EU Clinical Trials Register

Clinical trial results:
An Open-label Study to Evaluate Efficacy and Safety of Long-term Treatment with ACH-0144471 in Patients with PNH who Completed Clinical Study ACH471-100

Summary

EudraCT number	2017-000665-79
Trial protocol	GB IT
Global end of trial date	03 January 2022

Results information

Result version number	v1 (current)
This version publication date	06 January 2023
First version publication date	06 January 2023

Trial information

Trial identification

Sponsor protocol code	ACH471 103

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03181633
WHO universal trial number (UTN)	U1111-1196-0653

Notes:

Sponsors

Sponsor organisation name	Alexion Pharmaceuticals, Inc.
Sponsor organisation address	Alexion Pharmaceuticals, Inc., 100 College Street, 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	03 January 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 January 2022
Global end of trial reached?	Yes
Global end of trial date	03 January 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate the safety and efficacy of long term therapy with danicopan in participants with paroxysmal nocturnal hemoglobinuria (PNH).

Protection of trial subjects:

This study was conducted in accordance with the protocol and with the following:
•   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
•   Applicable laws and regulations

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 June 2017
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	New Zealand: 5
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Korea, Republic of: 1
Worldwide total number of subjects	8
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)	7
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants who demonstrated a clinical benefit from danicopan in the primary Study ACH471-100 (2016-002652-25), were eligible for long-term treatment with danicopan in this extension Study ACH471-103.

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	Danicopan

Arm description:

Participants in this study continued to receive danicopan tablets orally at the same dose (150, 175, or 200 milligrams [mg] 3 times daily [TID]) that they were receiving upon completion of the primary Study ACH471-100. Dose escalation was done in increments of 25 mg to a maximum of 250 mg TID, in case additional clinical benefit was expected as per Investigator and Sponsor decision.

Arm type	Experimental
Investigational medicinal product name	Danicopan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Danicopan was administered per dose and schedule specified in the arm description.

Number of subjects in period 1	Danicopan
Started	8
Received at least 1 dose of study drug	8
Completed	6
Not completed	2
Consent withdrawn by subject	1
Missing follow-up visit	1

Baseline characteristics

Reporting groups

Reporting group title	Danicopan
Reporting group description:	

Participants in this study continued to receive danicopan tablets orally at the same dose (150, 175, or 200 milligrams [mg] 3 times daily [TID]) that they were receiving upon completion of the primary Study ACH471-100. Dose escalation was done in increments of 25 mg to a maximum of 250 mg TID, in case additional clinical benefit was expected as per Investigator and Sponsor decision.

Reporting group values	Danicopan	Total	
Number of subjects	8	8	
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)	1	1	
Adults (18-64 years)	7	7	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous			
Units: years			
arithmetic mean	37.51		
standard deviation	± 14.752	-	
Sex: Female, Male			
Units: participants			
Female	4	4	
Male	4	4	
Race/Ethnicity, Customized			
Units: Subjects			
White	6	6	
Asian	1	1	
Other	1	1	
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	8	8	
Unknown or Not Reported	0	0	
Lactate Dehydrogenase (LDH) Level			
Units: units (U)/liter (L)			
arithmetic mean	1403.13		
standard deviation	± 602.824	-	
Hemoglobin (Hgb) Level in the Absence of Red Blood Cell (RBC) Transfusion			
Units: grams (g)/liter (L)			
arithmetic mean	96.50		

standard deviation	± 18.055	-	
Reticulocyte Counts			
Units: 10^12/L			
arithmetic mean	0.15		
standard deviation	± 0.078	-	
Paroxysmal Nocturnal Hemoglobinuria (PNH) Clone Size			
Number of participants analyzed = 6			
Units: percentage of the total cell population			
arithmetic mean	39.67		
standard deviation	± 29.696	-	
Free Hgb			
Units: mg/deciliter (dL)			
arithmetic mean	36.08		
standard deviation	± 42.417	-	
Alternative Pathway (AP) Complement Functional Activity			
Serum AP functional activity was measured by the Wieslab functional immunoassay method.			
Units: percentage of activity			
arithmetic mean	66.70		
standard deviation	± 12.732	-	

End points

End points reporting groups

Reporting group title	Danicopan

Reporting group description:

Participants in this study continued to receive danicopan tablets orally at the same dose (150, 175, or 200 milligrams [mg] 3 times daily [TID]) that they were receiving upon completion of the primary Study ACH471-100. Dose escalation was done in increments of 25 mg to a maximum of 250 mg TID, in case additional clinical benefit was expected as per Investigator and Sponsor decision.

Primary: Change From Baseline in LDH Level at Week 25

End point title	Change From Baseline in LDH Level at Week 25[1]

End point description:

Change from Baseline = Serum LDH levels at Week 25 - Baseline Serum LDH levels. Baseline was the baseline value from the primary Study ACH471-100. Full analysis set included all enrolled and treated participants. Here, 'Overall number of participants analyzed' = participants with both baseline and the postbaseline assessments for LDH level.

End point type	Primary

End point timeframe:

Baseline, Week 25

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: The statistical analysis was not planned for this endpoint.

End point values	Danicopan			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: U/L				
arithmetic mean (standard deviation)	-683.29 (± 845.175)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Hgb Level in the Absence of RBC Transfusion at Week 25

End point title	Change From Baseline in Hgb Level in the Absence of RBC Transfusion at Week 25[2]

End point description:

Change from Baseline = Hgb levels at Week 25 - Baseline Hgb levels. Baseline was the baseline value from the primary Study ACH471-100. Full analysis set included all enrolled and treated participants. Here, 'Overall number of participants analyzed' = participants with both baseline and the postbaseline assessments for Hgb level.

End point type	Primary

End point timeframe:

Baseline, Week 25

Notes:

[2] - 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: The statistical analysis was not planned for this endpoint.

End point values	Danicopan			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: g/L				
arithmetic mean (standard deviation)	24.67 (± 18.052)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Reticulocyte Counts at Week 25

End point title	Change From Baseline in Reticulocyte Counts at Week 25[3]

End point description:

Change from Baseline = reticulocyte count at Week 25 - Baseline reticulocyte count. Baseline was the baseline value from the primary Study ACH471-100. Full analysis set included all enrolled and treated participants. Here, 'Overall number of participants analyzed' = participants with both baseline and the postbaseline assessments for reticulocyte count.

End point type	Primary

End point timeframe:

Baseline, Week 25

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: The statistical analysis was not planned for this endpoint.

End point values	Danicopan			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: 10^12/L				
arithmetic mean (standard deviation)	-0.07 (± 0.063)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of RBC Units Transfused

End point title	Number of RBC Units Transfused[4]

End point description:

Full analysis set included all enrolled and treated participants.

End point type	Primary

End point timeframe:
Baseline up to Week 169

Notes:
[4] - 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: The statistical analysis was not planned for this endpoint.

End point values	Danicopan			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: RBC units				
arithmetic mean (standard deviation)	6.5 (± 16.83)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of RBC Transfusion Instances

End point title	Number of RBC Transfusion Instances[5]

End point description:
Full analysis set included all enrolled and treated participants.

End point type	Primary

End point timeframe:
Baseline up to Week 169

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: The statistical analysis was not planned for this endpoint.

End point values	Danicopan			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: RBC transfusion instances				
arithmetic mean (standard deviation)	3.4 (± 8.00)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in PNH Clone Size at Week 25

End point title	Change From Baseline in PNH Clone Size at Week 25[6]

End point description:
The PNH clone size refers to the percentage of PNH-affected cells versus normal cells within the total cell population. Change from Baseline = PNH clone size at Week 25 - Baseline PNH clone size. Baseline was the baseline value from the primary Study ACH471-100. Full analysis set included all enrolled and treated participants. Here, 'Overall number of participants analyzed' = participants with both baseline and the postbaseline assessments for PNH clone size.

End point type	Primary

End point timeframe:

Baseline, Week 25

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: The statistical analysis was not planned for this endpoint.

End point values	Danicopan			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: percentage of the total cell population				
arithmetic mean (standard deviation)	22.00 (± 5.831)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in AP Complement Functional Activity at Week 25

End point title	Change From Baseline in AP Complement Functional Activity at Week 25[7]

End point description:

Serum AP functional activity was measured by the Wieslab functional immunoassay method. Change from Baseline = Serum AP functional activity at Week 25 - Baseline Serum AP functional activity. Baseline was the baseline value from the primary Study ACH471-100. Full analysis set included all enrolled and treated participants. Here, 'Overall number of participants analyzed' = participants with both baseline and the postbaseline assessments for Serum AP functional activity.

End point type	Primary

End point timeframe:

Baseline, Week 25

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: The statistical analysis was not planned for this endpoint.

End point values	Danicopan			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: percentage of activity				
arithmetic mean (standard deviation)	-46.36 (± 25.316)			

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Free Hgb at Week 25

End point title	Change From Baseline in Free Hgb at Week 25[8]

End point description:

Change from Baseline = free Hgb at Week 25 - Baseline free Hgb. Baseline was the baseline value from the primary Study ACH471-100. Full analysis set included all enrolled and treated participants. Here, 'Overall number of participants analyzed' = participants with both baseline and the postbaseline assessments for free Hgb.

End point type	Primary

End point timeframe:

Baseline, Week 25

Notes:

[8] - 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: The statistical analysis was not planned for this endpoint.

End point values	Danicopan			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: mg/dL				
arithmetic mean (standard deviation)	59.83 (± 66.414)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Treatment-Emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs), Grade 3 and Grade 4 Adverse Events (AEs), And AEs Leading To Discontinuation

End point title	Number of Participants With Treatment-Emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs), Grade 3 and Grade 4 Adverse Events (AEs), And AEs Leading To Discontinuation[9]

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 all Serious Adverse Events and Other Adverse Events (nonserious) regardless of causality is located in the 'Reported Adverse Events' Section. Safety analysis set included all enrolled participants who received at least 1 dose of danicopan.

End point type	Primary

End point timeframe:

Baseline up to 4.5 years

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: The statistical analysis was not planned for this endpoint.

End point values	Danicopan			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: participants				
Any TEAEs	8			
SAEs	3			
TEAE Grade 3	2			
TEAE Grade 4	0			
AE leading to discontinuation	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in LDH Level at Weeks 49 and 169

End point title	Change From Baseline in LDH Level at Weeks 49 and 169

End point description:

Change from Baseline = Serum LDH levels at specified postbaseline visit - Baseline Serum LDH levels. Baseline was the baseline value from the primary Study ACH471-100. Full analysis set included all enrolled and treated participants. Here, 'Overall number of participants analyzed' = participants with both baseline and the postbaseline assessments for LDH level. 'n' = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 49 and 169

End point values	Danicopan			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: U/L				
arithmetic mean (standard deviation)				
Change at Week 49 (n = 6)	-862.50 (± 568.302)			
Change at Week 169 (n = 2)	-1388.00 (± 562.857)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Hgb Level in the Absence of RBC Transfusion at Weeks 49 and 169

End point title	Change From Baseline in Hgb Level in the Absence of RBC Transfusion at Weeks 49 and 169

End point description:
Change from Baseline = Hgb levels at specified postbaseline visit - Baseline Hgb levels. Baseline was the baseline value from the primary Study ACH471-100. Full analysis set included all enrolled and treated participants. Here, 'Overall number of participants analyzed' = participants with both baseline and the postbaseline assessments for Hgb level. 'n' = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:
Baseline, Weeks 49 and 169

End point values	Danicopan			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: g/L				
arithmetic mean (standard deviation)				
Change at Week 49 (n = 5)	21.40 (± 18.995)			
Change at Week 169 (n = 2)	54.50 (± 14.849)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Reticulocyte Counts at Weeks 49 and 169

End point title	Change From Baseline in Reticulocyte Counts at Weeks 49 and 169

End point description:
Change from Baseline = reticulocyte count at specified postbaseline visit - Baseline reticulocyte count. Baseline was the baseline value from the primary Study ACH471-100. Full analysis set included all enrolled and treated participants. Here, 'Overall number of participants analyzed' = participants with both baseline and the postbaseline assessments for reticulocyte count. 'n' = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:
Baseline, Weeks 49 and 169

End point values	Danicopan			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: 10^12/L				
arithmetic mean (standard deviation)				
Change at Week 49 (n = 6)	-0.05 (± 0.065)			
Change at Week 169 (n = 2)	-0.12 (± 0.049)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in PNH Clone Size at Weeks 49 and 73

End point title	Change From Baseline in PNH Clone Size at Weeks 49 and 73

End point description:

The PNH clone size refers to the percentage of PNH-affected cells versus normal cells within the total cell population. Change from Baseline = PNH clone size at specified postbaseline visit - Baseline PNH clone size. Baseline was the baseline value from the primary Study ACH471-100. Full analysis set included all enrolled and treated participants. Here, 'Overall number of participants analyzed' = participants with both baseline and the postbaseline assessments for PNH clone size. 'n' = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 49 and 73

End point values	Danicopan			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: percentage of the total cell population				
arithmetic mean (standard deviation)				
Change at Week 49 (n = 6)	30.83 (± 11.531)			
Change at Week 73 (n = 5)	32.00 (± 19.170)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in AP Complement Functional Activity at Weeks 49 and 145

End point title	Change From Baseline in AP Complement Functional Activity at Weeks 49 and 145

End point description:

Serum AP functional activity was measured by the Wieslab functional immunoassay method. Change from Baseline = Serum AP functional activity at specified postbaseline visit - Baseline Serum AP functional activity. Baseline was the baseline value from the primary Study ACH471-100. Full analysis set included all enrolled and treated participants. Here, 'Overall number of participants analyzed' = participants with both baseline and the postbaseline assessments for Serum AP functional activity. 'n' = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 49 and 145

End point values	Danicopan			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: percentage of activity				
arithmetic mean (standard deviation)				
Change at Week 49 (n = 6)	-59.80 (± 14.217)			
Change at Week 145 (n = 2)	-52.43 (± 2.779)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Free Hgb at Weeks 49 and 169

End point title	Change From Baseline in Free Hgb at Weeks 49 and 169

End point description:

Change from Baseline = free Hgb at specified postbaseline visit - Baseline free Hgb. Baseline was the baseline value from the primary Study ACH471-100. Full analysis set included all enrolled and treated participants. Here, 'Overall number of participants analyzed' = participants with both baseline and the postbaseline assessments for free Hgb. 'n' = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 49 and 169

End point values	Danicopan			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: mg/dL				
arithmetic mean (standard deviation)				
Change at Week 49 (n = 6)	105.92 (± 92.308)			
Change at Week 169 (n = 2)	-30.75 (± 54.942)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale Score at Weeks 21, 41, and 153

End point title	Change From Baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale Score at Weeks 21, 41, and 153

End point description:

The FACIT-Fatigue scale is a collection of quality of life questionnaires pertaining to the management of fatigue symptoms due to a chronic illness. The FACIT-Fatigue is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function over the preceding 7 days. Participants score each item on a 5-point scale: 0 (Not at all) to 4 (Very much). Total scores range from 0 to 52, with higher score indicating better quality of life. Full analysis set included all enrolled and treated participants. Here, 'Overall number of participants analyzed' = participants with both baseline and the postbaseline assessments for FACIT-Fatigue scale score. 'n' = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 21, 41, and 153

End point values	Danicopan			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: units on a scale				
arithmetic mean (standard deviation)				
Change at Week 21 (n = 8)	8.4 (± 11.75)			
Change at Week 41 (n = 7)	9.1 (± 13.37)			
Change at Week 153 (n = 2)	3.0 (± 0.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 Scale (EORTC-QLQ-C30): Global Health Status/Qol Score at Weeks 21, 41, and 153

End point title	Change From Baseline in European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 Scale (EORTC-QLQ-C30): Global Health Status/Qol Score at Weeks 21, 41, and 153

End point description:

EORTC-QLQ-C30 is comprised of 30 questions. First 28 questions used 4-point scale (1=not at all,2=a little,3=quite a bit,4=very much) for evaluating 5 functional scales (physical, role, emotional, cognitive, social), 3 symptom scales (fatigue, nausea/vomiting, pain) & other single items. For each item, high score = high level of symptomatology/problem. Last 2 questions represented participant's assessment of overall health (global health status) and quality of life, coded on 7-point scale (1=very poor to 7=excellent). Answers were converted into grading scale, with total score between 0 and 100. A high score represented a favourable outcome with a best quality of life for participant. Full analysis set included all enrolled and treated participants. Here, 'Overall number of participants analyzed' = participants with both baseline and the postbaseline assessments for EORTC-QLQ-C30 (Global Health Status/Qol) score. 'n' = participants evaluable at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 21, 41, and 153

End point values	Danicopan			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: units on a scale				
arithmetic mean (standard deviation)				
Change at Week 21 (n = 8)	16.67 (± 25.973)			
Change at Week 41 (n = 7)	11.90 (± 29.603)			
Change at Week 153 (n = 2)	4.17 (± 17.678)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:	
Baseline up to 4.5 years	
Adverse event reporting additional description:	
Safety analysis set included all enrolled participants who received at least 1 dose of danicopan.	
Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Danicopan

Reporting group description:

Participants in this study continued to receive danicopan tablets orally at the same dose (150, 175, or 200 mg TID) that they were receiving upon completion of the primary Study ACH471-100. Dose escalation was done in increments of 25 mg to a maximum of 250 mg TID, in case additional clinical benefit was expected as per Investigator and Sponsor decision.

Serious adverse events	Danicopan		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 8 (37.50%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Blood and lymphatic system disorders			
Haemolysis			
subjects affected / exposed	1 / 8 (12.50%)		
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 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cystitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			

subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infectious mononucleosis			
subjects affected / exposed	1 / 8 (12.50%)		
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 %

Non-serious adverse events	Danicopan		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	3 / 8 (37.50%)		
occurrences (all)	3		
Pyrexia			
subjects affected / exposed	3 / 8 (37.50%)		
occurrences (all)	3		
Fatigue			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Chest discomfort			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Influenza like illness			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			

Dry throat			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	4		
Intentional overdose			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	3		
Ligament sprain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Skin laceration			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 8 (37.50%)		
occurrences (all)	3		
Lethargy			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Haemolysis			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	5		
Eye disorders			
Conjunctival hyperaemia			

subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		

Gastrointestinal disorders

Dysphagia

subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	7		

Abdominal pain

subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		

Diarrhoea

subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		

Gastrooesophageal reflux disease

subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		

Vomiting

subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		

Constipation

subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		

Nausea

subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		

Skin and subcutaneous tissue disorders

Hand dermatitis

subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		

Renal and urinary disorders

Chromaturia

subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		

Haemoglobinuria

subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	15		

Haematuria

subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Paroxysmal nocturnal haemoglobinuria			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Limb discomfort			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	4 / 8 (50.00%)		
occurrences (all)	6		
Cellulitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Herpes simplex			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 May 2017	• Enrollment was restricted to participants who completed Study ACH471-100 and demonstrated clinical benefit from danicopan. • Study population was restricted to a maximum of 12 participants (from 30 participants). • Danicopan trough concentration measurement for pharmacokinetics (PK) and ECG for safety assessments were added. • Starting dose was increased to 150 mg TID and dose escalations up to 200 mg TID were permitted. A blood draw for LDH and liver function tests at 72 to 84 hours and the participants were required to have a clinic visit 2 weeks after dose escalation for safety evaluation and collection of samples for efficacy, pharmacodynamics (PD), and PK evaluation. • 75 mg danicopan tablet was added to the list of supplied formulations. • Dosing taper schedule corresponding to the newly updated permitted doses was added. • Added a clarification that samples used for complement analyses will be stored from the beginning of this clinical study to 1 year after the clinical study report is published. • Instructions for reporting SAEs or pregnancies were updated. • Patient-reported outcomes (PRO) assessments (FACIT Fatigue and EORTC QLQ C30) were added.
22 December 2017	• Dose escalations of up to 250 mg TID in increments of 25 mg permitted. • Dosing taper schedule corresponding to the newly updated permitted doses was added. • Details of highly effective contraception requirements for both female and male participants including hormonal contraception, intrauterine device (IUD) /intrauterie system (IUS), bilateral tubal occlusion, abstinence, sterility requirements, vasectomy, condom use with female partner contraception (hormonal, IUD/IUS, bilateral tubal occlusion) were either added or updated. • Requirement for urine pregnancy tests for females throughout the study as per the Schedule of Assessments, was added. • Revised text to mention that participants who terminate early may be interviewed for PRO assessments based on local regulations or ethics committee (EC) requirements. • Instructions for reporting SAEs were updated.
13 March 2018	• Inclusion criterion was updated for acceptable contraception (female) from date of informed consent to dosing Day 1 and highly effective contraception (male and female) from dosing Day 1 to 30 days (for females) and 90 days (for males) after the last dose of study intervention. • Guidance on booster vaccinations against bacterial infections as per national and/or local guidelines or in their absence as per Advisory Committee on Immunization Practices (ACIP) guidelines was added. • Female participants of childbearing potential were also required to have a negative serum pregnancy test during Screening and negative urine pregnancy test on Day 1. • Instructions for participants discontinuing during the extension phase to have danicopan tapered and have follow-up visits were added.

04 June 2021	• Instructions for dose tapering were updated and 75 mg dose was removed from the dose tapering schedule as 75 mg tablets used in the study were no longer manufactured. • PRO interviews were discontinued effective 30 Apr 2019. • PK/PD samples were no longer required at the long-term extension clinic visits, taper visits, or follow-up visits. • Instructions for reporting SAEs or pregnancies were updated due to a transition in the safety reporting process. • To ensure patient safety and treatment continuity during the COVID-19 outbreak, physical visits were allowed to become telephone or videoconference visits, and safety laboratory tests were allowed using home healthcare laboratory sampling, local laboratories, or other appropriate clinical facilities. • Language regarding COVID 19 risk assessment was added as per Medicines and Healthcare products Regulatory Agency (MHRA) requirements. • Clarification regarding study requirements for participants from Study ACH471-103 to enroll into Study ACH228-110 and option to enter in another appropriate Alexion clinical study (if available), were added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported