Clinical trial results:
A Phase 3, Open-Label Study of ALXN1210 in Children and Adolescents with Paroxysmal Nocturnal Hemoglobinuria (PNH)

Summary

EudraCT number	2017-002820-26
Trial protocol	GB NL FR NO
Global end of trial date	25 August 2022

Results information

Result version number	v3 (current)
This version publication date	02 March 2023
First version publication date	25 September 2021
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	ALXN1210-PNH-304

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03406507
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)	Yes
EMA paediatric investigation plan number(s)	EMEA-002077-PIP01-16
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	04 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 March 2020
Global end of trial reached?	Yes
Global end of trial date	25 August 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to assess the pharmacokinetics (PK), pharmacodynamics (PD), safety, and efficacy of ravulizumab in pediatric participants with paroxysmal nocturnal hemoglobinuria (PNH).

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (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	01 November 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 5
Country: Number of subjects enrolled	United States: 3
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	France: 1
Worldwide total number of subjects	13
EEA total number of subjects	3

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)	2

Adolescents (12-17 years)	11
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Thirteen participants, from birth to < 18 years, were planned to be enrolled to ensure at least 10 evaluable participants would complete the 26-week Primary Evaluation Period. Participants were recruited from 9 sites across 6 countries (United States, United Kingdom, France, Netherlands, Russia, and Norway).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment Naïve: Primary Evaluation Period

Arm description:

Complement inhibitor treatment-naïve participants received weight-based doses of ravulizumab.

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

Dosage and administration details:

Ravulizumab drug product is a sterile, preservative-free 10 mg/mL solution in single-use vials and is designed for infusion by diluting into commercially available saline (0.9% sodium chloride injection; country-specific pharmacopeia) for administration via intravenous (IV) infusion.

Arm title	Eculizumab Experienced: Primary Evaluation Period

Arm description:

Eculizumab-experienced participants received weight-based doses of ravulizumab.

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

Dosage and administration details:

Ravulizumab drug product is a sterile, preservative-free 10 mg/mL solution in single-use vials and is designed for infusion by diluting into commercially available saline (0.9% sodium chloride injection; country-specific pharmacopeia) for administration via IV infusion.

Number of subjects in period 1	Treatment Naïve: Primary Evaluation Period	Eculizumab Experienced: Primary Evaluation Period
Started	5	8
Received At Least 1 Dose of Study Drug	5	8
Completed	5	8

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	Treatment Naïve: Extension Period

Arm description:

Complement inhibitor treatment-naïve participants received weight-based doses of ravulizumab.

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

Dosage and administration details:

Ravulizumab drug product is a sterile, preservative-free 10 mg/mL solution in single-use vials and is designed for infusion by diluting into commercially available saline (0.9% sodium chloride injection; country-specific pharmacopeia) for administration via IV infusion.

Arm title	Eculizumab Experienced: Extension Period

Arm description:

Eculizumab-experienced participants received weight-based doses of ravulizumab.

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

Dosage and administration details:

Ravulizumab drug product is a sterile, preservative-free 10 mg/mL solution in single-use vials and is designed for infusion by diluting into commercially available saline (0.9% sodium chloride injection; country-specific pharmacopeia) for administration via IV infusion.

Number of subjects in period 2	Treatment Naïve: Extension Period	Eculizumab Experienced: Extension Period
Started	5	8
Received At Least 1 Dose of Study Drug	5	8
Completed	5	7
Not completed	0	1
Lack of efficacy	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Treatment Naïve: Primary Evaluation Period
Reporting group description:	
Complement inhibitor treatment-naïve participants received weight-based doses of ravulizumab.	
Reporting group title	Eculizumab Experienced: Primary Evaluation Period
Reporting group description:	
Eculizumab-experienced participants received weight-based doses of ravulizumab.	

Reporting group values	Treatment Naïve: Primary Evaluation Period	Eculizumab Experienced: Primary Evaluation Period	Total
Number of subjects	5	8	13
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)	1	1	2
Adolescents (12-17 years)	4	7	11
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Age at first infusion			
Units: years			
arithmetic mean	14.4	14.4	
standard deviation	± 2.19	± 3.07	-
Gender categorical Units: Subjects			
Female	1	7	8
Male	4	1	5
Race/Ethnicity, Customized			
Specific information pertaining to race and ethnicity undisclosed by Sponsor to ensure participant privacy.			
Units: Subjects			
Race/Ethnicity - Undisclosed	5	8	13

End points

End points reporting groups

Reporting group title	Treatment Naïve: Primary Evaluation Period
Reporting group description:	
Complement inhibitor treatment-naïve participants received weight-based doses of ravulizumab.	
Reporting group title	Eculizumab Experienced: Primary Evaluation Period
Reporting group description:	
Eculizumab-experienced participants received weight-based doses of ravulizumab.	
Reporting group title	Treatment Naïve: Extension Period
Reporting group description:	
Complement inhibitor treatment-naïve participants received weight-based doses of ravulizumab.	
Reporting group title	Eculizumab Experienced: Extension Period
Reporting group description:	
Eculizumab-experienced participants received weight-based doses of ravulizumab.	
Subject analysis set title	Pharmacokinetic (PK)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants enrolled into the study who received at least 1 dose of ravulizumab and who had evaluable interim PK data.	
Subject analysis set title	Pharmacodynamic (PD)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All participants who received at least 1 dose of ravulizumab and who had evaluable PD data.	
Subject analysis set title	Full Analysis
Subject analysis set type	Full analysis
Subject analysis set description:	
All participants who received at least 1 dose of ravulizumab and had at least 1 efficacy assessment after the first infusion of ravulizumab.	

Primary: Maximum Observed Serum Concentration (Cmax) Of Ravulizumab

End point title	Maximum Observed Serum Concentration (Cmax) Of Ravulizumab[1]
End point description:	
Blood samples for determination of ravulizumab Cmax were collected before and after administration of study drug at designated time points. Results are reported in micrograms/milliliter (µg/mL).	
End point type	Primary
End point timeframe:	
Week 1 (Day 1), Week 2 (Day 15), Week 10 (Day 71), and Week 18 (Day 127)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned to be reported for this endpoint.

End point values	Treatment Naïve: Primary Evaluation Period	Eculizumab Experienced: Primary Evaluation Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	8[2]		
Units: ug/mL				
arithmetic mean (standard deviation)				

Day 1: End of Infusion	725.40 (± 93.730)	884.63 (± 170.842)		
Day 15: End of Infusion	1161.60 (± 254.348)	1612.50 (± 211.441)		
Day 71: End of Infusion	1402.00 (± 344.267)	1581.43 (± 207.961)		
Day 127: End of Infusion	1396.00 (± 403.770)	1705.00 (± 164.751)		

Notes:

[2] - Day 71: N=7

Statistical analyses

No statistical analyses for this end point

Primary: Trough Serum Concentration (Ctrough) Of Ravulizumab

End point title	Trough Serum Concentration (Ctrough) Of Ravulizumab[3]

End point description:

Blood samples for determination of ravulizumab Ctrough were collected before and after administration of study drug at designated time points. Trough serum concentration was measured at end of dosing interval at steady state. Results are reported in µg/mL.

End point type	Primary

End point timeframe:

Week 2 (Day 15), Week 10 (Day 71), Week 18 (Day 127), Week 26 (Day 183)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned to be reported for this endpoint.

End point values	Treatment Naïve: Primary Evaluation Period	Eculizumab Experienced: Primary Evaluation Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	8[4]		
Units: ug/mL				
arithmetic mean (standard deviation)				
Day 15: Predose	358.20 (± 51.978)	452.25 (± 68.312)		
Day 71: Predose	370.20 (± 134.267)	521.00 (± 72.870)		
Day 127: Predose	410.80 (± 215.503)	554.88 (± 60.976)		
Day 183: Predose	419.00 (± 191.921)	565.63 (± 68.980)		

Notes:

[4] - Day 71: N=7

Statistical analyses

No statistical analyses for this end point

Primary: Mean Accumulation Ratio For Cmax Of Ravulizumab Following The Last Maintenance Dose Relative To The First Maintenance Dose

End point title	Mean Accumulation Ratio For Cmax Of Ravulizumab Following

	The Last Maintenance Dose Relative To The First Maintenance Dose[5]

End point description:

Blood samples for determination of ravulizumab accumulation ratio for Cmax were collected before and after administration of study drug at designated time points. The accumulation ratio was calculated as Cmax from the last maintenance dose (Week 18) divided by Cmax from the first maintenance dose (Week 2).

End point type	Primary

End point timeframe:

Week 18

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned to be reported for this endpoint.

End point values	Treatment Naïve: Primary Evaluation Period	Eculizumab Experienced: Primary Evaluation Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	8		
Units: ratio				
arithmetic mean (standard deviation)	1.1995 (± 0.21038)	1.0630 (± 0.06872)		

Statistical analyses

No statistical analyses for this end point

Primary: Change In Free Complement Component C5 (C5) Concentrations Over Time

End point title	Change In Free Complement Component C5 (C5) Concentrations Over Time[6]

End point description:

Blood samples for determination of free C5 were collected before and after administration of study drug at designated time points.

End point type	Primary

End point timeframe:

Baseline, Weeks 2, 10, 18, and 26 (end of infusion)

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned to be reported for this endpoint.

End point values	Treatment Naïve: Primary Evaluation Period	Eculizumab Experienced: Primary Evaluation Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	8		
Units: ug/mL				
arithmetic mean (standard deviation)				
Week 2	-105.319 (± 17.1118)	0 (± 0)		

Week 10	-105.310 (± 17.1139)	0.003 (± 0.0052)		
Week 18	-105.320 (± 17.1165)	0.006 (± 0.0067)		
Week 26	-105.320 (± 17.1184)	0.006 (± 0.0070)		

Statistical analyses

No statistical analyses for this end point

Primary: Change In Chicken Red Blood Cell (cRBC) Hemolytic Activity Over Time

End point title	Change In Chicken Red Blood Cell (cRBC) Hemolytic Activity Over Time[7]

End point description:

Blood samples for determination of cRBC hemolytic activity were collected before and after administration of study drug at designated time points.

End point type	Primary

End point timeframe:

Baseline, Weeks 2, 10, 18, and 26

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned to be reported for this endpoint.

End point values	Treatment Naïve: Primary Evaluation Period	Eculizumab Experienced: Primary Evaluation Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[8]	8		
Units: Percentage of hemolysis				
arithmetic mean (standard deviation)				
Week 2	-93.120 (± 9.2589)	1.95 (± 2.816)		
Week 10	-93.240 (± 9.2411)	3.97 (± 9.209)		
Week 18	-96.93 (± 4.5434)	2.78 (± 5.673)		
Week 26	-96.78 (± 4.816)	7.03 (± 12.680)		

Notes:

[8] - Weeks 18 and 26: N=4

Statistical analyses

No statistical analyses for this end point

Primary: Mean Accumulation Ratio For Ctrough Of Ravulizumab Following The Last Maintenance Dose Relative To The First Maintenance Dose

End point title	Mean Accumulation Ratio For Ctrough Of Ravulizumab Following The Last Maintenance Dose Relative To The First Maintenance Dose[9]

End point description:

Blood samples for determination of ravulizumab accumulation ratio for Ctrough were collected before and after administration of study drug at designated time points. The accumulation ratio was calculated as Ctrough from the last maintenance dose (Week 18) divided by Ctrough from the first maintenance dose (Week 2).

End point type	Primary

End point timeframe:

Week 18

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned to be reported for this endpoint.

End point values	Treatment Naïve: Primary Evaluation Period	Eculizumab Experienced: Primary Evaluation Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	8		
Units: ratio				
arithmetic mean (standard deviation)	1.2208 (± 0.32490)	1.0700 (± 0.09089)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change From Baseline At Week 26 In Lactate Dehydrogenase (LDH) Levels

End point title	Percentage Change From Baseline At Week 26 In Lactate Dehydrogenase (LDH) Levels

End point description:

Blood and urine samples for determination of LDH levels were collected at designated time points. Baseline was defined as the average of all assessments analyzed by the central laboratory prior to first study drug administration.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Treatment Naïve: Primary Evaluation Period	Eculizumab Experienced: Primary Evaluation Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	8		
Units: Percent Change				
arithmetic mean (standard deviation)	-47.91 (± 52.716)	4.65 (± 44.702)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Participants Who Achieved Transfusion Avoidance (TA)

End point title	Percentage Of Participants Who Achieved Transfusion Avoidance (TA)

End point description:

Transfusion avoidance was defined as the proportion of participants who remained transfusion-free and did not require a transfusion according to protocol-specified guidelines. Point estimates and 2-sided 95% exact confidence intervals (CIs) were computed. Participants who withdrew from the study due to lack of efficacy during the Primary Evaluation Period were considered as non-responders and were counted in the group needing transfusion. For participants who withdrew from the study for any other reason during the Primary Evaluation Period, their data up to the time of withdrawal was used to assess TA.

End point type	Secondary

End point timeframe:

Week 26

End point values	Treatment Naïve: Primary Evaluation Period	Eculizumab Experienced: Primary Evaluation Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	8		
Units: Percentage of Participants				
number (confidence interval 95%)	60.0 (14.66 to 94.73)	100.0 (63.06 to 100.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change In Quality Of Life (QoL) From Baseline To Week 26

End point title	Change In Quality Of Life (QoL) From Baseline To Week 26

End point description:

Quality of life was measured by Pediatric Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Questionnaire (participants ≥ 5 years of age), a 13-item questionnaire that assesses fatigue and its impact upon daily activities and function over the preceding 7 days. Each item is scored on a 5-point scale, and total scores range from 0 to 52, with a higher score indicating better QoL. The scoring guideline for the Pediatric FACIT-Fatigue instrument was used to calculate a FACIT-Fatigue score. Changes from baseline in FACIT-Fatigue scores were summarized at baseline and at the study visits where this assessment was collected up to Day 183 (Week 26). At each study visit, the proportion of participants who showed an improvement of at least 3 points for the Pediatric FACIT-Fatigue scores were summarized by point estimates and 2-sided 95% exact CIs.

End point type	Secondary
End point timeframe: Baseline, Week 26	

End point values	Treatment Naïve: Primary Evaluation Period	Eculizumab Experienced: Primary Evaluation Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	8		
Units: Units on a scale				
arithmetic mean (standard deviation)	3.40 (± 6.107)	1.28 (± 5.235)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Participants With Stabilized Hemoglobin At Week 26

End point title	Percentage Of Participants With Stabilized Hemoglobin At Week 26

End point description:

Stabilized hemoglobin was defined as avoidance of a ≥ 2 g/dL decrease in hemoglobin level from baseline in the absence of transfusion through Week 26. Point estimates and 2-sided 95% exact CIs were computed. Participants who withdrew from the study due to lack of efficacy during the Primary Evaluation Period were considered as non-responders and were counted in the group who did not meet the stabilized hemoglobin definition. For participants who withdrew from the study for any other reason during the Primary Evaluation Period, their data up to the time of withdrawal were used to assess stabilized hemoglobin.

End point type	Secondary
End point timeframe: Week 26	

End point values	Treatment Naïve: Primary Evaluation Period	Eculizumab Experienced: Primary Evaluation Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	8		
Units: Percentage of Participants				
number (confidence interval 95%)	60.0 (14.66 to 94.73)	75.0 (34.91 to 96.81)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change In Free Hemoglobin From Baseline To Week 26

End point title	Percentage Change In Free Hemoglobin From Baseline To Week 26

End point description:

Percentage change from baseline in free hemoglobin was summarized at all study visits up to Day 183 (Week 26). Baseline was defined as the last non-missing assessment value prior to the first study drug infusion.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Treatment Naïve: Primary Evaluation Period	Eculizumab Experienced: Primary Evaluation Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	8		
Units: Percentage Change				
arithmetic mean (standard deviation)	87.32 (± 226.816)	-15.29 (± 71.780)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Participants With Breakthrough Hemolysis (BTH) At Week 26

End point title	Percentage Of Participants With Breakthrough Hemolysis (BTH) At Week 26

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, major adverse vascular event [including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH as follows: for participants who entered the study naïve to complement inhibitor treatment, elevated LDH ≥ 2 × the upper limit of normal (ULN) after prior LDH reduction to < 1.5 × ULN on therapy; for participants who entered the study stabilized on eculizumab treatment, elevated LDH ≥ 2 × ULN. Participants who withdrew from the study due to lack of efficacy during the Primary Evaluation Period were considered as non-responders and were counted in the group with BTH. For participants who withdrew from the study for any other reason during the Primary Evaluation Period, their data up to the time of withdrawal were used to assess BTH. No participants experienced BTH.

End point type	Secondary

End point timeframe:

Week 26

End point values	Treatment Naïve: Primary Evaluation Period	Eculizumab Experienced: Primary Evaluation Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	8		
Units: Participants				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Day 1 through Week 26.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups	
Reporting group title	Eculizumab Experienced: Primary Evaluation Period
Reporting group description: Eculizumab-experienced participants received weight-based doses of ravulizumab.	
Reporting group title	Treatment Naïve: Primary Evaluation Period
Reporting group description: Complement inhibitor treatment-naïve participants received weight-based doses of ravulizumab.	

Serious adverse events	Eculizumab Experienced: Primary Evaluation Period	Treatment Naïve: Primary Evaluation Period	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 8 (25.00%)	2 / 5 (40.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Device related thrombosis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Breakthrough haemolysis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aplastic anaemia			

subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Device related sepsis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Eculizumab Experienced: Primary Evaluation Period	Treatment Naïve: Primary Evaluation Period	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 8 (87.50%)	4 / 5 (80.00%)	
Vascular disorders			
Haematoma			

subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Pallor			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
Fatigue			
subjects affected / exposed	2 / 8 (25.00%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Administration site pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Asthenia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Catheter site pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Chest pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Serum sickness			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Dysmenorrhoea	Additional description: The N for this adverse event has been adjusted to the number of females in the study as it is a sex-specific event.		
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	

Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	2 / 8 (25.00%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Rhinitis allergic			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Nasal congestion			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Blood bilirubin increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Blood creatinine increased2			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Electric shock			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Sunburn			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Wound			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Tooth fracture			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	

Toxicity to various agents			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Transfusion reaction			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Congenital, familial and genetic disorders			
Chromosomal deletion			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	2 / 8 (25.00%)	1 / 5 (20.00%)	
occurrences (all)	3	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 8 (25.00%)	0 / 5 (0.00%)	
occurrences (all)	5	0	
Aplastic anaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Lymphadenitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	2	
Thrombocytopenia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	3 / 8 (37.50%)	0 / 5 (0.00%)	
occurrences (all)	3	0	
Dysphagia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	2 / 8 (25.00%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Constipation			
subjects affected / exposed	2 / 8 (25.00%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Rectal haemorrhage			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Abdominal pain			
subjects affected / exposed	3 / 8 (37.50%)	0 / 5 (0.00%)	
occurrences (all)	3	0	
Vomiting			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Abdominal pain upper			
subjects affected / exposed	3 / 8 (37.50%)	0 / 5 (0.00%)	
occurrences (all)	3	0	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	
occurrences (all)	1	3	
Cholelithiasis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Acne			

subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
In growing nail			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Cushing's syndrome			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Neck pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	3	0	
Pain in extremity			
subjects affected / exposed	2 / 8 (25.00%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Arthritis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Back pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Juvenile idiopathic arthritis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Kyphosis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Pharyngitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Rhinitis			

subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 8 (25.00%)	0 / 5 (0.00%)	
occurrences (all)	3	0	
Urinary tract infection			
subjects affected / exposed	2 / 8 (25.00%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Paronychia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	2 / 8 (25.00%)	1 / 5 (20.00%)	
occurrences (all)	2	1	
Hordeolum			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Cystitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	4	0	
COVID-19			
subjects affected / exposed	1 / 8 (12.50%)	2 / 5 (40.00%)	
occurrences (all)	1	2	
Ear infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Infected bite			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection viral			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Viral infection			

subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Iron deficiency			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 August 2018	• Increased loading dose for participants who were ≥ 5 to < 10 kilograms (kg) in body weight based on analysis of interim PK/PD data from an ongoing atypical hemolytic uremic syndrome pediatric study. • Allowed loading dose to be administered as 2 infusions (no more than approximately 24 hours apart) for participants who were ≥ 5 to < 10 kg in body weight at study entry; predose PK/PD sample collected before the first infusion and end of infusion sample collected after the second infusion. • Allowed supplemental dose of ravulizumab upon agreement of the Alexion Medical Monitor. • Follow-up phone call 8 weeks after participant's last dose of study drug was added for monitoring of concomitant medications, procedures, and adverse events.
22 April 2020	• Extension Period was prolonged from 2 years to 4 years and the Schedules of Assessments were revised accordingly. • Number of participants to be enrolled was increased to allow for the enrollment of participants currently identified and to comply with European Medicines Agency PIP requisites. • Urine pregnancy tests were to be performed prior to each every 8 weeks study drug administration for participants who have reached menarche. • Transfusions were to be recorded at every visit. • To ensure participant safety and treatment continuity during the coronavirus disease 2019 pandemic, the option for participants to receive ravulizumab administration remotely at a medical facility that was located near the participant's home or at the participant's home was added. • Timepoints for interim analyses and clinical study reports were clarified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported