as a sterile, preservative-free, 10 mg/milliliter (mL) solution for IV administration in 20-mL single-use vials.

Arm title	Cohort 2: Treatment Period

Arm description:

During the Treatment Period, participants were administered ravulizumab 2000 mg on Day 1, ravulizumab 1600 mg on Day 22 and Day 43, and then ravulizumab 1600 mg every 6 weeks for 4 doses.

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

Dosage and administration details:

During the Treatment Period, participants were administered ravulizumab 2000 mg on Day 1, ravulizumab 1600 mg on Day 22 and Day 43, and then ravulizumab 1600 mg every 6 weeks for 4 doses. Ravulizumab was formulated at pH 7.0 and was to be supplied as a sterile, preservative-free, 10 mg/mL solution for IV administration in 20-mL single-use vials.

Arm title	Cohort 3: Treatment Period

Arm description:

During the Treatment Period, participants were administered ravulizumab 1600 mg on Day 1 and Day 15, ravulizumab 2400 mg on Day 29, and then ravulizumab 2400 mg every 8 weeks for 3 doses.

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

Dosage and administration details:

During the Treatment Period, participants were administered ravulizumab 1600 mg on Day 1 and Day 15, ravulizumab 2400 mg on Day 29, and then ravulizumab 2400 mg every 8 weeks for 3 doses. Ravulizumab was formulated at pH 7.0 and was to be supplied as a sterile, preservative-free, 10 mg/mL solution for IV administration in 20-mL single-use vials.

Arm title	Cohort 4: Treatment Period

Arm description:

During the Treatment Period, participants were administered ravulizumab 3000 mg on Day 1, ravulizumab 5400 mg on Day 29, and then ravulizumab 5400 mg every 12 weeks for 2 doses.

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

Dosage and administration details:

During the Treatment Period, participants were administered ravulizumab 3000 mg on Day 1, ravulizumab 5400 mg on Day 29, and then ravulizumab 5400 mg every 12 weeks for 2 doses. Ravulizumab was formulated at pH 7.0 and was to be supplied as a sterile, preservative-free, 10 mg/mL solution for IV administration in 20-mL single-use vials.

Number of subjects in period 1	Cohort 1: Treatment Period	Cohort 2: Treatment Period	Cohort 3: Treatment Period
Started	6	6	7
Received at Least 1 Dose of Study Drug	6	6	7
Completed	6	6	7

Number of subjects in period 1	Cohort 4: Treatment Period
Started	7
Received at Least 1 Dose of Study Drug	7
Completed	7

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: Extension Period

Arm description:

In the Extension Period, participants initially continued to receive their dose. During the second year of the study, participants were administered weight-based doses of ravulizumab every 8 weeks for up to 5 years: 3000 mg for participants weighing 40 to less than 60 kilograms (kg), 3300 mg for participants weighing 60 to less than 100 kg, and 3600 mg for participants weighing 100 kg or more.

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

Dosage and administration details:

In the Extension Period, participants initially continued to receive their dose. During the second year of the study, participants were administered weight-based doses of ravulizumab every 8 weeks for up to 5 years: 3000 mg for participants weighing 40 to less than 60 kg, 3300 mg for participants weighing 60 to less than 100 kg, and 3600 mg for participants weighing 100 kg or more. Ravulizumab was formulated at pH 7.0 and was to be supplied as a sterile, preservative-free, 10 mg/mL solution for IV administration in 20-mL single-use vials.

Arm title	Cohort 2: Extension Period

Arm description:

In the Extension Period, participants initially continued to receive their dose. During the second year of the study, participants were administered weight-based doses of ravulizumab every 8 weeks for up to 5 years: 3000 mg for participants weighing 40 to less than 60 kg, 3300 mg for participants weighing 60 to less than 100 kg, and 3600 mg for participants weighing 100 kg or more.

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

Dosage and administration details:

In the Extension Period, participants initially continued to receive their dose. During the second year of the study, participants were administered weight-based doses of ravulizumab every 8 weeks for up to 5 years: 3000 mg for participants weighing 40 to less than 60 kg, 3300 mg for participants weighing 60 to less than 100 kg, and 3600 mg for participants weighing 100 kg or more. Ravulizumab was formulated at pH 7.0 and was to be supplied as a sterile, preservative-free, 10 mg/mL solution for IV administration in 20-mL single-use vials.

Arm title	Cohort 3: Extension Period

Arm description:

In the Extension Period, participants initially continued to receive their dose. During the second year of the study, participants were administered weight-based doses of ravulizumab every 8 weeks for up to 5 years: 3000 mg for participants weighing 40 to less than 60 kg, 3300 mg for participants weighing 60 to less than 100 kg, and 3600 mg for participants weighing 100 kg or more.

Arm type	Experimental

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

Dosage and administration details:

In the Extension Period, participants initially continued to receive their dose. During the second year of the study, participants were administered weight-based doses of ravulizumab every 8 weeks for up to 5 years: 3000 mg for participants weighing 40 to less than 60 kg, 3300 mg for participants weighing 60 to less than 100 kg, and 3600 mg for participants weighing 100 kg or more. Ravulizumab was formulated at pH 7.0 and was to be supplied as a sterile, preservative-free, 10 mg/mL solution for IV administration in 20-mL single-use vials.

Arm title	Cohort 4: Extension Period

Arm description:

During the Extension Period, participants were administered ravulizumab 5400 mg every 12 weeks for up to 5 years.

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

Dosage and administration details:

During the Extension Period, participants were administered ravulizumab 5400 mg every 12 weeks for up to 5 years. Ravulizumab was formulated at pH 7.0 and was to be supplied as a sterile, preservative-free, 10 mg/mL solution for IV administration in 20-mL single-use vials.

Number of subjects in period 2	Cohort 1: Extension Period	Cohort 2: Extension Period	Cohort 3: Extension Period
Started	6	6	7
Completed	0	0	0
Not completed	6	6	7
Extension Period ongoing	6	6	7

Number of subjects in period 2	Cohort 4: Extension Period
Started	7
Completed	0
Not completed	7
Extension Period ongoing	7

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: Treatment Period
Reporting group description:	
During the Treatment Period, participants were administered ravulizumab 1400 milligram (mg) on Day 1, ravulizumab 1000 mg on Day 15 and Day 29, and then ravulizumab 1000 mg every 4 weeks for 7 doses.	
Reporting group title	Cohort 2: Treatment Period
Reporting group description:	
During the Treatment Period, participants were administered ravulizumab 2000 mg on Day 1, ravulizumab 1600 mg on Day 22 and Day 43, and then ravulizumab 1600 mg every 6 weeks for 4 doses.	
Reporting group title	Cohort 3: Treatment Period
Reporting group description:	
During the Treatment Period, participants were administered ravulizumab 1600 mg on Day 1 and Day 15, ravulizumab 2400 mg on Day 29, and then ravulizumab 2400 mg every 8 weeks for 3 doses.	
Reporting group title	Cohort 4: Treatment Period
Reporting group description:	
During the Treatment Period, participants were administered ravulizumab 3000 mg on Day 1, ravulizumab 5400 mg on Day 29, and then ravulizumab 5400 mg every 12 weeks for 2 doses.	

Reporting group values	Cohort 1: Treatment Period	Cohort 2: Treatment Period	Cohort 3: Treatment Period
Number of subjects	6	6	7
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)	5	4	7
From 65-84 years	1	2	0
85 years and over	0	0	0
Age continuous			
Age at first infusion of study drug.			
Units: years			
arithmetic mean	43.1	48.6	37.3
standard deviation	± 14.57	± 23.48	± 14.03
Gender categorical Units: Subjects			
Female	2	1	1
Male	4	5	6
Ethnicity Units: Subjects			
Hispanic or Latino	1	0	0
Not Hispanic or Latino	4	4	7
Not reported	1	2	0

Race Units: Subjects			
White	5	4	3
Asian	0	0	4
Not reported	1	2	0
Other	0	0	0
Lactate Dehydrogenase Levels Units: U/L			
arithmetic mean	1026.88	1223.55	2127.57
standard deviation	± 547.843	± 149.693	± 815.875

Reporting group values	Cohort 4: Treatment Period	Total	
Number of subjects	7	26	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	7	23	
From 65-84 years	0	3	
85 years and over	0	0	
Age continuous			
Age at first infusion of study drug.			
Units: years			
arithmetic mean	48.5		
standard deviation	± 13.43	-	
Gender categorical Units: Subjects			
Female	2	6	
Male	5	20	
Ethnicity Units: Subjects			
Hispanic or Latino	0	1	
Not Hispanic or Latino	7	22	
Not reported	0	3	
Race Units: Subjects			
White	3	15	
Asian	3	7	
Not reported	0	3	
Other	1	1	
Lactate Dehydrogenase Levels Units: U/L			
arithmetic mean	2142.24		
standard deviation	± 366.511	-	

End points

End points reporting groups

Reporting group title	Cohort 1: Treatment Period
Reporting group description:	
During the Treatment Period, participants were administered ravulizumab 1400 milligram (mg) on Day 1, ravulizumab 1000 mg on Day 15 and Day 29, and then ravulizumab 1000 mg every 4 weeks for 7 doses.	
Reporting group title	Cohort 2: Treatment Period
Reporting group description:	
During the Treatment Period, participants were administered ravulizumab 2000 mg on Day 1, ravulizumab 1600 mg on Day 22 and Day 43, and then ravulizumab 1600 mg every 6 weeks for 4 doses.	
Reporting group title	Cohort 3: Treatment Period
Reporting group description:	
During the Treatment Period, participants were administered ravulizumab 1600 mg on Day 1 and Day 15, ravulizumab 2400 mg on Day 29, and then ravulizumab 2400 mg every 8 weeks for 3 doses.	
Reporting group title	Cohort 4: Treatment Period
Reporting group description:	
During the Treatment Period, participants were administered ravulizumab 3000 mg on Day 1, ravulizumab 5400 mg on Day 29, and then ravulizumab 5400 mg every 12 weeks for 2 doses.	
Reporting group title	Cohort 1: Extension Period
Reporting group description:	
In the Extension Period, participants initially continued to receive their dose. During the second year of the study, participants were administered weight-based doses of ravulizumab every 8 weeks for up to 5 years: 3000 mg for participants weighing 40 to less than 60 kilograms (kg), 3300 mg for participants weighing 60 to less than 100 kg, and 3600 mg for participants weighing 100 kg or more.	
Reporting group title	Cohort 2: Extension Period
Reporting group description:	
In the Extension Period, participants initially continued to receive their dose. During the second year of the study, participants were administered weight-based doses of ravulizumab every 8 weeks for up to 5 years: 3000 mg for participants weighing 40 to less than 60 kg, 3300 mg for participants weighing 60 to less than 100 kg, and 3600 mg for participants weighing 100 kg or more.	
Reporting group title	Cohort 3: Extension Period
Reporting group description:	
In the Extension Period, participants initially continued to receive their dose. During the second year of the study, participants were administered weight-based doses of ravulizumab every 8 weeks for up to 5 years: 3000 mg for participants weighing 40 to less than 60 kg, 3300 mg for participants weighing 60 to less than 100 kg, and 3600 mg for participants weighing 100 kg or more.	
Reporting group title	Cohort 4: Extension Period
Reporting group description:	
During the Extension Period, participants were administered ravulizumab 5400 mg every 12 weeks for up to 5 years.	

Primary: Percent Change In Lactate Dehydrogenase Levels From Baseline To Day 253 And Day 281

End point title	Percent Change In Lactate Dehydrogenase Levels From Baseline To Day 253 And Day 281
End point description:	
The percent change in lactate dehydrogenase (LDH) levels was assessed from Baseline to Day 253 for Cohorts 1 to 4 and from Baseline to Day 281 for Cohort 4 only.	
End point type	Primary
End point timeframe:	
Baseline, Day 253 (Cohorts 1 to 4) and Day 281 (Cohort 4)	

End point values	Cohort 1: Treatment Period	Cohort 2: Treatment Period	Cohort 3: Treatment Period	Cohort 4: Treatment Period
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	7	7
Units: percent change				
arithmetic mean (standard deviation)				
Day 253 (n=6, n=6, n=7, n=7)	-72.85 (± 12.082)	-77.82 (± 6.474)	-84.96 (± 4.423)	-87.63 (± 6.923)
Day 281 (n=0, n=0, n=0, n=6)	0 (± 0)	0 (± 0)	0 (± 0)	-89.58 (± 3.037)

Statistical analyses

Statistical analysis title	Percent Change In LDH Levels

Statistical analysis description:

Data from Cohorts 1 to 4 combined at Day 253 was used. A sample size of 20 participants from the combined cohorts was required to provide approximately 95% power to detect a mean paired difference in LDH from baseline of –40% at Day 253 for Cohorts 1 to 4, and at Day 281 for Cohort 4 only, with an estimated standard deviation of 45%. This was based on a 2-sided paired t-test, with 5% type I error rate. To account for a possible 15% dropout rate, up to 26 participants were enrolled.

Comparison groups	Cohort 1: Treatment Period v Cohort 2: Treatment Period v Cohort 3: Treatment Period v Cohort 4: Treatment Period
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [1]
Method	Mixed Model for Repeated Measures (MMRM)

Notes:

[1] - Hypothesis testing was performed at the 0.05 level of significance. P-value tested whether the percent changes differed from zero at each time point for the combined cohorts.
Cohort 4 (n=6) only at Day 281: P-value < 0.0001.

Secondary: Percent Change In Free Hemoglobin Levels From Baseline To Day 253 And Day 281

End point title	Percent Change In Free Hemoglobin Levels From Baseline To Day 253 And Day 281

End point description:

The percent change in free hemoglobin levels was assessed from Baseline to Day 253 for Cohorts 1 to 4 and from Baseline to Day 281 for Cohort 4 only.

End point type	Secondary

End point timeframe:

Baseline, Day 253 (Cohorts 1 to 4) and Day 281 (Cohort 4)

End point values	Cohort 1: Treatment Period	Cohort 2: Treatment Period	Cohort 3: Treatment Period	Cohort 4: Treatment Period
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	7	7
Units: percent change				
arithmetic mean (standard deviation)				
Day 253 (n=6, n=6, n=7, n=5)	14.07 (± 124.755)	-10.00 (± 55.812)	-22.14 (± 94.388)	-40.80 (± 27.474)
Day 281 (n=0, n=0, n=0, n=5)	0 (± 0)	0 (± 0)	0 (± 0)	-34.74 (± 26.534)

Statistical analyses

Statistical analysis title	Change In Free Hemoglobin Levels

Statistical analysis description:

Statistical analysis presented is of Cohorts 1 to 4 combined at Day 253 and for Cohort 4 at Day 281 only.

Comparison groups	Cohort 1: Treatment Period v Cohort 2: Treatment Period v Cohort 3: Treatment Period v Cohort 4: Treatment Period
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.698 [2]
Method	MMRM

Notes:

[2] - Hypothesis testing was performed at the 0.05 level of significance. P-value tested whether the percent changes differed from zero at each time point for the combined cohorts.
Cohort 4 (n=5) only at Day 281: P-value = 0.3641.

Secondary: Percent Change In Haptoglobin Levels From Baseline To Day 253 And Day 281

End point title	Percent Change In Haptoglobin Levels From Baseline To Day 253 And Day 281

End point description:

The percent change in haptoglobin levels was assessed from Baseline to Day 253 for Cohorts 1 to 4 and from Baseline to Day 281 for Cohort 4 only.

End point type	Secondary

End point timeframe:

Baseline, Day 253 (Cohorts 1 to 4) and Day 281 (Cohort 4)

End point values	Cohort 1: Treatment Period	Cohort 2: Treatment Period	Cohort 3: Treatment Period	Cohort 4: Treatment Period
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	7	7
Units: percent change				
arithmetic mean (standard deviation)				

Day 253 (n=6, n=6, n=7, n=6)	21.67 (± 53.072)	81.67 (± 200.042)	4.29 (± 11.339)	34.29 (± 74.578)
Day 281 (n=0, n=0, n=0, n=6)	0 (± 0)	0 (± 0)	0 (± 0)	6.67 (± 16.330)

Statistical analyses

Statistical analysis title	Change In Haptoglobin Levels

Statistical analysis description:

Statistical analysis presented is of Cohorts 1 to 4 combined at Day 253 and for Cohort 4 at Day 281 only.

Comparison groups	Cohort 1: Treatment Period v Cohort 2: Treatment Period v Cohort 3: Treatment Period v Cohort 4: Treatment Period
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4037 [3]
Method	MMRM

Notes:

[3] - Hypothesis testing was performed at the 0.05 level of significance. P-value tested whether the percent changes differed from zero at each time point for the combined cohorts.
Cohort 4 (n=6) only at Day 281: P-value = 0.2520.

Secondary: Percent Change In Reticulocyte/Erythrocyte Count From Baseline To Day 253 And Day 281

End point title	Percent Change In Reticulocyte/Erythrocyte Count From Baseline To Day 253 And Day 281

End point description:

The percent change in reticulocyte/erythrocyte count levels was assessed from Baseline to Day 253 for Cohorts 1 to 4 and from Baseline to Day 281 for Cohort 4 only.

End point type	Secondary

End point timeframe:

Baseline, Day 253 (Cohorts 1 to 4) and Day 281 (Cohort 4)

End point values	Cohort 1: Treatment Period	Cohort 2: Treatment Period	Cohort 3: Treatment Period	Cohort 4: Treatment Period
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	7	7
Units: percent change				
arithmetic mean (standard deviation)				
Day 253 (n=6, n=6, n=7, n=7)	-1.27 (± 43.019)	-2.35 (± 34.538)	10.46 (± 59.510)	14.66 (± 81.390)
Day 281 (n=0, n=0, n=0, n=7)	0 (± 0)	0 (± 0)	0 (± 0)	2.12 (± 72.427)

Statistical analyses

Statistical analysis title	Change In Reticulocyte/Erythrocyte Count

Statistical analysis description:

Statistical analysis presented is of Cohorts 1 to 4 combined at Day 253 and for Cohort 4 at Day 281 only.

Comparison groups	Cohort 1: Treatment Period v Cohort 2: Treatment Period v Cohort 3: Treatment Period v Cohort 4: Treatment Period
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4686 [4]
Method	MMRM

Notes:

[4] - Hypothesis testing was performed at the 0.05 level of significance. P-value tested whether the percent changes differed from zero at each time point for the combined cohorts.
Cohort 4 (n=7) only at Day 281: P-value = 0.6296.

Secondary: Percent Change In PNH Red Blood Cell Types II And III Clone Size From Baseline To Day 253

End point title	Percent Change In PNH Red Blood Cell Types II And III Clone Size From Baseline To Day 253

End point description:

The percent change in PNH red blood cell (RBC), summed types II and III, clone size levels were assessed from Baseline to Day 253 for Cohorts 1 to 4.

End point type	Secondary

End point timeframe:

Baseline, Day 253 (Cohorts 1 to 4)

End point values	Cohort 1: Treatment Period	Cohort 2: Treatment Period	Cohort 3: Treatment Period	Cohort 4: Treatment Period
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	7	6
Units: percent change				
arithmetic mean (standard deviation)	-5.28 (± 35.096)	-1.15 (± 19.175)	36.44 (± 103.514)	46.53 (± 54.093)

Statistical analyses

Statistical analysis title	Change in PNH RBC Size

Statistical analysis description:

Statistical analysis presented is of Cohorts 1 to 4 combined at Day 253.

Comparison groups	Cohort 1: Treatment Period v Cohort 2: Treatment Period v Cohort 3: Treatment Period v Cohort 4: Treatment Period

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0705 [5]
Method	MMRM

Notes:

[5] - Hypothesis testing was performed at the 0.05 level of significance. P-value tested whether the percent changes differed from zero at each time point for the combined cohorts.

Secondary: Percent Change In D-dimer From Baseline To Day 253 And Day 281

End point title	Percent Change In D-dimer From Baseline To Day 253 And Day 281

End point description:

The percent change in D-dimer levels were assessed from Baseline to Day 253 for Cohorts 1 to 4 and from Baseline to Day 281 for Cohort 4 only.

End point type	Secondary

End point timeframe:

Baseline to Day 253 (Cohorts 1 to 4) and Day 281 (Cohort 4)

End point values	Cohort 1: Treatment Period	Cohort 2: Treatment Period	Cohort 3: Treatment Period	Cohort 4: Treatment Period
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	7	7
Units: percent change				
arithmetic mean (standard deviation)				
Day 253 (n=6, n=6, n=7, n=7)	-24.80 (± 32.436)	-29.47 (± 26.547)	-10.90 (± 41.032)	-16.08 (± 34.783)
Day 281 (n=0, n=0, n=0, n=5)	0 (± 0)	0 (± 0)	0 (± 0)	-32.46 (± 27.149)

Statistical analyses

Statistical analysis title	Change In D-dimer

Statistical analysis description:

Statistical analysis presented is of Cohorts 1 to 4 combined at Day 253 and for Cohort 4 at Day 281 only.

Comparison groups	Cohort 1: Treatment Period v Cohort 2: Treatment Period v Cohort 3: Treatment Period v Cohort 4: Treatment Period
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.09 [6]
Method	MMRM

Notes:

[6] - Hypothesis testing was performed at the 0.05 level of significance. P-value tested whether the percent changes differed from zero at each time point for the combined cohorts.
Cohort 4 (n=5) only at Day 281: P-value = 0.2302.

Secondary: Change In Clinical Manifestations Of PNH From Baseline To Day 253 And

Day 281

End point title	Change In Clinical Manifestations Of PNH From Baseline To Day 253 And Day 281

End point description:

Clinical manifestations were assessed from Baseline to Day 253 for Cohorts 1 to 4 and from Baseline to Day 281 for Cohort 4 only. Clinical manifestations were defined as fatigue, abdominal pain, dyspnea, dysphagia, chest pain, and erectile dysfunction (ED) (male participants only). Improvement was defined as present at Baseline and absent at Day end point. Worsening was defined as absent at Baseline and present at Day end point. No Change was defined as no change from Baseline and time point of end point.

End point type	Secondary

End point timeframe:

Baseline, Day 253 (Cohorts 1 to 4) and Day 281 (Cohort 4)

End point values	Cohort 1: Treatment Period	Cohort 2: Treatment Period	Cohort 3: Treatment Period	Cohort 4: Treatment Period
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6[7]	6[8]	7[9]	7[10]
Units: count of participants				
Fatigue at Day 253: Improved from Baseline	4	2	3	3
Fatigue at Day 253: No Change	2	4	4	4
Fatigue at Day 253: Worsened from Baseline	0	0	0	0
Fatigue at Day 281: Improved from Baseline	0	0	0	4
Fatigue at Day 281: Worsened from Baseline	0	0	0	0
Fatigue at Day 281: No Change	0	0	0	2
Abdominal Pain at Day 253: Improved from Baseline	1	1	1	0
Abdominal Pain at Day 253: Worsened from Baseline	0	0	0	0
Abdominal Pain at Day 253: No Change	5	5	6	7
Abdominal Pain at Day 281: Improved from Baseline	0	0	0	0
Abdominal Pain at Day 281: Worsened from Baseline	0	0	0	0
Abdominal Pain at Day 281: No Change	0	0	0	6
Dyspnea at Day 253: Improved from Baseline	1	1	4	2
Dyspnea at Day 253: Worsened from Baseline	0	0	0	0
Dyspnea at Day 253: No Change	5	5	3	5
Dyspnea at Day 281: Improved from Baseline	0	0	0	2
Dyspnea at Day 281: Worsened from Baseline	0	0	0	0
Dyspnea at Day 281: No Change	0	0	0	4
Dysphagia at Day 253: Improved from Baseline	0	1	1	1
Dysphagia at Day 253: Worsened from Baseline	0	0	0	0
Dysphagia at Day 253: No Change	6	5	6	6

Dysphagia at Day 281: Improved from Baseline	0	0	0	1
Dysphagia at Day 281: Worsened from Baseline	0	0	0	0
Dysphagia at Day 281: No Change	0	0	0	5
Chest Pain at Day 253: Improved from Baseline	1	0	2	0
Chest Pain at Day 253: Worsened from Baseline	0	0	0	0
Chest Pain at Day 253: No Change	5	6	5	7
Chest Pain at Day 281: Improved from Baseline	0	0	0	0
Chest Pain at Day 281: Worsened from Baseline	0	0	0	0
Chest Pain at Day 281: No Change	0	0	0	6
ED at Day 253: Improved from Baseline	2	0	1	1
ED at Day 253: Worsened from Baseline	0	0	0	0
ED at Day 253: No Change	2	5	5	4
ED at Day 281: Improved from Baseline	0	0	0	1
ED at Day 281: Worsened from Baseline	0	0	0	0
ED at Day 281: No Change	0	0	0	3

Notes:

[7] - Day 281, data not collected: N=0; ED: N=4 (male participants only)

[8] - Day 281, data not collected: N=0; ED: N=5 (male participants only)

[9] - Day 281, data not collected: N=0; ED: N=6 (male participants only)

[10] - ED at Day 253: N=5 (male participants only); ED at Day 281: N=4 (male participants only)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were monitored continuously from Screening to Day 253 (for Cohorts 1, 2, and 3) and Day 281 (for Cohort 4) (Treatment Period).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Cohort 1: Treatment Period

Reporting group description:

During the Treatment Period, participants were administered ravulizumab 1400 mg on Day 1, ravulizumab 1000 mg on Day 15 and Day 29, and then ravulizumab 1000 mg every 4 weeks for 7 doses.

Reporting group title	Cohort 2: Treatment Period

Reporting group description:

During the Treatment Period, participants were administered ravulizumab 2000 mg on Day 1, ravulizumab 1600 mg on Day 22 and Day 43, and then ravulizumab 1600 mg every 6 weeks for 4 doses.

Reporting group title	Cohort 3: Treatment Period

Reporting group description:

During the Treatment Period, participants were administered ravulizumab 1600 mg on Day 1 and Day 15, ravulizumab 2400 mg on Day 29, and then ravulizumab 2400 mg every 8 weeks for 3 doses.

Reporting group title	Cohort 4: Treatment Period

Reporting group description:

During the Treatment Period, participants were administered ravulizumab 3000 mg on Day 1, ravulizumab 5400 mg on Day 29, and then ravulizumab 5400 mg every 12 weeks for 2 doses.

Serious adverse events	Cohort 1: Treatment Period	Cohort 2: Treatment Period	Cohort 3: Treatment Period
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	3 / 7 (42.86%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Papillary thyroid cancer			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Post procedural complication			

subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolysis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Meningococcal infection			

subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningococcal sepsis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 4: Treatment Period		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 7 (14.29%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Papillary thyroid cancer			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Post procedural complication			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemolysis				
subjects affected / exposed	1 / 7 (14.29%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Pyrexia				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Nausea				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Rash maculo-papular				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Meningococcal infection				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Meningococcal sepsis				
subjects affected / exposed	0 / 7 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				

subjects affected / exposed	0 / 7 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Cohort 1: Treatment Period	Cohort 2: Treatment Period	Cohort 3: Treatment Period
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	6 / 6 (100.00%)	7 / 7 (100.00%)
Vascular disorders			
Extremity necrosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Hypertension			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Thrombophlebitis superficial			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Chest pain			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Fatigue			
subjects affected / exposed	3 / 6 (50.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	4	1	0
Infusion site swelling			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Localised oedema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0

Mass			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Vaccination site bruising			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	2
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed[1]	1 / 2 (50.00%)	0 / 1 (0.00%)	0 / 1 (0.00%)
occurrences (all)	2	0	0
Ovarian cyst			
subjects affected / exposed[2]	1 / 2 (50.00%)	0 / 1 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Testicular pain			
subjects affected / exposed[3]	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Testicular swelling			
subjects affected / exposed[4]	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 7 (28.57%)
occurrences (all)	0	0	3
Dyspnoea			
subjects affected / exposed	3 / 6 (50.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	3	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	1 / 7 (14.29%)
occurrences (all)	1	1	1

Pleural effusion			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Restlessness			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Antinuclear antibody positive			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Blood bilirubin increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Neutrophil count decreased			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Post-traumatic pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Cardiogenic shock			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Myocarditis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Tachycardia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 7 (28.57%)
occurrences (all)	0	0	2
Headache			
subjects affected / exposed	3 / 6 (50.00%)	3 / 6 (50.00%)	3 / 7 (42.86%)
occurrences (all)	8	4	4
Presyncope			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0

Extravascular haemolysis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Photophobia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Aphthous ulcer			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Diarrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Dyspepsia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Dysphagia			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Gastritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Gastrointestinal sounds abnormal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	4	0	1
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 7 (28.57%)
occurrences (all)	0	0	2
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Petechiae			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Skin lesion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Swelling face			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Haemoglobinuria			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Renal colic			

subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	3	0	5
Bone pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Flank pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Muscle spasms			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal stiffness			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Myalgia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Neck pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Tendonitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Cystitis			

subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	3	0
Gastroenteritis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Hordeolum			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	2
Otitis media			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Tooth abscess			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	2 / 7 (28.57%)
occurrences (all)	2	0	5
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	3	0
Viral infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Viral skin infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	2	1	0
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0

Fluid overload			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Hypokalaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Hypophosphataemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Iron deficiency			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Cohort 4: Treatment Period		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)		
Vascular disorders			
Extremity necrosis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Thrombophlebitis superficial			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Chest pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		

Infusion site swelling subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Localised oedema subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Mass subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Pain subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Vaccination site bruising subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed[1] occurrences (all)	0 / 2 (0.00%) 0		
Ovarian cyst subjects affected / exposed[2] occurrences (all)	0 / 2 (0.00%) 0		
Testicular pain subjects affected / exposed[3] occurrences (all)	0 / 5 (0.00%) 0		
Testicular swelling subjects affected / exposed[4] occurrences (all)	0 / 5 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		

Dyspnoea subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Pleural effusion subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Rhinitis allergic subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Restlessness subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Antinuclear antibody positive subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Blood bilirubin increased subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Blood creatinine increased			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Neutrophil count decreased			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Post-traumatic pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Cardiogenic shock			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Myocarditis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Tachycardia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	3 / 7 (42.86%)		
occurrences (all)	7		
Presyncope			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Extravascular haemolysis subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all)	 1 / 7 (14.29%) 2 1 / 7 (14.29%) 1 0 / 7 (0.00%) 0		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	 0 / 7 (0.00%) 0		
Eye disorders Dry eye subjects affected / exposed occurrences (all) Photophobia subjects affected / exposed occurrences (all)	 1 / 7 (14.29%) 1 0 / 7 (0.00%) 0		
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Aphthous ulcer subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea	 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 1 / 7 (14.29%) 1 		

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Dyspepsia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Dysphagia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Gastritis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Gastrointestinal sounds abnormal subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Nausea subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Vomiting subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Skin and subcutaneous tissue disorders Night sweats subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Petechiae subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Skin lesion subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Swelling face subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Renal and urinary disorders Chromaturia			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Haemoglobinuria			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Renal colic			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Bone pain			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Flank pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Musculoskeletal stiffness			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Neck pain			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Tendonitis			

subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Cystitis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Hordeolum			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Otitis media			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Tooth abscess			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	3 / 7 (42.86%)		
occurrences (all)	5		
Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)		
occurrences (all)	0		
Viral infection			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Viral skin infection			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		

Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0		
Metabolism and nutrition disorders Dyslipidaemia subjects affected / exposed occurrences (all) Fluid overload subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all) Hypophosphataemia subjects affected / exposed occurrences (all) Iron deficiency subjects affected / exposed occurrences (all)	 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0		

Notes:

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 March 2016	- Incorporated updated information from the ALXN1210-HV-101 study (single ascending dose study) and included overall conclusions of the study; additional information provided on administration of 400- and 800-mg doses (ongoing, multiple ascending dose study; ALXN1210-HV-102) and administration of ravulizumab in participants with PNH (ongoing, dose-escalation study; ALXN1210-PNH-103). - Updated study rationale with current Phase 1 status. - Added new treatment cohort (Cohort 4) to investigate longer dosing interval. - Clarified the scheduled time points at which the data monitoring committee will conduct a review of the safety data. - Described new pharmacokinetics/pharmacodynamics (PK/PD) information from Phase 1 healthy volunteer studies and explained rationale for adding new cohort with longer treatment interval. - Exclusion Criteria: #5, removed 90-day requirement to align with exclusion criterion #12, which specifies infections within 14 days prior to dosing; #8, revised for clarity and to specify that stable international normalized ratio was per investigator discretion; #14, to clarify that only interventional studies are exclusionary; #16, to ensure that low-grade fevers do not result in exclusion. - Revised infusion rates and approximate infusion duration; added new dosing information for Cohort 4. - Corrected inconsistencies between the Schedule of Assessments and the table of PK/PD assessments. - Added sentence stating that samples should not be drawn from the same arm where the infusion takes place on dosing days. - Added information regarding cancellation by central laboratory of hemolyzed samples and the potential need for local laboratory results. - Noted that the visual analog scale should be completed as soon as practical after completion of the infusion.
02 August 2016	- Change in duration of contraception required following last dose of study drug. - Reduction in frequency of abbreviated physical examinations during the Extension Period.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30171081