



Clinical trial results:

A Multi-Center, Randomized, Double-blind, Placebo-controlled, Dose-finding Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of CK-3773274 in Adults with Symptomatic Hypertrophic Cardiomyopathy

Summary

EudraCT number	2019-002785-12
Trial protocol	ES GB NL IT
Global end of trial date	28 February 2023

Results information

Result version number	v1 (current)
This version publication date	31 March 2024
First version publication date	31 March 2024

Trial information

Trial identification

Sponsor protocol code	CY 6021
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04219826
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cytokinetics, Inc.
Sponsor organisation address	350 Oyster Point Blvd, South San Francisco, United States, CA 94080
Public contact	Medical Affairs, Cytokinetics Inc, +1 8336332986, medicalaffairs@cytokinetics.com
Scientific contact	Medical Affairs, Cytokinetics Inc, +1 8336332986, medicalaffairs@cytokinetics.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	28 February 2023
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	28 February 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to determine the safety and tolerability of aficamten in participants with symptomatic hypertrophic cardiomyopathy (HCM).

Protection of trial subjects:

This study was conducted in accordance with the protocol, consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable International Council for Harmonisation guidelines for Good Clinical Practices, and all applicable laws and regulations.

Background therapy:

Cohorts 1 and 2: participants with symptomatic obstructive HCM (oHCM) continued taking background medications.

Cohort 3: participants with symptomatic oHCM were receiving disopyramide as a background therapy in addition to beta-blockers and/or calcium channel blockers.

Cohort 4: participants with symptomatic non-obstructive HCM (nHCM) continued taking standard of care background medications. Disopyramide as background therapy was excluded in Cohorts 1, 2, and 4.

Evidence for comparator: -

Actual start date of recruitment	10 January 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	United States: 87
Worldwide total number of subjects	96
EEA total number of subjects	9

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	65
From 65 to 84 years	31
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 96 participants were enrolled at 19 study centers in Italy, Spain, and the United States between January 2020 and February 2023. One participant in the placebo group was discontinued from the study prior to receiving treatment and is represented within the pre-assignment period.

Pre-assignment

Screening details:

All participants had a 4-week screening period, after which, eligible participants were randomized to once daily aficamten or matching placebo in a 2:1 ratio for Cohorts 1 and 2 or given once daily aficamten in Cohorts 3 and 4.

Pre-assignment period milestones

Number of subjects started	96
Number of subjects completed	95

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Protocol deviation: 1
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Period 1

Period 1 title	Overall Study (overall period)
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	Cohort 1: Aficamten (oHCM)

Arm description:

Participants with symptomatic obstructive HCM (oHCM) receiving background therapy (not including disopyramide) were randomized 2:1 to active or matching placebo treatment and received up to 3 escalating doses of aficamten (5, 10, and 15 mg) or matching placebo based on echocardiographic guidance. Treatment duration was 10 weeks with a 4-week follow-up period after the last dose.

Arm type	Experimental
Investigational medicinal product name	Aficamten
Investigational medicinal product code	CK-3773274
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Aficamten tablets administered orally.

Arm title	Cohort 1: Placebo (oHCM)
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Arm description:

Participants with symptomatic oHCM receiving background therapy (not including disopyramide) were randomized 2:1 to active or matching placebo treatment and received up to 3 escalating doses of aficamten (5, 10, and 15 mg) or matching placebo based on echocardiographic guidance. Treatment duration was 10 weeks with a 4-week follow-up period after the last dose.

Arm type	Placebo
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Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Placebo tablets administered orally.	
Arm title	Cohort 2: Aficamten (oHCM)

Arm description:

Participants with symptomatic oHCM receiving background therapy (not including disopyramide) were randomized 2:1 to active or placebo treatment and received up to 3 escalating doses of aficamten (10, 20, and 30 mg) or matching placebo based on echocardiographic guidance. Treatment duration was 10 weeks with a 4-week follow-up period after the last dose.

Arm type	Experimental
Investigational medicinal product name	Aficamten
Investigational medicinal product code	CK-3773274
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Aficamten tablets administered orally.	
Arm title	Cohort 2: Placebo (oHCM)

Arm description:

Participants with symptomatic oHCM receiving background therapy (not including disopyramide) were randomized 2:1 to active or matching placebo treatment and received up to 3 escalating doses of aficamten (10, 20, and 30 mg) or matching placebo based on echocardiographic guidance. Treatment duration was 10 weeks with a 4-week follow-up period after the last dose.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Placebo tablets administered orally.	
Arm title	Cohort 3: Aficamten and Background Disopyramide (oHCM)

Arm description:

Participants with symptomatic oHCM whose background HCM therapy included disopyramide. All participants in Cohort 3 received up to 3 escalating doses of aficamten (5, 10, and 15 mg) based on echocardiographic guidance. Treatment duration was 10 weeks with a 4-week follow-up period after the last dose.

Arm type	Experimental
Investigational medicinal product name	Aficamten
Investigational medicinal product code	CK-3773274
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Aficamten tablets administered orally.	
Arm title	Cohort 4: Aficamten (nHCM)

Arm description:

Participants with symptomatic nHCM whose standard of care background therapy included beta-blockers and/or calcium channel blockers. Participants receiving disopyramide were excluded from Cohort 4.

Cohort 4 participants received up to 3 doses of aficamten (5, 10, and 15 mg), titrated based on echocardiographic guidance. Treatment duration was 10 weeks with a 4-week follow-up period after the last dose.

Arm type	Experimental
Investigational medicinal product name	Aficamten
Investigational medicinal product code	CK-3773274
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Aficamten tablets administered orally.

Number of subjects in period 1^[1]	Cohort 1: Aficamten (oHCM)	Cohort 1: Placebo (oHCM)	Cohort 2: Aficamten (oHCM)
Started	14	7	14
Completed	14	6	14
Not completed	0	1	0
Death	-	-	-
Withdrawal by participant	-	-	-
Protocol deviation	-	1	-

Number of subjects in period 1^[1]	Cohort 2: Placebo (oHCM)	Cohort 3: Aficamten and Background Disopyramide (oHCM)	Cohort 4: Aficamten (nHCM)
Started	6	13	41
Completed	6	13	39
Not completed	0	0	2
Death	-	-	1
Withdrawal by participant	-	-	1
Protocol deviation	-	-	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: One participant in the placebo group was discontinued from the study prior to receiving treatment due to a protocol deviation.

Baseline characteristics

Reporting groups

Reporting group title	Cohort 1: Aficamten (oHCM)
Reporting group description: Participants with symptomatic obstructive HCM (oHCM) receiving background therapy (not including disopyramide) were randomized 2:1 to active or matching placebo treatment and received up to 3 escalating doses of aficamten (5, 10, and 15 mg) or matching placebo based on echocardiographic guidance. Treatment duration was 10 weeks with a 4-week follow-up period after the last dose.	
Reporting group title	Cohort 1: Placebo (oHCM)
Reporting group description: Participants with symptomatic oHCM receiving background therapy (not including disopyramide) were randomized 2:1 to active or matching placebo treatment and received up to 3 escalating doses of aficamten (5, 10, and 15 mg) or matching placebo based on echocardiographic guidance. Treatment duration was 10 weeks with a 4-week follow-up period after the last dose.	
Reporting group title	Cohort 2: Aficamten (oHCM)
Reporting group description: Participants with symptomatic oHCM receiving background therapy (not including disopyramide) were randomized 2:1 to active or placebo treatment and received up to 3 escalating doses of aficamten (10, 20, and 30 mg) or matching placebo based on echocardiographic guidance. Treatment duration was 10 weeks with a 4-week follow-up period after the last dose.	
Reporting group title	Cohort 2: Placebo (oHCM)
Reporting group description: Participants with symptomatic oHCM receiving background therapy (not including disopyramide) were randomized 2:1 to active or matching placebo treatment and received up to 3 escalating doses of aficamten (10, 20, and 30 mg) or matching placebo based on echocardiographic guidance. Treatment duration was 10 weeks with a 4-week follow-up period after the last dose.	
Reporting group title	Cohort 3: Aficamten and Background Disopyramide (oHCM)
Reporting group description: Participants with symptomatic oHCM whose background HCM therapy included disopyramide. All participants in Cohort 3 received up to 3 escalating doses of aficamten (5, 10, and 15 mg) based on echocardiographic guidance. Treatment duration was 10 weeks with a 4-week follow-up period after the last dose.	
Reporting group title	Cohort 4: Aficamten (nHCM)
Reporting group description: Participants with symptomatic nHCM whose standard of care background therapy included beta-blockers and/or calcium channel blockers. Participants receiving disopyramide were excluded from Cohort 4. Cohort 4 participants received up to 3 doses of aficamten (5, 10, and 15 mg), titrated based on echocardiographic guidance. Treatment duration was 10 weeks with a 4-week follow-up period after the last dose.	

Reporting group values	Cohort 1: Aficamten (oHCM)	Cohort 1: Placebo (oHCM)	Cohort 2: Aficamten (oHCM)
Number of subjects	14	7	14
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	54.3 ± 13.69	61.4 ± 6.40	58.9 ± 13.65
Gender categorical Units: Subjects			
Female	4	6	11
Male	10	1	3

Race			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Black or African American	0	0	0
White	14	7	14
Other	0	0	0
Ethnicity			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	14	7	14

Reporting group values	Cohort 2: Placebo (oHCM)	Cohort 3: Aficamten and Background Disopyramide (oHCM)	Cohort 4: Aficamten (nHCM)
Number of subjects	6	13	41
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	52.3	59.4	55.9
standard deviation	± 10.78	± 14.43	± 15.76
Gender categorical			
Units: Subjects			
Female	2	7	24
Male	4	6	17
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	1
Asian	0	1	2
Black or African American	1	1	8
White	5	11	27
Other	0	0	3
Ethnicity			
Units: Subjects			
Hispanic or Latino	0	1	2
Not Hispanic or Latino	6	12	39

Reporting group values	Total		
Number of subjects	95		
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	54		

Male	41		
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Race			
Units: Subjects			
American Indian or Alaska Native	1		
Asian	3		
Black or African American	10		
White	78		
Other	3		
Ethnicity			
Units: Subjects			
Hispanic or Latino	3		
Not Hispanic or Latino	92		

End points

End points reporting groups

Reporting group title	Cohort 1: Aficamten (oHCM)
Reporting group description: Participants with symptomatic obstructive HCM (oHCM) receiving background therapy (not including disopyramide) were randomized 2:1 to active or matching placebo treatment and received up to 3 escalating doses of aficamten (5, 10, and 15 mg) or matching placebo based on echocardiographic guidance. Treatment duration was 10 weeks with a 4-week follow-up period after the last dose.	
Reporting group title	Cohort 1: Placebo (oHCM)
Reporting group description: Participants with symptomatic oHCM receiving background therapy (not including disopyramide) were randomized 2:1 to active or matching placebo treatment and received up to 3 escalating doses of aficamten (5, 10, and 15 mg) or matching placebo based on echocardiographic guidance. Treatment duration was 10 weeks with a 4-week follow-up period after the last dose.	
Reporting group title	Cohort 2: Aficamten (oHCM)
Reporting group description: Participants with symptomatic oHCM receiving background therapy (not including disopyramide) were randomized 2:1 to active or placebo treatment and received up to 3 escalating doses of aficamten (10, 20, and 30 mg) or matching placebo based on echocardiographic guidance. Treatment duration was 10 weeks with a 4-week follow-up period after the last dose.	
Reporting group title	Cohort 2: Placebo (oHCM)
Reporting group description: Participants with symptomatic oHCM receiving background therapy (not including disopyramide) were randomized 2:1 to active or matching placebo treatment and received up to 3 escalating doses of aficamten (10, 20, and 30 mg) or matching placebo based on echocardiographic guidance. Treatment duration was 10 weeks with a 4-week follow-up period after the last dose.	
Reporting group title	Cohort 3: Aficamten and Background Disopyramide (oHCM)
Reporting group description: Participants with symptomatic oHCM whose background HCM therapy included disopyramide. All participants in Cohort 3 received up to 3 escalating doses of aficamten (5, 10, and 15 mg) based on echocardiographic guidance. Treatment duration was 10 weeks with a 4-week follow-up period after the last dose.	
Reporting group title	Cohort 4: Aficamten (nHCM)
Reporting group description: Participants with symptomatic nHCM whose standard of care background therapy included beta-blockers and/or calcium channel blockers. Participants receiving disopyramide were excluded from Cohort 4. Cohort 4 participants received up to 3 doses of aficamten (5, 10, and 15 mg), titrated based on echocardiographic guidance. Treatment duration was 10 weeks with a 4-week follow-up period after the last dose.	

Primary: Number of Participants who Experienced a Treatment-emergent Adverse Event (TEAE)

End point title	Number of Participants who Experienced a Treatment-emergent Adverse Event (TEAE) ^[1]
End point description: An adverse event (AE) was defined as any untoward medical occurrence in a clinical trial participant. The AE did not necessarily have a causal relationship with the study treatment. A serious AE was defined as an AE that met at least one of the following regulatory criteria: <ul style="list-style-type: none">• fatal• immediately life-threatening• requires hospitalization or prolongation of existing hospitalization• results in persistent disability/incapacity• congenital anomaly/birth defect• other medically important serious event. TEAEs were defined as the AEs which were not present prior to the first dose of study treatment and	

start thereafter, or were present prior to the first dose of study treatment and increased in severity, frequency, or outcome thereafter. Only TEAEs and treatment-emergent serious AEs (TESAEs) are summarized.

Safety Analysis Set: included all participants who received at least one dose of study treatment.

End point type	Primary
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End point timeframe:

Up to 14 weeks

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: No additional statistical analysis was pre-specified for this endpoint.

End point values	Cohort 1: Aficamten (oHCM)	Cohort 1: Placebo (oHCM)	Cohort 2: Aficamten (oHCM)	Cohort 2: Placebo (oHCM)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	7	14	6
Units: participants				
≥ 1 TEAE	10	7	11	4
≥ 1 TESAE	1	1	1	0

End point values	Cohort 3: Aficamten and Background Disopyramide (oHCM)	Cohort 4: Aficamten (nHCM)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	41		
Units: participants				
≥ 1 TEAE	9	28		
≥ 1 TESAE	0	4		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants who Experienced Left Ventricular Ejection Fraction (LVEF) < 50%

End point title	Number of Participants who Experienced Left Ventricular Ejection Fraction (LVEF) < 50% ^[2]
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End point description:

LVEF < 50% was assessed per core laboratory assessment of echocardiography.

Safety Analysis Set: included all participants who received at least one dose of study treatment.

End point type	Primary
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End point timeframe:

Up to 12 weeks

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: No additional statistical analysis was pre-specified for this endpoint.

End point values	Cohort 1: Aficamten (oHCM)	Cohort 1: Placebo (oHCM)	Cohort 2: Aficamten (oHCM)	Cohort 2: Placebo (oHCM)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	7	14	6
Units: participants	0	0	2	0

End point values	Cohort 3: Aficamten and Background Disopyramide (oHCM)	Cohort 4: Aficamten (nHCM)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	41		
Units: participants	0	3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 14 weeks

Adverse event reporting additional description:

Safety Analysis Set: included all participants who received at least one dose of study treatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.0
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Reporting groups

Reporting group title	Cohort 1: Aficamten (oHCM)
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Reporting group description:

Participants with symptomatic oHCM receiving background therapy (not including disopyramide) were randomized 2:1 to active or matching placebo treatment and received up to 3 escalating doses of aficamten (5, 10, and 15 mg) or matching placebo based on echocardiographic guidance. Treatment duration was 10 weeks with a 4-week follow-up period after the last dose.

Reporting group title	Cohort 1: Placebo (oHCM)
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Reporting group description:

Participants with symptomatic oHCM receiving background therapy (not including disopyramide) were randomized 2:1 to active or matching placebo treatment and received up to 3 escalating doses of aficamten (5, 10, and 15 mg) or matching placebo based on echocardiographic guidance. Treatment duration was 10 weeks with a 4-week follow-up period after the last dose.

Reporting group title	Cohort 2: Aficamten (oHCM)
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Reporting group description:

Participants with symptomatic oHCM receiving background therapy (not including disopyramide) were randomized 2:1 to active or placebo treatment and received up to 3 escalating doses of aficamten (10, 20, and 30 mg) or matching placebo based on echocardiographic guidance. Treatment duration was 10 weeks with a 4-week follow-up period after the last dose.

Reporting group title	Cohort 2: Placebo (oHCM)
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Reporting group description:

Participants with symptomatic oHCM receiving background therapy (not including disopyramide) were randomized 2:1 to active or matching placebo treatment and received up to 3 escalating doses of aficamten (10, 20, and 30 mg) or matching placebo based on echocardiographic guidance. Treatment duration was 10 weeks with a 4-week follow-up period after the last dose.

Reporting group title	Cohort 3: Aficamten and Background Disopyramide (oHCM)
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Reporting group description:

Participants with symptomatic oHCM whose background HCM therapy included disopyramide. All participants in Cohort 3 received up to 3 escalating doses of aficamten (5, 10, and 15 mg) based on echocardiographic guidance. Treatment duration was 10 weeks with a 4-week follow-up period after the last dose.

Reporting group title	Cohort 4: Aficamten (nHCM)
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Reporting group description:

Participants with symptomatic nHCM whose standard of care background therapy included beta-blockers and/or calcium channel blockers. Participants receiving disopyramide were excluded from Cohort 4. Cohort 4 participants received up to 3 doses of aficamten (5, 10, and 15 mg), titrated based on echocardiographic guidance. Treatment duration was 10 weeks with a 4-week follow-up period after the last dose.

Serious adverse events	Cohort 1: Aficamten (oHCM)	Cohort 1: Placebo (oHCM)	Cohort 2: Aficamten (oHCM)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 14 (7.14%)	1 / 7 (14.29%)	1 / 14 (7.14%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	0 / 14 (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
Cardiac disorders			
Stress cardiomyopathy			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	0 / 14 (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
Acute coronary syndrome			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	0 / 14 (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 arrest			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	0 / 14 (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			
Syncope			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	0 / 14 (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
Immune system disorders			
Myasthenia gravis			

subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	0 / 14 (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			
Acute respiratory failure			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	0 / 14 (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 oedema			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	0 / 14 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	0 / 14 (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
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	0 / 14 (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

Serious adverse events	Cohort 2: Placebo (oHCM)	Cohort 3: Aficamten and Background Disopyramide (oHCM)	Cohort 4: Aficamten (nHCM)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	4 / 41 (9.76%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events			
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	0 / 41 (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			

Stress cardiomyopathy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	0 / 41 (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
Acute coronary syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	0 / 41 (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
Atrial fibrillation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	0 / 41 (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
Immune system disorders			
Myasthenia gravis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	0 / 41 (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 oedema			

subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	0 / 41 (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			
Back pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	0 / 41 (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			
Bronchitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Cohort 1: Aficamten (oHCM)	Cohort 1: Placebo (oHCM)	Cohort 2: Aficamten (oHCM)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 14 (71.43%)	7 / 7 (100.00%)	11 / 14 (78.57%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Seborrhoeic keratosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 14 (7.14%)	1 / 7 (14.29%)	0 / 14 (0.00%)
occurrences (all)	1	1	0
Chest discomfort			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Complication associated with device			

subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Non-cardiac chest pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Oedema peripheral			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	2 / 14 (14.29%)
occurrences (all)	1	0	3
Pyrexia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Chills			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Peripheral swelling			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Dyspnoea			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	2 / 14 (14.29%)
occurrences (all)	1	0	2
Nasal congestion			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Dyspnoea exertional			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Pleurisy			

subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Sneezing			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Orthopnoea			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Pulmonary mass			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Wheezing			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Abnormal dreams			
subjects affected / exposed	1 / 14 (7.14%)	1 / 7 (14.29%)	0 / 14 (0.00%)
occurrences (all)	1	1	0
Anxiety			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Insomnia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Sleep disorder			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Blood magnesium decreased			

subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Blood potassium decreased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Weight increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram PR prolongation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
International normalised ratio increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Prothrombin time prolonged			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Fall			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Scratch			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Muscle strain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Palpitations			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Tachycardia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Angina pectoris			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Bradycardia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 14 (21.43%)	3 / 7 (42.86%)	0 / 14 (0.00%)
occurrences (all)	3	4	0
Dizziness			
subjects affected / exposed	3 / 14 (21.43%)	1 / 7 (14.29%)	2 / 14 (14.29%)
occurrences (all)	3	2	3
Paraesthesia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 7 (14.29%)	0 / 14 (0.00%)
occurrences (all)	1	1	0
Syncope			
subjects affected / exposed	1 / 14 (7.14%)	1 / 7 (14.29%)	0 / 14 (0.00%)
occurrences (all)	1	1	0
Dizziness postural			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Migraine			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			

Tinnitus subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	0 / 14 (0.00%) 0
Eye disorders			
Visual impairment subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 7 (14.29%) 1	0 / 14 (0.00%) 0
Dry eye subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0	0 / 14 (0.00%) 0
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2	1 / 7 (14.29%) 1	0 / 14 (0.00%) 0
Bowel movement irregularity subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 7 (14.29%) 2	0 / 14 (0.00%) 0
Dry mouth subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	0 / 14 (0.00%) 0
Dyspepsia subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0	0 / 14 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 7 (14.29%) 1	0 / 14 (0.00%) 0
Constipation subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0	0 / 14 (0.00%) 0
Defaecation urgency subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0	0 / 14 (0.00%) 0
Flatulence subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0	0 / 14 (0.00%) 0
Abdominal distension			

subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0	0 / 14 (0.00%) 0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Urticaria			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Dermatitis contact			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Glycosuria			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Pollakiuria			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Dysuria			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	1 / 14 (7.14%)	1 / 7 (14.29%)	0 / 14 (0.00%)
occurrences (all)	1	1	0
Pain in extremity			
subjects affected / exposed	2 / 14 (14.29%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Back pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Bursitis			

subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Arthralgia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Joint swelling			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Muscular weakness			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 14 (0.00%)	1 / 7 (14.29%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
COVID-19			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Bronchitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Pertussis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 7 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0

Pneumonia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0	0 / 14 (0.00%) 0
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0	0 / 14 (0.00%) 0
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0	0 / 14 (0.00%) 0
Metabolism and nutrition disorders Hyponatraemia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 7 (14.29%) 1	0 / 14 (0.00%) 0

Non-serious adverse events	Cohort 2: Placebo (oHCM)	Cohort 3: Aficamten and Background Disopyramide (oHCM)	Cohort 4: Aficamten (nHCM)
Total subjects affected by non-serious adverse events subjects affected / exposed	4 / 6 (66.67%)	9 / 13 (69.23%)	26 / 41 (63.41%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Seborrhoeic keratosis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 13 (0.00%) 0	0 / 41 (0.00%) 0
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 13 (0.00%) 0	1 / 41 (2.44%) 1
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 13 (7.69%) 1	7 / 41 (17.07%) 9
Chest discomfort subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 13 (0.00%) 0	1 / 41 (2.44%) 1
Complication associated with device subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 13 (0.00%) 0	0 / 41 (0.00%) 0
Non-cardiac chest pain			

subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Chills			
subjects affected / exposed	0 / 6 (0.00%)	1 / 13 (7.69%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Peripheral swelling			
subjects affected / exposed	0 / 6 (0.00%)	1 / 13 (7.69%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	1 / 6 (16.67%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 6 (0.00%)	1 / 13 (7.69%)	2 / 41 (4.88%)
occurrences (all)	0	1	2
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	2 / 13 (15.38%)	2 / 41 (4.88%)
occurrences (all)	0	2	2
Nasal congestion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Dyspnoea exertional			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Pleurisy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Sneezing			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	2 / 13 (15.38%) 2	0 / 41 (0.00%) 0
Orthopnoea subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 13 (7.69%) 1	0 / 41 (0.00%) 0
Pulmonary mass subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 13 (7.69%) 1	0 / 41 (0.00%) 0
Wheezing subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 13 (0.00%) 0	2 / 41 (4.88%) 2
Psychiatric disorders Abnormal dreams subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 13 (0.00%) 0	0 / 41 (0.00%) 0
Anxiety subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 13 (7.69%) 1	0 / 41 (0.00%) 0
Insomnia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 13 (0.00%) 0	0 / 41 (0.00%) 0
Sleep disorder subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 13 (0.00%) 0	0 / 41 (0.00%) 0
Investigations Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 13 (0.00%) 0	0 / 41 (0.00%) 0
Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 13 (0.00%) 0	0 / 41 (0.00%) 0
Blood magnesium decreased subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 13 (0.00%) 0	1 / 41 (2.44%) 1
Blood potassium decreased			

subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 13 (7.69%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Weight increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Electrocardiogram PR prolongation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 13 (7.69%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
International normalised ratio increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 13 (7.69%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Prothrombin time prolonged			
subjects affected / exposed	0 / 6 (0.00%)	1 / 13 (7.69%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Scratch			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Muscle strain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 13 (7.69%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 13 (7.69%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Palpitations			

subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	3 / 41 (7.32%)
occurrences (all)	0	0	3
Tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Angina pectoris			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	2 / 41 (4.88%)
occurrences (all)	0	0	2
Bradycardia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 13 (7.69%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 6 (16.67%)	2 / 13 (15.38%)	1 / 41 (2.44%)
occurrences (all)	1	2	1
Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	4 / 41 (9.76%)
occurrences (all)	0	0	4
Paraesthesia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Dizziness postural			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Eye disorders			

Visual impairment subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 13 (0.00%) 0	0 / 41 (0.00%) 0
Dry eye subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 13 (0.00%) 0	0 / 41 (0.00%) 0
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 13 (0.00%) 0	2 / 41 (4.88%) 2
Bowel movement irregularity subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 13 (0.00%) 0	0 / 41 (0.00%) 0
Dry mouth subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	0 / 13 (0.00%) 0	0 / 41 (0.00%) 0
Dyspepsia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 13 (7.69%) 1	0 / 41 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 13 (7.69%) 1	3 / 41 (7.32%) 3
Constipation subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 13 (7.69%) 1	1 / 41 (2.44%) 1
Defaecation urgency subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 13 (7.69%) 1	0 / 41 (0.00%) 0
Flatulence subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 13 (7.69%) 1	0 / 41 (0.00%) 0
Abdominal distension subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 13 (0.00%) 0	2 / 41 (4.88%) 2
Skin and subcutaneous tissue disorders			

Pruritus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Dermatitis contact			
subjects affected / exposed	0 / 6 (0.00%)	1 / 13 (7.69%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Glycosuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Pollakiuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Dysuria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 13 (7.69%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Back pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 13 (7.69%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Bursitis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 13 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Muscle spasms			

subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Arthralgia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 13 (15.38%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Joint swelling			
subjects affected / exposed	0 / 6 (0.00%)	1 / 13 (7.69%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Muscular weakness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 13 (7.69%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 13 (7.69%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 13 (7.69%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
COVID-19			
subjects affected / exposed	0 / 6 (0.00%)	0 / 13 (0.00%)	3 / 41 (7.32%)
occurrences (all)	0	0	3
Bronchitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 13 (7.69%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Pertussis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 13 (7.69%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 13 (7.69%)	0 / 41 (0.00%)
occurrences (all)	0	1	0

Urinary tract infection subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 13 (7.69%) 2	0 / 41 (0.00%) 0
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 13 (0.00%) 0	2 / 41 (4.88%) 2
Metabolism and nutrition disorders Hyponatraemia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 13 (0.00%) 0	0 / 41 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 August 2019	Exclusion criteria revised to disallow use of disopyramide and other antiarrhythmic drugs.
13 July 2020	Requirements for screening echocardiograms and dose titration/withdrawal for scheduled and unscheduled visits clarified, exclusion criteria regarding CYP2D6 removed, and option for re-testing laboratory assessments during screening added.
17 February 2021	Study design updated for addition of Cohort 3.
09 November 2021	Study design updated for addition of Cohort 4.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported