



## Clinical trial results:

### Phase 4, Single-Arm Study of Ravulizumab in Adult Participants with Paroxysmal Nocturnal Hemoglobinuria Currently Treated with High-Dose Eculizumab

#### Summary

EudraCT number	2019-003440-74
Trial protocol	GB
Global end of trial date	20 December 2022

#### Results information

Result version number	v1 (current)
This version publication date	17 December 2023
First version publication date	17 December 2023

#### Trial information

##### Trial identification

Sponsor protocol code	ALXN1210-PNH-401
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04320602
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Alexion Pharmaceuticals Inc.
Sponsor organisation address	100 College Street, New Haven, CT, United States, 06510
Public contact	Alexion Europe SAS European Clinical Trial Information, Alexion Pharmaceuticals Inc., +33 7 87148158, clinicaltrials.eu@alexion.com
Scientific contact	Alexion Europe SAS European Clinical Trial Information, Alexion Pharmaceuticals Inc., +33 7 87148158, clinicaltrials.eu@alexion.com

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 December 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 December 2022
Global end of trial reached?	Yes
Global end of trial date	20 December 2022
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the prevalence of free complement component 5 (C5)-associated breakthrough hemolysis (BTH) in participants on high-dose eculizumab who switched to ravulizumab (per approved dose regimen).

Protection of trial subjects:

This study was conducted in accordance with the protocol and with the consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable laws and regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 March 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 18
Worldwide total number of subjects	18
EEA total number of subjects	0

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)	15
From 65 to 84 years	3

85 years and over	0
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## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

The study consisted of a Screening Period of approximately 3 months and a Treatment Period of 351 days. Eligible participants were administered eculizumab 1200 milligrams (mg) every 2 weeks (q2w) optionally at home at the discretion of the Investigator, and preference of the participant during the Screening Period.

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Arm title	Ravulizumab
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Arm description:

Participants received a loading dose of ravulizumab on Day 1 and maintenance treatment with ravulizumab on Day 15 and every 8 weeks (q8w) thereafter until Day 351. Ravulizumab loading and maintenance doses were based on the participant's body weight measured at the prior visit, per approved dosing regimen.

Arm type	Experimental
Investigational medicinal product name	Ravulizumab
Investigational medicinal product code	ALXN1210
Other name	Ultomiris
Pharmaceutical forms	Sterile concentrate
Routes of administration	Intravenous use

Dosage and administration details:

Ravulizumab was administered per schedule specified in the arm description.

Number of subjects in period 1	Ravulizumab
Started	18
Received at least 1 dose of study drug	18
Completed	18

## Baseline characteristics

### Reporting groups

Reporting group title	Ravulizumab
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Reporting group description:

Participants received a loading dose of ravulizumab on Day 1 and maintenance treatment with ravulizumab on Day 15 and every 8 weeks (q8w) thereafter until Day 351. Ravulizumab loading and maintenance doses were based on the participant's body weight measured at the prior visit, per approved dosing regimen.

Reporting group values	Ravulizumab	Total	
Number of subjects	18	18	
Age Categorical			
Units: participants			
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)	15	15	
From 65-84 years	3	3	
85 years and over	0	0	
Age Continuous			
Units: years			
arithmetic mean	55.7		
standard deviation	± 11.34	-	
Gender Categorical			
Units: participants			
Female	6	6	
Male	12	12	
Ethnicity			
Units: Subjects			
Not of Hispanic, Latino/a, or Spanish Origin	18	18	
Race			
Units: Subjects			
White	13	13	
Black or African American	2	2	
Asian	2	2	
Other	1	1	

## End points

### End points reporting groups

Reporting group title	Ravulizumab
Reporting group description:	
Participants received a loading dose of ravulizumab on Day 1 and maintenance treatment with ravulizumab on Day 15 and every 8 weeks (q8w) thereafter until Day 351. Ravulizumab loading and maintenance doses were based on the participant's body weight measured at the prior visit, per approved dosing regimen.	

### Primary: Percentage of Participants Who Experienced Free C5-associated BTH

End point title	Percentage of Participants Who Experienced Free C5-associated BTH <sup>[1]</sup>
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End point description:

Free C5-associated BTH was defined as BTH concurrent with free C5 concentrations  $\geq 0.5$  micrograms ( $\mu\text{g}$ )/milliliter (mL). BTH was defined as at least one new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin  $< 10$  grams {g}/deciliter {dL}], major adverse vascular event [MAVE], including thrombosis, dysphagia, or erectile dysfunction) in the presence of elevated lactate dehydrogenase (LDH)  $\geq 2 \times$  upper limit of normal (ULN). The full analysis set (FAS) included all participants who received at least 1 dose of ravulizumab.

End point type	Primary
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End point timeframe:

Baseline through Day 351

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.

<b>End point values</b>	Ravulizumab			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: percentage of participants				
number (confidence interval 95%)	0 (0 to 18.5)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants Who Experienced BTH

End point title	Percentage of Participants Who Experienced BTH
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End point description:

BTH was defined as at least one new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin  $< 10$  g/dL], MAVE, including thrombosis, dysphagia, or erectile dysfunction) in the presence of elevated LDH  $\geq 2 \times$  ULN. The FAS included all participants who received at least 1 dose of ravulizumab.

End point type	Secondary
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End point timeframe:

Baseline through Day 351

<b>End point values</b>	Ravulizumab			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: percentage of participants				
number (confidence interval 95%)	5.6 (0.1 to 27.3)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change From Baseline in LDH at Day 351

End point title	Percent Change From Baseline in LDH at Day 351
End point description: The FAS included all participants who received at least 1 dose of ravulizumab. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.	
End point type	Secondary
End point timeframe: Baseline, Day 351	

<b>End point values</b>	Ravulizumab			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: percent change				
least squares mean (standard error)	-0.81 (± 6.132)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants Who Received a Red Blood Cell (RBC) Transfusion

End point title	Percentage of Participants Who Received a Red Blood Cell (RBC) Transfusion
End point description: The FAS included all participants who received at least 1 dose of ravulizumab.	
End point type	Secondary
End point timeframe: Baseline through Day 351	

<b>End point values</b>	Ravulizumab			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: percentage of participants				
number (confidence interval 95%)	33.3 (13.3 to 59.0)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With Stabilized Hemoglobin

End point title	Percentage of Participants With Stabilized Hemoglobin
End point description:	
Stabilized hemoglobin was defined as avoidance of a $\geq 2$ g/dL decrease in hemoglobin level from baseline in the absence of transfusion from Baseline to Day 351.	
End point type	Secondary
End point timeframe:	
Baseline through Day 351	

<b>End point values</b>	Ravulizumab			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: percentage of participants				
number (confidence interval 95%)	61.1 (35.7 to 82.7)			

### Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline through Day 351

Adverse event reporting additional description:

Safety set included all participants who receive at least 1 dose of ravulizumab.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.1
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### Reporting groups

Reporting group title	Ravulizumab
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Reporting group description:

Participants received a loading dose of ravulizumab on Day 1 and maintenance treatment with ravulizumab on Day 15 and q8w thereafter until Day 351. Ravulizumab loading and maintenance doses were based on the participant's body weight measured at the prior visit, per approved dosing regimen.

Serious adverse events	Ravulizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 18 (16.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 18 (5.56%)		
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	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal haemorrhage			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			

Pneumonia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	Ravulizumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 18 (83.33%)		
Investigations			
Haemoglobin decreased			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		
Body temperature abnormal			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
SARS-CoV-2 test positive			
subjects affected / exposed	3 / 18 (16.67%)		
occurrences (all)	3		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 18 (33.33%)		
occurrences (all)	8		
Non-cardiac chest pain			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Pain			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Influenza like illness			

subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Chest discomfort			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Asthenia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Peripheral swelling			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Extravascular haemolysis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 18 (16.67%)		
occurrences (all)	3		
Constipation			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Cough			
subjects affected / exposed	3 / 18 (16.67%)		
occurrences (all)	3		
Upper respiratory tract congestion			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			

Neurodermatitis subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Rash subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Skin lesion subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Nail ridging subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Renal and urinary disorders Chromaturia subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Haemoglobinuria subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Nephrolithiasis subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2		
Arthralgia subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Pain in extremity subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		

Herpes zoster			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	3		
COVID-19			
subjects affected / exposed	3 / 18 (16.67%)		
occurrences (all)	3		
Urinary tract infection			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 January 2020	The main rationale for this amendment was to allow administration of eculizumab at the participant's home at the discretion of the Investigator during Screening to reduce the burden of clinical visits. In addition, 2 specific patient-reported outcomes (Patient-Reported Symptoms [PRS] and Healthcare Resource Utilization [HRU]) are being included for exploratory data analysis.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported