Clinical trial results:
A Phase 2 Open-Label Proof of Concept Study to Assess the Efficacy, Safety, and Pharmacokinetics of ACH-0144471 in Untreated Patients With Paroxysmal Nocturnal Hemoglobinuria

Summary

EudraCT number	2016-002652-25
Trial protocol	GB IT
Global end of trial date	14 November 2018

Results information

Result version number	v3 (current)
This version publication date	23 July 2022
First version publication date	23 May 2021
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	ACH471-100

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03053102
WHO universal trial number (UTN)	U1111-1190-3490

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., +33 787-148-158, clinicaltrials.eu@alexion.com
Scientific contact	European Clinical Trial Information, Alexion Pharmaceuticals, Inc., +33 787-148-158, 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	30 October 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 November 2018
Global end of trial reached?	Yes
Global end of trial date	14 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the safety and efficacy of ACH-0144471 (danicopan) in currently untreated participants with paroxysmal nocturnal hemoglobinuria. After 12 weeks of treatment, participants deriving clinical benefit were offered enrollment in a separate long-term extension study (ACH471-103, 2017-000665-79).

Protection of trial subjects:

The study was conducted in accordance with the ethical principles outlined in the 2013 (Fortaleza, Brazil) revision of the 1964 Declaration of Helsinki, Good Clinical Practice (GCP) as required by the International Council of Harmonisation (ICH) guidelines, applicable regional and local laws legislation in the USA, and standard operating procedures (SOPs) in place.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 March 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	4 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	New Zealand: 6
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 1
Worldwide total number of subjects	10
EEA total number of subjects	2

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)	1
Adults (18-64 years)	9
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were evaluated for eligibility. A window of up to 60 days was permitted to allow screening followed by any required vaccinations.

Pre-assignment

Screening details:

In Part 1, participants received danicopan (100 or 150 mg TID) for 28 days. A dose increase up to 175 mg TID (N=8 participants) and 200 mg TID (N=4 participants) was conducted. Participants with reductions in lactate dehydrogenase (LDH) meeting specified criteria were offered continued dosing beyond Day 28, up to 8 additional weeks (Part 2).

Period 1

Period 1 title	Study Part 1: 28-Day Treatment
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Danicopan

Arm description:

Participants received danicopan 100 to 200 milligrams (mg) three times per day (TID).

Arm type	Experimental
Investigational medicinal product name	Danicopan
Investigational medicinal product code	ACH-0144471
Other name	ACH-4471, ACH4471, 4471, ALXN2040
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

In Part 1, participants received danicopan for 28 days. Starting doses were 100 or 150 mg TID. A further dose increase up to 175 mg TID (N=8 participants) and 200 mg TID (N=4 participants) was conducted.

Number of subjects in period 1	Danicopan
Started	10
Completed	10

Period 2

Period 2 title	Study Part 2: 84-Day Treatment
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Danicopan

Arm description:

Participants received danicopan 100 to 200 mg TID.

Arm type	Experimental
Investigational medicinal product name	Danicopan
Investigational medicinal product code	ACH-0144471
Other name	ACH-4471, ACH4471, 4471, ALXN2040
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants with reductions in LDH meeting specified criteria in Part 1 were offered continued dosing beyond Day 28, for up to 8 additional weeks in Part 2. After 12 weeks of treatment, participants deriving clinical benefit were offered enrollment in a separate long-term extension study (ACH471-103, 2017-000665-79).

Number of subjects in period 2	Danicopan
Started	10
Completed	8
Not completed	2
Adverse event, serious fatal	1
Consent withdrawn by subject	1

Baseline characteristics

Reporting groups	
Reporting group title	Study Part 1: 28-Day Treatment
Reporting group description:	
Participants received danicopan 100 to 200 mg TID.	

Reporting group values	Study Part 1: 28-Day Treatment	Total	
Number of subjects	10	10	
Age categorical Units: Subjects			
Adolescents (12-17 years)	1	1	
Adults (18-64 years)	9	9	
Age continuous Units: years			
arithmetic mean	35.94		
standard deviation	± 13.575	-	
Gender categorical			
Sex: Female, Male			
Units: Subjects			
Female	5	5	
Male	5	5	
Ethnicity Units: Subjects			
Not Hispanic or Latino	10	10	
Hispanic or Latino	0	0	
Unknown or Not Reported	0	0	
Race Units: Subjects			
Asian	1	1	
Native Hawaiian or Other Pacific Islander	1	1	
White	7	7	
Other	1	1	

End points

End points reporting groups

Reporting group title	Danicopan
Reporting group description:	
Participants received danicopan 100 to 200 milligrams (mg) three times per day (TID).	
Reporting group title	Danicopan
Reporting group description:	
Participants received danicopan 100 to 200 mg TID.	
Subject analysis set title	Danicopan
Subject analysis set type	Full analysis
Subject analysis set description:	
All participants who received at least 1 dose of study drug and had analysable data at the timepoints specified.	

Primary: Change From Baseline In Serum LDH Levels At Day 28

End point title	Change From Baseline In Serum LDH Levels At Day 28[1]
End point description:	
Change from Baseline = Serum LDH levels on Day 28 - Baseline Serum LDH levels.	
End point type	Primary
End point timeframe:	
Baseline, Day 28	
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	Danicopan			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: international units per liter (IU/L)				
arithmetic mean (standard deviation)				
Baseline	1416 (± 540.25)			
Day 28 (Part 1)	444.3 (± 255.78)			
Change from Baseline	-971.7 (± 549.76)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Hemoglobin (Hgb) At Days 28 And 84

End point title	Change From Baseline In Hemoglobin (Hgb) At Days 28 And 84
End point description:	
Change from Baseline = Hgb levels on Days 28 or 84 - Baseline Hgb levels.	
End point type	Secondary

End point timeframe:

Baseline, Days 28 and 84

End point values	Danicopan			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: grams/deciliter (g/dL)				
arithmetic mean (standard deviation)				
Baseline	9.76 (± 1.758)			
Part 1: Day 28 (n=10)	10.94 (± 1.651)			
Part 1: Change from Baseline at Day 28 (n=10)	1.18 (± 0.877)			
Part 2: Day 84 (n=8)	11.45 (± 1.414)			
Part 2: Change from Baseline at Day 84 (n=8)	1.80 (± 1.166)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Serum LDH Levels At Day 84

End point title	Change From Baseline In Serum LDH Levels At Day 84

End point description:

Change from Baseline = Serum LDH levels on Day 84 - Baseline Serum LDH levels. All participants who received at least 1 dose of study drug and had analyzable data at the timepoints specified.

End point type	Secondary

End point timeframe:

Baseline, Day 84

End point values	Danicopan			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: IU/L				
arithmetic mean (standard deviation)				
Baseline (n=10)	1416 (± 540.25)			
Day 84 (Part 2) (n=8)	537.3 (± 260.42)			
Change from Baseline (n=8)	-865.9 (± 447.86)			

Statistical analyses

No statistical analyses for this end point

Secondary: Paroxysmal Nocturnal Hemoglobinuria (PNH) Type III Red Blood Cell (RBC) Clone Size

End point title	Paroxysmal Nocturnal Hemoglobinuria (PNH) Type III Red Blood Cell (RBC) Clone Size

End point description:

PNH RBC, summed type III, clone size levels were assessed from Baseline to Day 28 and Day 84. The PNH clone size refers to the percentage of PNH-affected cells versus normal cells within the total cell population. All participants who received at least 1 dose of study drug and had analyzable data at the timepoints specified.

End point type	Secondary

End point timeframe:

Baseline, Day 28, and Day 84

End point values	Danicopan			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: percentage of the total cell population				
arithmetic mean (standard deviation)				
Baseline (n=10)	31.5363 (± 24.62004)			
Day 28 (n=9)	43.6279 (± 15.58021)			
Day 84 (n=8)	56.2953 (± 19.85086)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serious Adverse Events (SAEs), Grade 3 And Grade 4 Treatment-emergent Adverse Events (TEAEs), And Adverse Events (AEs) Leading To Discontinuation

End point title	Serious Adverse Events (SAEs), Grade 3 And Grade 4 Treatment-emergent Adverse Events (TEAEs), And Adverse Events (AEs) Leading To Discontinuation

End point description:

An AE was as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An SAE was an AE that met at least 1 of the following criteria: resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization for the AE, persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions, congenital anomaly/birth defect (in the child of a participant who was exposed to the study drug), important medical event or reaction. The intensity of an AE was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Adverse Event Severity Grading Table. A summary of SAEs and other non-serious AEs regardless of causality is located in the Adverse Events section.

End point type	Secondary

End point timeframe:

After the first dose of study medication (Day 1) through 14 days after the last dose of study drug (up to Day 104)

End point values	Danicopan			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: participants				
SAE	1			
TEAE Grade 3	1			
TEAE Grade 4	1			
AE leading to discontinuation	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Grade 3 And Grade 4 Laboratory Abnormalities

End point title	Grade 3 And Grade 4 Laboratory Abnormalities

End point description:

Laboratory abnormalities were determined from laboratory measurements analyzed at the central or local laboratories, and were graded using CTCAE.

End point type	Secondary

End point timeframe:

After the first dose of study medication (Day 1) through 14 days after the last dose of study drug (up to Day 104).

End point values	Danicopan			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: participants				
Alanine aminotransferase increased	1			
Aspartate aminotransferase increased	1			
Low Hemoglobin	1			
Low neutrophil count	4			
High triglycerides	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK): Area Under The Plasma Concentration-time Curve From Time Of Administration To 8 Hours Post-dose (AUC0-8)

End point title	Pharmacokinetics (PK): Area Under The Plasma Concentration-time Curve From Time Of Administration To 8 Hours Post-dose (AUC0-8)

End point description:

Serial blood samples were collected predose and up to 8 hours postdose.

End point type	Secondary

End point timeframe:

Days 6 and 20

End point values	Danicopan			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: hour (hr)*nanograms/milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Day 6: 100 mg TID (n=2)	1432.611 (± 19.41)			
Day 20: 150 mg TID (n=4)	2370.421 (± 14.92)			
Day 20: 175 mg TID (n=6)	2278.038 (± 37.30)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Maximum Plasma Concentration (Cmax)

End point title	PK: Maximum Plasma Concentration (Cmax)

End point description:

Serial blood samples were collected predose and up to 12 hours postdose.

End point type	Secondary

End point timeframe:

Days 6 and 20

End point values	Danicopan			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Day 6: 100 mg TID (n=2)	347.7 (± 9.57)			

Day 20: 150 mg TID (n=4)	583.6 (± 27.29)			
Day 20: 175 mg TID (n=6)	516.8 (± 33.39)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Time To Maximum Concentration (Tmax)

End point title	PK: Time To Maximum Concentration (Tmax)

End point description:

Serial blood samples were collected predose and up to 12 hours postdose.

End point type	Secondary

End point timeframe:

Days 6 and 20

End point values	Danicopan			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: hr				
median (full range (min-max))				
Day 6: 100 mg TID (n=2)	4.17 (3.67 to 4.67)			
Day 20: 150 mg TID (n=4)	3.67 (1.05 to 4.67)			
Day 20: 175 mg TID (n=6)	4.11 (1.67 to 4.65)			

Statistical analyses

No statistical analyses for this end point

Secondary: Complement Alternative Pathway (AP) Functional Activity

End point title	Complement Alternative Pathway (AP) Functional Activity

End point description:

Serum AP functional activity was measured by the Wieslab functional immunoassay method.

End point type	Secondary

End point timeframe:

Baseline and Day 28

End point values	Danicopan			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: percentage of activity				
arithmetic mean (standard deviation)				
Baseline	65.216 (± 13.7143)			
Day 28	12.730 (± 14.37670)			

Statistical analyses

No statistical analyses for this end point

Secondary: Complement Bb

End point title	Complement Bb

End point description:

Plasma Bb was measured by enzyme-linked immunosorbent assay (ELISA).

End point type	Secondary

End point timeframe:

Baseline and Day 28

End point values	Danicopan			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: microgram (ug)/mL				
arithmetic mean (standard deviation)				
Baseline	2.24160 (± 0.773962)			
Day 28	0.83913 (± 0.83821)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After the first dose of study medication (Day 1) through 14 days after the last dose of study drug (up to Day 104).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Danicopan

Reporting group description:

Participants received danicopan 100 to 200 mg TID.

Serious adverse events	Danicopan		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 10 (10.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Alanine aminotransferase increased			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Haemolysis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Danicopan		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 10 (90.00%)		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Vaccination site erythema			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Non-cardiac chest pain			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Psychiatric disorders			
Irritability			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 10 (40.00%)		
occurrences (all)	5		
Blood and lymphatic system disorders			

Haemolysis			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	3		
Paroxysmal nocturnal haemoglobinuria			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Mouth ulceration			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Abdominal pain			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Rash papular			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Renal and urinary disorders			
Haemoglobinuria			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Infections and infestations			

Pharyngitis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	4 / 10 (40.00%) 4		
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Metabolism and nutrition disorders Iron deficiency subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 March 2017	• Updated the dose levels based on the current PK modelling and clinical safety in healthy volunteers • Reworded the primary objective for clarity • Updated the previous human experience • Addressed discrepancies between this protocol and the ACH471-102 screening protocol
19 April 2017	• Upgraded the AE grading criteria used in the study to CTCAE and clarified language around the classification of AEs • Updated the previous human experience • Clarified the collection of information about red blood cell transfusions at each visit
18 May 2017	• Increased the starting dose from 100 mg TID (per the original protocol) to 150 mg TID • Increased the maximum permitted dose to 200 mg TID • Allowed vaccination concurrent with dosing, if local practice dictated
05 December 2017	• Updated the contraception section to include definitions requested by Health Authorities • Updated the contact information for SAE reporting • Added wording to permit the conducting of patient-reported outcomes interviews as questionnaires, where required
21 December 2017	• Increased the maximum permitted dose from 200 mg TID (Amendment 3) to 250 mg TID • Updated the contact information for SAE reporting
13 March 2018	• Specified that vaccination against bacterial infections should be performed, when necessary, based on vaccination history • Updated and clarified requirements for "acceptable" and "highly effecting" methods of contraception

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/33121236