Clinical trial results:
A Phase 3 Study of Danicopan (ALXN2040) as Add-on Therapy to a C5 Inhibitor (Eculizumab or Ravulizumab) in Patients With Paroxysmal Nocturnal Hemoglobinuria Who Have Clinically Evident Extravascular Hemolysis (EVH)

Summary

EudraCT number	2019-003829-18
Trial protocol	FR DE GB NL PL IT GR
Global end of trial date	16 January 2024

Results information

Result version number	v1 (current)
This version publication date	25 October 2024
First version publication date	25 October 2024

Trial information

Trial identification

Sponsor protocol code	ALXN2040-PNH-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04469465
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., +35 3874162507, clinicaltrials.eu@alexion.com
Scientific contact	European Clinical Trial Information, Alexion Pharmaceuticals, Inc., +35 3874162507, 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	16 January 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 January 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study is to evaluate the efficacy of danicopan as add-on therapy to a complement component 5 (C5) inhibitor (ravulizumab or eculizumab) in participants with paroxysmal nocturnal hemoglobinuria (PNH) who have clinically evident EVH.

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:

C5 Inhibitor (ravulizumab or eculizumab)

Evidence for comparator:

Danicopan and placebo were administered as add-on therapies to background C5 inhibitor (ravulizumab or eculizumab) therapy.

Actual start date of recruitment	06 January 2021
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Czechia: 1
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Japan: 12
Country: Number of subjects enrolled	Brazil: 4
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	United States: 9
Country: Number of subjects enrolled	Korea, Republic of: 13

Country: Number of subjects enrolled	Malaysia: 5
Country: Number of subjects enrolled	Thailand: 1
Worldwide total number of subjects	86
EEA total number of subjects	29

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)	64
From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study consists of 2 treatment periods and a long-term extension period.

Period 1

Period 1 title	Treatment Period 1 (TP1)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Danicopan-Danicopan

Arm description:

Participants received danicopan 3 times daily (TID) for 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during treatment period 1 (TP1). Participants continued to receive danicopan TID for an additional 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during treatment period 2 (TP2). After completing TP2 (Week 24), participants entered the long-term extension (LTE) for 2 years at the same danicopan dose received at Week 24, in addition to their background ravulizumab or eculizumab therapy.

Arm type	Experimental
Investigational medicinal product name	C5 Inhibitor
Investigational medicinal product code	
Other name	Eculizumab, Ravulizumab
Pharmaceutical forms	Infusion, Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received their ongoing C5 inhibitor (ravulizumab or eculizumab) therapy according to their usual dose and schedule.

Investigational medicinal product name	Danicopan
Investigational medicinal product code	
Other name	ALXN2040
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received danicopan TID.

Arm title	Placebo-Danicopan

Arm description:

Participants received placebo TID for 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during TP1. At the end of Week 12, participants were switched to receive danicopan TID for 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during TP2. After completing TP2 (Week 24), participants entered the LTE for 2 years at the same danicopan dose received at Week 24, in addition to their background ravulizumab or eculizumab therapy.

Arm type	Placebo

Investigational medicinal product name	C5 Inhibitor
Investigational medicinal product code	
Other name	Eculizumab, Ravulizumab
Pharmaceutical forms	Infusion, Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received their ongoing C5 inhibitor (ravulizumab or eculizumab) therapy according to their usual dose and schedule.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received placebo TID.

Number of subjects in period 1	Danicopan-Danicopan	Placebo-Danicopan
Started	57	29
Received at least 1 dose of study drug	57	29
Interim Efficacy Analysis Set	42 [1]	21 [2]
Completed	55	27
Not completed	2	2
Consent withdrawn by subject	-	1
Adverse event, non-fatal	2	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Per the prespecified plan for interim analysis, the first 75% of randomized participants formed the Interim Analysis Set for efficacy analysis.
[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Per the prespecified plan for interim analysis, the first 75% of randomized participants formed the Interim Analysis Set for efficacy analysis.

Period 2

Period 2 title	Treatment Period 2 (TP2)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes

Arm title	Danicopan-Danicopan

Arm description:

Participants received danicopan TID for 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during TP1. Participants continued to receive danicopan TID for an additional 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during TP2. After completing TP2 (Week 24), participants entered the LTE for 2 years at the same danicopan dose received at Week 24, in addition to their background ravulizumab or eculizumab therapy.

Arm type	Experimental
Investigational medicinal product name	C5 Inhibitor
Investigational medicinal product code	
Other name	Eculizumab, Ravulizumab
Pharmaceutical forms	Infusion, Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received their ongoing C5 inhibitor (ravulizumab or eculizumab) therapy according to their usual dose and schedule.

Investigational medicinal product name	Danicopan
Investigational medicinal product code	
Other name	ALXN2040
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received danicopan TID.

Arm title	Placebo-Danicopan

Arm description:

Participants received placebo TID for 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during TP1. At the end of Week 12, participants were switched to receive danicopan TID for 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during TP2. After completing TP2 (Week 24), participants entered the LTE for 2 years at the same danicopan dose received at Week 24, in addition to their background ravulizumab or eculizumab therapy.

Arm type	Experimental
Investigational medicinal product name	C5 Inhibitor
Investigational medicinal product code	
Other name	Eculizumab, Ravulizumab
Pharmaceutical forms	Infusion, Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received their ongoing C5 inhibitor (ravulizumab or eculizumab) therapy according to their usual dose and schedule.

Investigational medicinal product name	Danicopan
Investigational medicinal product code	
Other name	ALXN2040
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received danicopan TID.

Number of subjects in period 2	Danicopan-Danicopan	Placebo-Danicopan
Started	55	27
Received at least 1 dose of study drug	55	27
Completed	54	26
Not completed	1	1
Adverse event, non-fatal	1	1

Period 3

Period 3 title	Long-Term Extension (LTE)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Danicopan-Danicopan

Arm description:

Participants received danicopan TID for 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during TP1. Participants continued to receive danicopan TID for an additional 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during TP2. After completing TP2 (Week 24), participants entered the LTE for 2 years at the same danicopan dose received at Week 24, in addition to their background ravulizumab or eculizumab therapy.

Arm type	Experimental
Investigational medicinal product name	C5 Inhibitor
Investigational medicinal product code	
Other name	Eculizumab, Ravulizumab
Pharmaceutical forms	Infusion, Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received their ongoing C5 inhibitor (ravulizumab or eculizumab) therapy according to their usual dose and schedule.

Investigational medicinal product name	Danicopan
Investigational medicinal product code	
Other name	ALXN2040
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received danicopan TID.

Arm title	Placebo-Danicopan

Arm description:

Participants received placebo TID for 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during TP1. At the end of Week 12, participants were switched to receive danicopan TID for 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during TP2. After completing TP2 (Week 24), participants entered the LTE for 2 years at the same danicopan dose received at Week 24, in addition to their background ravulizumab or eculizumab therapy.

Arm type	Experimental

Investigational medicinal product name	Danicopan
Investigational medicinal product code	
Other name	ALXN2040
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received danicopan TID.

Investigational medicinal product name	C5 Inhibitor
Investigational medicinal product code	
Other name	Eculizumab, Ravulizumab
Pharmaceutical forms	Infusion, Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received their ongoing C5 inhibitor (ravulizumab or eculizumab) therapy according to their usual dose and schedule.

Number of subjects in period 3	Danicopan-Danicopan	Placebo-Danicopan
Started	54	26
Received at least 1 dose of study drug	54	26
Completed	46	24
Not completed	8	2
Adverse event, serious fatal	-	1
Consent withdrawn by subject	3	-
Physician decision	3	-
Adverse event, non-fatal	1	1
Noncompliance with study intervention	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Danicopan-Danicopan
Reporting group description:	
Participants received danicopan 3 times daily (TID) for 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during treatment period 1 (TP1). Participants continued to receive danicopan TID for an additional 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during treatment period 2 (TP2). After completing TP2 (Week 24), participants entered the long-term extension (LTE) for 2 years at the same danicopan dose received at Week 24, in addition to their background ravulizumab or eculizumab therapy.	
Reporting group title	Placebo-Danicopan
Reporting group description:	
Participants received placebo TID for 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during TP1. At the end of Week 12, participants were switched to receive danicopan TID for 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during TP2. After completing TP2 (Week 24), participants entered the LTE for 2 years at the same danicopan dose received at Week 24, in addition to their background ravulizumab or eculizumab therapy.	

Reporting group values	Danicopan-Danicopan	Placebo-Danicopan	Total
Number of subjects	57	29	86
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	41	23	64
From 65-84 years	16	6	22
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	52.8	52.9	
standard deviation	± 17.00	± 14.34	-
Sex: Female, Male Units: participants			
Female	34	20	54
Male	23	9	32
Ethnicity (NIH/OMB)			
NIH/OMB = National Institutes of Health/Office of Management and Budget			
Units: Subjects			
Hispanic or Latino	6	1	7
Not Hispanic or Latino	46	24	70
Unknown or Not Reported	5	4	9
Race (NIH/OMB)			
NIH/OMB = National Institutes of Health/Office of Management and Budget			
Units: Subjects			
American Indian or Alaska Native	1	0	1

Asian	22	10	32
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	0	2
White	28	14	42
More than one race	0	0	0
Unknown or Not Reported	4	5	9
Hemoglobin (Hgb)			
g/L = grams/litre			
Units: g/L			
arithmetic mean	76.7	78.9	
standard deviation	± 9.47	± 10.11	-

End points

End points reporting groups

Reporting group title	Danicopan-Danicopan

Reporting group description:

Participants received danicopan 3 times daily (TID) for 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during treatment period 1 (TP1). Participants continued to receive danicopan TID for an additional 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during treatment period 2 (TP2). After completing TP2 (Week 24), participants entered the long-term extension (LTE) for 2 years at the same danicopan dose received at Week 24, in addition to their background ravulizumab or eculizumab therapy.

Reporting group title	Placebo-Danicopan

Reporting group description:

Participants received placebo TID for 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during TP1. At the end of Week 12, participants were switched to receive danicopan TID for 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during TP2. After completing TP2 (Week 24), participants entered the LTE for 2 years at the same danicopan dose received at Week 24, in addition to their background ravulizumab or eculizumab therapy.

Reporting group title	Danicopan-Danicopan

Reporting group description:

Participants received danicopan TID for 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during TP1. Participants continued to receive danicopan TID for an additional 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during TP2. After completing TP2 (Week 24), participants entered the LTE for 2 years at the same danicopan dose received at Week 24, in addition to their background ravulizumab or eculizumab therapy.

Reporting group title	Placebo-Danicopan

Reporting group description:

Participants received placebo TID for 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during TP1. At the end of Week 12, participants were switched to receive danicopan TID for 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during TP2. After completing TP2 (Week 24), participants entered the LTE for 2 years at the same danicopan dose received at Week 24, in addition to their background ravulizumab or eculizumab therapy.

Reporting group title	Danicopan-Danicopan

Reporting group description:

Participants received danicopan TID for 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during TP1. Participants continued to receive danicopan TID for an additional 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during TP2. After completing TP2 (Week 24), participants entered the LTE for 2 years at the same danicopan dose received at Week 24, in addition to their background ravulizumab or eculizumab therapy.

Reporting group title	Placebo-Danicopan

Reporting group description:

Participants received placebo TID for 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during TP1. At the end of Week 12, participants were switched to receive danicopan TID for 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during TP2. After completing TP2 (Week 24), participants entered the LTE for 2 years at the same danicopan dose received at Week 24, in addition to their background ravulizumab or eculizumab therapy.

Subject analysis set title	Interim Efficacy Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

Per the prespecified plan for interim analysis, the first 75% of enrolled participants that were randomized to either the danicopan or placebo treatment group.

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

All enrolled participants that were randomized to either the danicopan or placebo treatment group.

Subject analysis set title	Danicopan (TP1)
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received danicopan TID for 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during TP1.

Subject analysis set title	Placebo (TP1)
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received placebo TID for 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during TP1.

Subject analysis set title	Danicopan (TP1): Interim Efficacy Analysis
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received danicopan TID for 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during TP1.

Subject analysis set title	Placebo (TP1): Interim Efficacy Analysis
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received placebo TID for 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during TP1.

Subject analysis set title	Danicopan (TP1): Full Analysis
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received danicopan TID for 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during TP1.

Subject analysis set title	Placebo (TP1): Full Analysis
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received placebo TID for 12 weeks, in addition to their background ravulizumab or eculizumab therapy, during TP1.

Primary: Change From Baseline in Hgb at Week 12

End point title	Change From Baseline in Hgb at Week 12

End point description:

Baseline was defined as the lowest Hgb value observed between and including Screening and Day 1. The least square (LS) mean and standard error (SE) were produced using mixed-effect model for repeated measures (MMRM). Hgb values collected within 4 weeks after transfusion were not included in the MMRM. Here, 'Number of subjects analysed' signifies those participants who were evaluable for this end point.

End point type	Primary

End point timeframe:

Baseline, Week 12

End point values	Danicopan (TP1): Interim Efficacy Analysis	Placebo (TP1): Interim Efficacy Analysis	Danicopan (TP1): Full Analysis	Placebo (TP1): Full Analysis
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	42[1]	21[2]	57[3]	28[4]
Units: g/L				
least squares mean (standard error)				
Interim Efficacy Analysis	29.40 (± 2.107)	4.96 (± 3.128)	9999 (± 9999)	9999 (± 9999)
Full Analysis	9999 (± 9999)	9999 (± 9999)	28.08 (± 1.957)	4.62 (± 3.018)

Notes:
[1] - 9999 = Interim Efficacy Analysis only (N=42)
[2] - 9999 = Interim Efficacy Analysis only (N=21)
[3] - 9999 = Full Analysis only (N=57)
[4] - 9999 = Full Analysis only (N=28)

Statistical analyses

Statistical analysis title	Hgb at Week 12: Danicopan versus Placebo
Statistical analysis description: Interim Efficacy Analysis	
Comparison groups	Danicopan (TP1): Interim Efficacy Analysis v Placebo (TP1): Interim Efficacy Analysis
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007
Method	Re-randomization Test

Statistical analysis title	Hgb at Week 12: Danicopan versus Placebo
Statistical analysis description: Full Analysis	
Comparison groups	Danicopan (TP1): Full Analysis v Placebo (TP1): Full Analysis
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007
Method	Re-randomization Test

Statistical analysis title	Hgb at Week 12: Danicopan versus Placebo
Statistical analysis description: Full Analysis	
Comparison groups	Danicopan (TP1): Full Analysis v Placebo (TP1): Full Analysis
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Difference
Point estimate	23.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.31
upper limit	30.61

Variability estimate	Standard error of the mean
Dispersion value	3.585

Statistical analysis title	Hgb at Week 12: Danicopan versus Placebo
Statistical analysis description:	
Interim Efficacy Analysis	
Comparison groups	Danicopan (TP1): Interim Efficacy Analysis v Placebo (TP1): Interim Efficacy Analysis
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	24.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.9
upper limit	31.99
Variability estimate	Standard error of the mean
Dispersion value	3.751

Secondary: Percentage of Participants with Hgb Increase of ≥2 Grams/Decilitre (g/dL) (≥20 g/L) From Baseline in the Absence of Transfusion at Week 12

End point title	Percentage of Participants with Hgb Increase of ≥2 Grams/Decilitre (g/dL) (≥20 g/L) From Baseline in the Absence of Transfusion at Week 12
End point description:	
The criterion was defined as ≥20 g/L increase in Hgb from Baseline to Week 12 and remaining transfusion free during the 12-Week TP1. Participants who withdrew from the study early during the 12-Week TP1 or had missing Hgb value at Week 12 were considered as not achieving the criterion.	
End point type	Secondary
End point timeframe:	
Week 12	

End point values	Danicopan (TP1)	Placebo (TP1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	57[5]	29[6]		
Units: percentage of participants				
number (confidence interval 95%)				
Interim Efficacy Analysis	59.5 (43.28 to 74.37)	0 (0.00 to 16.11)		
Full Analysis	54.4 (40.66 to 67.64)	0 (0.00 to 11.94)		

Notes:

[5] - Interim Efficacy Analysis (N=42); Full Analysis (N=57)

[6] - Interim Efficacy Analysis (N=21); Full Analysis (N=29)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Score at Week 12

End point title	Change From Baseline in Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Score at Week 12

End point description:

The FACIT-Fatigue was 13-item questionnaire scored on a 5-point Likert scale (0 = not at all, 4 = very much) that assesses self-reported fatigue and its impact on daily activities and function. Total scores range from 0 to 52 with higher score indicating less fatigue and better health-related quality of life. LS mean and SE were produced using MMRM. Here, 'Number of subjects analysed' signifies those participants who were evaluable for this end point.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Danicopan (TP1)	Placebo (TP1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	57[7]	28[8]		
Units: units on a scale				
least squares mean (standard error)				
Interim Efficacy Analysis	7.97 (± 1.128)	1.85 (± 1.581)		
Full Analysis	8.13 (± 0.919)	2.35 (± 1.289)		

Notes:

[7] - Interim Efficacy Analysis (N=42); Full Analysis (N=56)

[8] - Interim Efficacy Analysis (N=21); Full Analysis (N=28)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Transfusion Avoidance Through Week 12

End point title	Percentage of Participants with Transfusion Avoidance Through Week 12

End point description:

Participants achieved transfusion avoidance if they remained transfusion free and did not require a transfusion as per protocol-specified guidelines from Week 1 through Week 12. Participants who discontinued study treatment early before Week 12 were considered as not achieving transfusion avoidance.

End point type	Secondary

End point timeframe:

Week 12

End point values	Danicopan (TP1)	Placebo (TP1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	57[9]	29[10]		
Units: percentage of participants				
number (confidence interval 95%)				
Interim Efficacy Analysis	83.3 (68.64 to 93.03)	38.1 (18.11 to 61.56)		
Full Analysis	78.9 (66.11 to 88.62)	27.6 (12.73 to 47.24)		

Notes:

[9] - Interim Efficacy Analysis (N=42); Full Analysis (N=57)

[10] - Interim Efficacy Analysis (N=21); Full Analysis (N=29)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Absolute Reticulocyte Count at Week 12

End point title	Change From Baseline in Absolute Reticulocyte Count at Week 12

End point description:

LS mean and SE were produced using MMRM. Here, 'Number of subjects analysed' signifies those participants who were evaluable for this end point.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Danicopan (TP1)	Placebo (TP1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	57[11]	26[12]		
Units: 10^12 cells/L				
least squares mean (standard error)				
Interim Efficacy Analysis	-0.0838 (± 0.00893)	0.0035 (± 0.01268)		
Full Analysis	0.0925 (± 0.00816)	-0.0008 (± 0.01184)		

Notes:

[11] - Interim Efficacy Analysis (N=42); Full Analysis (N=57)

[12] - Interim Efficacy Analysis (N=20); Full Analysis (N=26)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Number of Transfusion Instances From 24 Weeks Prior to Initiation of Treatment to Post 24 Weeks of Treatment

End point title	Change in Number of Transfusion Instances From 24 Weeks Prior to Initiation of Treatment to Post 24 Weeks of Treatment

End point description:

Here, 'Number of subjects analysed' signifies those participants who were evaluable for this end point.

End point type	Secondary

End point timeframe:

24 weeks prior to initiation of treatment to 24 weeks post initiation of treatment

End point values	Danicopan-Danicopan			
Subject group type	Reporting group			
Number of subjects analysed	55[13]			
Units: transfusion instances				
arithmetic mean (standard deviation)	-1.5 (± 2.41)			

Notes:

[13] - Full Analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the Number of Red Blood Cell (RBC) Units Transfused From 24 Weeks Prior to Initiation of Treatment to Post 24 Weeks of Treatment

End point title	Change in the Number of Red Blood Cell (RBC) Units Transfused From 24 Weeks Prior to Initiation of Treatment to Post 24 Weeks of Treatment

End point description:

Here, 'Number of subjects analysed' signifies those participants who were evaluable for this end point.

End point type	Secondary

End point timeframe:

24 weeks prior to initiation of treatment to 24 weeks post initiation of treatment

End point values	Danicopan-Danicopan			
Subject group type	Reporting group			
Number of subjects analysed	55[14]			
Units: RBC units				
arithmetic mean (standard deviation)	-2.7 (± 4.86)			

Notes:

[14] - Full Analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Number of Transfusion Instances From 12 Weeks Prior to Initiation of Treatment to Post 12 Weeks of Treatment

End point title	Change in Number of Transfusion Instances From 12 Weeks Prior to Initiation of Treatment to Post 12 Weeks of Treatment

End point description:

LS mean and SE were produced using ANCOVA.

End point type	Secondary

End point timeframe:

12 weeks prior to initiation of treatment to post 12 weeks of treatment

End point values	Danicopan (TP1)	Placebo (TP1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	57[15]	29[16]		
Units: transfusion instances				
least squares mean (standard error)				
Interim Efficacy Analysis	-0.92 (± 0.174)	-0.21 (± 0.246)		
Full Analysis	-0.91 (± 0.138)	-0.11 (± 0.193)		

Notes:

[15] - Interim Efficacy Analysis (N=42); Full Analysis (N=57)

[16] - Interim Efficacy Analysis (N=21); Full Analysis (N=29)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the Number of RBC Units Transfused From 12 Weeks Prior to Initiation of Treatment to Post 12 Weeks of Treatment

End point title	Change in the Number of RBC Units Transfused From 12 Weeks Prior to Initiation of Treatment to Post 12 Weeks of Treatment

End point description:

LS mean and SE were produced using analysis of covariance (ANCOVA).

End point type	Secondary

End point timeframe:

12 weeks prior to initiation of treatment to 12 weeks post initiation of treatment

End point values	Danicopan (TP1)	Placebo (TP1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	57[17]	29[18]		
Units: RBC units				
least squares mean (standard error)				
Interim Efficacy Analysis	-1.48 (± 0.271)	-0.18 (± 0.383)		
Full Analysis	-1.44 (± 0.212)	-0.14 (± 0.297)		

Notes:

[17] - Interim Efficacy Analysis (N=42); Full Analysis (N=57)

[18] - Interim Efficacy Analysis (N=21); Full Analysis (N=29)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Transfusion Avoidance Through Week 24

End point title	Percentage of Participants with Transfusion Avoidance Through Week 24

End point description:

Participants achieved transfusion avoidance if they remained transfusion free and did not require a transfusion as per protocol-specified guidelines from Week 1 through Week 24. Participants who discontinued study treatment early before Week 24 were considered as not achieving transfusion avoidance. Here, 'Number of subjects analysed' signifies those participants who were evaluable for this end point.

End point type	Secondary

End point timeframe:

24 weeks

End point values	Danicopan-Danicopan			
Subject group type	Reporting group			
Number of subjects analysed	55[19]			
Units: percentage of participants				
number (confidence interval 95%)	69.1 (55.19 to 80.86)			

Notes:

[19] - Full Analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Total and Direct Bilirubin at Week 12

End point title	Change From Baseline in Total and Direct Bilirubin at Week 12

End point description:

Baseline was defined as the last non-missing value prior to first dose of study intervention. LS mean and SE were produced using MMRM.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Danicopan (TP1)	Placebo (TP1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	57[20]	29[21]		
Units: micromoles/L				
least squares mean (standard error)				
Total Bilirubin (Interim Efficacy Analysis)	-9.77 (± 1.692)	-2.15 (± 2.377)		
Direct Bilirubin (Interim Efficacy Analysis)	-2.88 (± 0.357)	0.30 (± 0.503)		
Total Bilirubin (Full Analysis)	-11.55 (± 1.541)	-1.42 (± 2.172)		
Direct Bilirubin (Full Analysis)	-2.85 (± 0.317)	0.17 (± 0.447)		

Notes:

[20] - Interim Efficacy Analysis (N=42); Full Analysis (N=57)

[21] - Interim Efficacy Analysis (N=21); Full Analysis (N=29)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline FACIT Fatigue Scores at Week 24

End point title	Change From Baseline FACIT Fatigue Scores at Week 24

End point description:

The FACIT-Fatigue was 13-item questionnaire scored on a 5-point Likert scale (0 = not at all, 4 = very much) that assesses self-reported fatigue and its impact on daily activities and function. Total scores range from 0 to 52 with higher score indicating less fatigue and better health-related quality of life. LS mean and SE were produced using MMRM. Here, 'Number of subjects analysed' signifies those participants who were evaluable for this end point.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Danicopan-Danicopan	Placebo-Danicopan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52[22]	27[23]		
Units: units on a scale				
least squares mean (standard error)	6.21 (± 1.046)	5.64 (± 1.921)		

Notes:

[22] - Full Analysis

[23] - Full Analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Hgb Stabilization During Last 12 Weeks of Treatment in Participants Receiving 24 Weeks of Danicopan

End point title	Percentage of Participants with Hgb Stabilization During Last 12 Weeks of Treatment in Participants Receiving 24 Weeks of Danicopan

End point description:

The criterion was defined as Hgb stabilization avoidance of a > 1 g/dL (> 10 g/L) decrease in Hgb level at Week 24 from Week 12. Participants with transfusions within 4 weeks prior to Week 24 were considered as not meeting Hgb stabilization regardless of the actual value observed at Week 24. Here, 'Number of subjects analysed' signifies those participants who were evaluable for this end point.

End point type	Secondary

End point timeframe:

Week 12 to Week 24

End point values	Danicopan-Danicopan			
Subject group type	Reporting group			
Number of subjects analysed	55[24]			
Units: percentage of participants				
number (confidence interval 95%)	58.2 (44.11 to 71.35)			

Notes:

[24] - Full Analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Hgb Increase of ≥2 g/dL (≥20 g/L) From Baseline in the Absence of Transfusion at Week 24

End point title	Percentage of Participants with Hgb Increase of ≥2 g/dL (≥20 g/L) From Baseline in the Absence of Transfusion at Week 24

End point description:

The criterion was defined as ≥20 g/L increase in Hgb from Baseline to Week 24 and remaining transfusion free during the 12-Week TP2. Participants who withdrew from the study early during the 12-Week TP2 or had missing Hgb value at Week 24 were considered as not achieving the criterion. Here, 'Number of subjects analysed' signifies those participants who were evaluable for this end point.

End point type	Secondary

End point timeframe:

Week 24

End point values	Danicopan-Danicopan			
Subject group type	Reporting group			
Number of subjects analysed	55[25]			
Units: percentage of participants				
number (confidence interval 95%)	41.8 (28.65 to 55.89)			

Notes:

[25] - Full Analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Complement Component 3 Fragment Deposition (C3d PNH Type 3 Cells) on PNH RBCs at Week 12

End point title	Change From Baseline in Complement Component 3 Fragment Deposition (C3d PNH Type 3 Cells) on PNH RBCs at Week 12

End point description:

Baseline was defined as the last non-missing value prior to first dose of study intervention. LS mean and SE were produced using MMRM. Here, 'Number of subjects analysed' signifies those participants who were evaluable for this end point.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Danicopan (TP1)	Placebo (TP1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56[26]	28[27]		
Units: percentage of the total cell population				
least squares mean (standard error)				
Interim Efficacy Analysis	-15.06 (± 2.824)	0.89 (± 4.394)		
Full Analysis	-19.00 (± 1.814)	0.68 (± 2.690)		

Notes:

[26] - Interim Efficacy Analysis (N=23); Full Analysis (N=56)

[27] - Interim Efficacy Analysis (N=10); Full Analysis (N=26)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in PNH RBC Clone Size at Week 12

End point title	Change From Baseline in PNH RBC Clone Size at Week 12

End point description:

The PNH clone size refers to the percentage of PNH-affected cells versus normal cells within the total cell population. Baseline was defined as the last non-missing value prior to first dose of study intervention. LS mean and SE were produced using MMRM. Here, 'Number of subjects analysed' signifies those participants who were evaluable for this end point.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Danicopan (TP1)	Placebo (TP1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37[28]	24[29]		
Units: percentage of the total cell population				
least squares mean (standard error)				
Interim Efficacy Analysis	24.60 (± 4.180)	-3.04 (± 5.864)		
Full Analysis	26.35 (± 2.369)	-0.18 (± 2.960)		

Notes:

[28] - Interim Efficacy Analysis (N=14); Full Analysis (N=37)

[29] - Interim Efficacy Analysis (N=8); Full Analysis (N=24)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Lactate Dehydrogenase at Week 12

End point title	Change From Baseline in Lactate Dehydrogenase at Week 12

End point description:

Baseline was defined as the average of all available assessments prior to the first dose of study intervention. LS mean and SE were produced using MMRM. Here, 'Number of subjects analysed' signifies those participants who were evaluable for this end point.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Danicopan (TP1)	Placebo (TP1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56[30]	28[31]		
Units: units/L				
least squares mean (standard error)				
Interim Efficacy Analysis	-23.49 (± 8.287)	-2.92 (± 11.914)		
Full Analysis	-25.60 (± 7.932)	-16.92 (± 11.380)		

Notes:

[30] - Interim Efficacy Analysis (N=42); Full Analysis (N=56)

[31] - Interim Efficacy Analysis (N=20); Full Analysis (N=28)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Hgb Normalization at Week 12

End point title	Percentage of Participants with Hgb Normalization at Week 12

End point description:

Hgb normalization was defined as Hgb value above lower limit of normal (LLN) reference range. For male, the LLN was 125 g/L, for female, the LLN was 110 g/L. Participants with transfusions within 4 weeks prior to Week 12 were considered as not meeting Hgb normalization regardless of actual value

observed at Week 12.

End point type	Secondary

End point timeframe:

Week 12

End point values	Danicopan (TP1)	Placebo (TP1)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	57[32]	29[33]		
Units: percentage of participants				
number (confidence interval 95%)				
Interim Efficacy Analysis	28.6 (15.72 to 44.58)	0 (0.00 to 16.11)		
Full Analysis	26.3 (15.54 to 39.66)	0 (0.00 to 11.94)		

Notes:

[32] - Interim Efficacy Analysis (N=42); Full Analysis (N=57)

[33] - Interim Efficacy Analysis (N=21); Full Analysis (N=29)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Hgb Normalization at Week 24

End point title	Percentage of Participants with Hgb Normalization at Week 24

End point description:

Hgb normalization was defined as Hgb value above LLN reference range. For male, the LLN was 125 g/L, for female, the LLN was 110 g/L. Participants with transfusions within 4 weeks prior to Week 24 were considered as not meeting Hgb normalization regardless of actual value observed at Week 24. Here, 'Number of subjects analysed' signifies those participants who were evaluable for this end point.

End point type	Secondary

End point timeframe:

Week 24

End point values	Danicopan-Danicopan			
Subject group type	Reporting group			
Number of subjects analysed	55[34]			
Units: percentage of participants				
number (confidence interval 95%)	20.0 (10.43 to 32.97)			

Notes:

[34] - Full Analysis

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline (Day 1) up to 30 days after last dose of study drug (approximately 2 years)	
Adverse event reporting additional description:	
The Safety Set included all participants that received at least 1 dose of study drug (danicopan or placebo).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups	
Reporting group title	Danicopan (TP1)
Reporting group description:	
Participants received danicopan TID for 12 weeks, in addition to their background eculizumab or ravulizumab therapy, during TP.	
Reporting group title	Placebo (TP1)
Reporting group description:	
Participants received placebo TID for 12 weeks, in addition to their background eculizumab or ravulizumab therapy, during TP1.	
Reporting group title	Placebo-Danicopan (LTE)
Reporting group description:	
After completing TP2 (Week 24), participants entered the LTE for 2 years at the same danicopan dose received at Week 24, in addition to their background ravulizumab or eculizumab therapy.	
Reporting group title	Placebo-Danicopan (TP2)
Reporting group description:	
At the end of Week 12, participants were switched to receive danicopan TID for 12 weeks, in addition to their background eculizumab or ravulizumab therapy, during TP2.	
Reporting group title	Danicopan-Danicopan (LTE)
Reporting group description:	
After completing TP2 (Week 24), participants entered the LTE for 2 years at the same danicopan dose received at Week 24, in addition to their background ravulizumab or eculizumab therapy.	
Reporting group title	Danicopan-Danicopan (TP2)
Reporting group description:	
Participants continued to receive danicopan TID for an additional 12 weeks, in addition to their background eculizumab or ravulizumab therapy, during TP2.	

Serious adverse events	Danicopan (TP1)	Placebo (TP1)	Placebo-Danicopan (LTE)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 57 (5.26%)	2 / 29 (6.90%)	6 / 26 (23.08%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			

subjects affected / exposed	0 / 57 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stent-graft endoleak			
subjects affected / exposed	0 / 57 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 57 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 57 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 57 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 57 (1.75%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			

subjects affected / exposed	0 / 57 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Body temperature increased			
subjects affected / exposed	0 / 57 (0.00%)	0 / 29 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	0 / 57 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 57 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	0 / 57 (0.00%)	0 / 29 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 57 (0.00%)	1 / 29 (3.45%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 29 (3.45%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolysis			

subjects affected / exposed	0 / 57 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic diathesis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 29 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 57 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 57 (0.00%)	1 / 29 (3.45%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dieulafoy's vascular malformation			
subjects affected / exposed	0 / 57 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 57 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 57 (0.00%)	0 / 29 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			

subjects affected / exposed	0 / 57 (0.00%)	0 / 29 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 57 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Paroxysmal nocturnal haemoglobinuria			
subjects affected / exposed	0 / 57 (0.00%)	0 / 29 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 29 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 57 (1.75%)	0 / 29 (0.00%)	2 / 26 (7.69%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			

subjects affected / exposed	0 / 57 (0.00%)	0 / 29 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 29 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 29 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Serious adverse events	Placebo-Danicopan (TP2)	Danicopan-Danicopan (LTE)	Danicopan-Danicopan (TP2)
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 27 (22.22%)	7 / 54 (12.96%)	3 / 55 (5.45%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 27 (0.00%)	1 / 54 (1.85%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	0 / 27 (0.00%)	1 / 54 (1.85%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stent-graft endoleak			
subjects affected / exposed	0 / 27 (0.00%)	1 / 54 (1.85%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 27 (0.00%)	1 / 54 (1.85%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 27 (0.00%)	1 / 54 (1.85%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 27 (0.00%)	1 / 54 (1.85%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 27 (0.00%)	0 / 54 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 54 (1.85%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Body temperature increased			
subjects affected / exposed	0 / 27 (0.00%)	0 / 54 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Platelet count decreased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 54 (1.85%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 27 (3.70%)	0 / 54 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	0 / 27 (0.00%)	0 / 54 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 27 (3.70%)	0 / 54 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 54 (1.85%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolysis			
subjects affected / exposed	2 / 27 (7.41%)	0 / 54 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic diathesis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 54 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			

subjects affected / exposed	1 / 27 (3.70%)	0 / 54 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 27 (0.00%)	1 / 54 (1.85%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 54 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dieulafoy's vascular malformation			
subjects affected / exposed	0 / 27 (0.00%)	0 / 54 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 27 (0.00%)	1 / 54 (1.85%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 27 (0.00%)	0 / 54 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 27 (0.00%)	0 / 54 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 27 (0.00%)	1 / 54 (1.85%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Cholecystitis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 54 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 54 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Paroxysmal nocturnal haemoglobinuria			
subjects affected / exposed	0 / 27 (0.00%)	0 / 54 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 27 (0.00%)	0 / 54 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 27 (0.00%)	1 / 54 (1.85%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 54 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 54 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			

subjects affected / exposed	0 / 27 (0.00%)	0 / 54 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 54 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 27 (0.00%)	0 / 54 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Danicopan (TP1)	Placebo (TP1)	Placebo-Danicopan (LTE)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 57 (75.44%)	18 / 29 (62.07%)	24 / 26 (92.31%)
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 57 (5.26%)	1 / 29 (3.45%)	0 / 26 (0.00%)
occurrences (all)	3	1	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 57 (5.26%)	0 / 29 (0.00%)	3 / 26 (11.54%)
occurrences (all)	6	0	5
Chest discomfort			
subjects affected / exposed	1 / 57 (1.75%)	0 / 29 (0.00%)	2 / 26 (7.69%)
occurrences (all)	1	0	2
Fatigue			
subjects affected / exposed	2 / 57 (3.51%)	1 / 29 (3.45%)	1 / 26 (3.85%)
occurrences (all)	2	1	1
Asthenia			
subjects affected / exposed	0 / 57 (0.00%)	4 / 29 (13.79%)	4 / 26 (15.38%)
occurrences (all)	0	5	9
Non-cardiac chest pain			

subjects affected / exposed	0 / 57 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 57 (3.51%)	0 / 29 (0.00%)	1 / 26 (3.85%)
occurrences (all)	2	0	1
Dyspnoea			
subjects affected / exposed	0 / 57 (0.00%)	1 / 29 (3.45%)	2 / 26 (7.69%)
occurrences (all)	0	1	2
Productive cough			
subjects affected / exposed	0 / 57 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 57 (1.75%)	3 / 29 (10.34%)	3 / 26 (11.54%)
occurrences (all)	1	3	3
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 57 (5.26%)	1 / 29 (3.45%)	0 / 26 (0.00%)
occurrences (all)	4	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 57 (3.51%)	3 / 29 (10.34%)	0 / 26 (0.00%)
occurrences (all)	2	4	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 57 (3.51%)	3 / 29 (10.34%)	0 / 26 (0.00%)
occurrences (all)	2	3	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 29 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	2
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 57 (10.53%)	2 / 29 (6.90%)	1 / 26 (3.85%)
occurrences (all)	8	2	1
Dizziness			

subjects affected / exposed	1 / 57 (1.75%)	2 / 29 (6.90%)	1 / 26 (3.85%)
occurrences (all)	1	2	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 57 (1.75%)	3 / 29 (10.34%)	1 / 26 (3.85%)
occurrences (all)	1	3	3
Haemolysis			
subjects affected / exposed	2 / 57 (3.51%)	0 / 29 (0.00%)	2 / 26 (7.69%)
occurrences (all)	2	0	4
Neutropenia			
subjects affected / exposed	2 / 57 (3.51%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	2	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 29 (3.45%)	3 / 26 (11.54%)
occurrences (all)	0	1	12
Breakthrough haemolysis			
subjects affected / exposed	0 / 57 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	3 / 57 (5.26%)	0 / 29 (0.00%)	1 / 26 (3.85%)
occurrences (all)	4	0	2
Constipation			
subjects affected / exposed	2 / 57 (3.51%)	1 / 29 (3.45%)	4 / 26 (15.38%)
occurrences (all)	2	1	4
Dyspepsia			
subjects affected / exposed	1 / 57 (1.75%)	1 / 29 (3.45%)	2 / 26 (7.69%)
occurrences (all)	1	1	2
Abdominal pain			
subjects affected / exposed	0 / 57 (0.00%)	1 / 29 (3.45%)	2 / 26 (7.69%)
occurrences (all)	0	1	2
Diarrhoea			
subjects affected / exposed	4 / 57 (7.02%)	3 / 29 (10.34%)	2 / 26 (7.69%)
occurrences (all)	4	4	5
Nausea			

subjects affected / exposed	5 / 57 (8.77%)	3 / 29 (10.34%)	1 / 26 (3.85%)
occurrences (all)	7	3	3
Abdominal pain upper			
subjects affected / exposed	1 / 57 (1.75%)	2 / 29 (6.90%)	2 / 26 (7.69%)
occurrences (all)	1	2	2
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	1 / 57 (1.75%)	1 / 29 (3.45%)	0 / 26 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 57 (7.02%)	2 / 29 (6.90%)	1 / 26 (3.85%)
occurrences (all)	4	2	2
Pain in extremity			
subjects affected / exposed	3 / 57 (5.26%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	3	0	0
Back pain			
subjects affected / exposed	0 / 57 (0.00%)	0 / 29 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	2
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 57 (1.75%)	0 / 29 (0.00%)	7 / 26 (26.92%)
occurrences (all)	1	0	7
Urinary tract infection			
subjects affected / exposed	3 / 57 (5.26%)	1 / 29 (3.45%)	2 / 26 (7.69%)
occurrences (all)	3	2	3
Ear infection			
subjects affected / exposed	0 / 57 (0.00%)	2 / 29 (6.90%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
Nasopharyngitis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 29 (0.00%)	1 / 26 (3.85%)
occurrences (all)	1	0	1
Herpes zoster			
subjects affected / exposed	0 / 57 (0.00%)	0 / 29 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	2
Gastroenteritis			

subjects affected / exposed	0 / 57 (0.00%)	0 / 29 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	2

Non-serious adverse events	Placebo-Danicopan (TP2)	Danicopan-Danicopan (LTE)	Danicopan-Danicopan (TP2)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 27 (66.67%)	48 / 54 (88.89%)	40 / 55 (72.73%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 27 (0.00%)	1 / 54 (1.85%)	0 / 55 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 27 (0.00%)	13 / 54 (24.07%)	7 / 55 (12.73%)
occurrences (all)	0	14	8
Chest discomfort			
subjects affected / exposed	0 / 27 (0.00%)	0 / 54 (0.00%)	1 / 55 (1.82%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	1 / 27 (3.70%)	4 / 54 (7.41%)	3 / 55 (5.45%)
occurrences (all)	1	6	3
Asthenia			
subjects affected / exposed	2 / 27 (7.41%)	4 / 54 (7.41%)	2 / 55 (3.64%)
occurrences (all)	3	4	2
Non-cardiac chest pain			
subjects affected / exposed	0 / 27 (0.00%)	3 / 54 (5.56%)	0 / 55 (0.00%)
occurrences (all)	0	4	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 27 (0.00%)	3 / 54 (5.56%)	1 / 55 (1.82%)
occurrences (all)	0	3	1
Dyspnoea			
subjects affected / exposed	0 / 27 (0.00%)	1 / 54 (1.85%)	2 / 55 (3.64%)
occurrences (all)	0	2	2
Productive cough			
subjects affected / exposed	0 / 27 (0.00%)	3 / 54 (5.56%)	0 / 55 (0.00%)
occurrences (all)	0	3	0

Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 54 (1.85%)	1 / 55 (1.82%)
occurrences (all)	0	1	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 27 (0.00%)	0 / 54 (0.00%)	0 / 55 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 27 (3.70%)	0 / 54 (0.00%)	1 / 55 (1.82%)
occurrences (all)	1	0	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 27 (3.70%)	2 / 54 (3.70%)	1 / 55 (1.82%)
occurrences (all)	1	2	3
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 54 (1.85%)	0 / 55 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 27 (3.70%)	8 / 54 (14.81%)	6 / 55 (10.91%)
occurrences (all)	1	8	6
Dizziness			
subjects affected / exposed	0 / 27 (0.00%)	2 / 54 (3.70%)	2 / 55 (3.64%)
occurrences (all)	0	2	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 27 (0.00%)	2 / 54 (3.70%)	3 / 55 (5.45%)
occurrences (all)	0	2	3
Haemolysis			
subjects affected / exposed	0 / 27 (0.00%)	2 / 54 (3.70%)	0 / 55 (0.00%)
occurrences (all)	0	2	0
Neutropenia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 54 (0.00%)	3 / 55 (5.45%)
occurrences (all)	1	0	3
Thrombocytopenia			

subjects affected / exposed	1 / 27 (3.70%)	2 / 54 (3.70%)	1 / 55 (1.82%)
occurrences (all)	1	2	1
Breakthrough haemolysis			
subjects affected / exposed	0 / 27 (0.00%)	4 / 54 (7.41%)	2 / 55 (3.64%)
occurrences (all)	0	5	2
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 27 (3.70%)	1 / 54 (1.85%)	1 / 55 (1.82%)
occurrences (all)	1	1	1
Constipation			
subjects affected / exposed	1 / 27 (3.70%)	0 / 54 (0.00%)	1 / 55 (1.82%)
occurrences (all)	1	0	1
Dyspepsia			
subjects affected / exposed	2 / 27 (7.41%)	0 / 54 (0.00%)	0 / 55 (0.00%)
occurrences (all)	2	0	0
Abdominal pain			
subjects affected / exposed	2 / 27 (7.41%)	1 / 54 (1.85%)	1 / 55 (1.82%)
occurrences (all)	2	1	1
Diarrhoea			
subjects affected / exposed	2 / 27 (7.41%)	1 / 54 (1.85%)	6 / 55 (10.91%)
occurrences (all)	3	2	7
Nausea			
subjects affected / exposed	3 / 27 (11.11%)	3 / 54 (5.56%)	1 / 55 (1.82%)
occurrences (all)	3	3	1
Abdominal pain upper			
subjects affected / exposed	0 / 27 (0.00%)	0 / 54 (0.00%)	0 / 55 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	2 / 27 (7.41%)	1 / 54 (1.85%)	1 / 55 (1.82%)
occurrences (all)	2	1	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 27 (3.70%)	1 / 54 (1.85%)	1 / 55 (1.82%)
occurrences (all)	1	3	1
Pain in extremity			

subjects affected / exposed	0 / 27 (0.00%)	4 / 54 (7.41%)	1 / 55 (1.82%)
occurrences (all)	0	5	1
Back pain			
subjects affected / exposed	1 / 27 (3.70%)	2 / 54 (3.70%)	2 / 55 (3.64%)
occurrences (all)	1	2	2
Infections and infestations			
COVID-19			
subjects affected / exposed	2 / 27 (7.41%)	11 / 54 (20.37%)	1 / 55 (1.82%)
occurrences (all)	2	11	1
Urinary tract infection			
subjects affected / exposed	1 / 27 (3.70%)	4 / 54 (7.41%)	1 / 55 (1.82%)
occurrences (all)	1	4	1
Ear infection			
subjects affected / exposed	0 / 27 (0.00%)	0 / 54 (0.00%)	0 / 55 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 27 (0.00%)	7 / 54 (12.96%)	1 / 55 (1.82%)
occurrences (all)	0	7	1
Herpes zoster			
subjects affected / exposed	0 / 27 (0.00%)	0 / 54 (0.00%)	0 / 55 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 54 (0.00%)	2 / 55 (3.64%)
occurrences (all)	0	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 April 2020	• Major administrative updates made: - Sponsor name change from Achillion Pharmaceuticals, Inc to Alexion Pharmaceuticals Inc., danicopan compound number ACH-0144471 to ALXN2040, and study number ACH471-105 to ALXN2040-PNH-301. - All changes resulting from new Sponsor's process and language were added. • Study was changed to a double-blind design, and this was reflected in the schedule of assessments, other sections, and operational aspects. • Participant population was specifically defined as those with EVH. • Vaccination requirements were clarified. • Study sample size was increased. • Key secondary endpoints and other secondary endpoints were clarified. • Analysis of primary endpoint and secondary endpoints was clarified. • Interim analysis was added. • New sections on data monitoring committee and transfusion guidelines before and during the study were added. • Section on individual stopping criteria was deleted. Individual and study stopping requirements were updated in the study stopping criteria section. • Patient-reported outcomes and quality of life assessments were added; laboratory assessments were updated to include additional assessments. • Updates to inclusion and exclusion criteria: - Inclusion: The criterion on anemia was defined further to be linked to clinically evident EVH and transfusion. - Exclusion: Clarity was provided on laboratory abnormalities.
10 June 2020	• Clarified to distinguish between concomitant and background therapies. • Added review of the safety card at various timepoints in the schedule of assessments tables. • Added a new section on intervention after the end of the study. • Added information on blind breaking.
11 August 2020	• Text in specific sections to clarify potential risk of hepatic injury and guidance for participant discontinuation was updated. • Added language that approved dosages of the background C5 inhibitors are to be used. • Added information on switching between different C5 inhibitors. • Added text to mitigate the risk of unblinding in relation to certain laboratory tests. • Added details on data protection with respect to data security. • Updates to inclusion and exclusion criteria: - Revised inclusion criterion to clarify duration of contraception requirements. - Added a new exclusion criterion on bleeding and anemia not primarily caused by EVH.

21 October 2020	• Removed the 100 milligrams starting dose of danicopan. • Removed one of two Follow-up Visits and established a single Follow-up Visit at approximately 30 (+ 7) days after the last dose of study intervention. • Updated the instructions for dose taper. • Added text to allow enhanced pharmacokinetics/pharmacodynamics (PK/PD) sampling and added a PK/PD table describing the blood sampling schedule and approximate blood volumes. • Added an exploratory objective and endpoints to characterize the PK and PD of the study intervention. • Removed the Fever Management Plan. • Revised the transfusion guidelines to recommend administering packed red blood cells when a participant had a Hgb value of <7 g/dL (<70 g/L), instead of <6 g/dL (<60 g/L). • Added coronavirus disease 2019 (COVID-19) risk assessment and mitigation. • Updates to inclusion and exclusion criteria: - Added an inclusion criterion to allow enrollment of participants who are on a stable dose of iron, folic acid, and/or vitamin B12 supplementation. - Removed the exclusion criterion that excluded participants with a Screening alkaline phosphatase result >2 × upper limit of normal. - Introduced a cap of a maximum 30% of participants to be enrolled with <2 transfusions 6 months prior to Screening - Reduced the number of timepoints for dose escalation and simplified the dose escalation process.
16 July 2021	• Laboratory sampling text added to allow for flexibility. • Instead of 30%, up to approximately 40% of participants with < 2 transfusions in the prior 6 months to be enrolled in the study. • Provisions for the interim analysis revised. • Revised the statistical method used for the secondary analyses. • Added appendix on COVID-19 Vaccine Risk Assessment. • Clarifications in inclusion/exclusion criteria and stopping criteria: - Participants with iron overload and liver enzyme abnormalities. - Participants on concomitant steroids and other immunosuppressants. - C5 inhibition dose frequency changes for participant convenience.
25 February 2022	• Additional secondary objectives and endpoints. • Extension of the LTE Period to 2 years. • Addition of text on dose interruptions. • Updates to the statistical sections to reflect these changes. • Updates in inclusion criteria: - Transfusion requirement prior to start of study removed. - Neutrophil count threshold changed from ≥750/microlitre (µL) to ≥500/µL.

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/38030318