



Clinical trial results:

A Phase 3, Multi-Center, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy and Safety of CK-3773274 in Adults with Symptomatic Hypertrophic Cardiomyopathy and Left Ventricular Outflow Tract Obstruction

Summary

EudraCT number	2021-003536-92
Trial protocol	HU DK ES NL CZ PL PT IT
Global end of trial date	18 December 2023

Results information

Result version number	v1 (current)
This version publication date	28 December 2024
First version publication date	28 December 2024

Trial information

Trial identification

Sponsor protocol code	CY 6031
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05186818
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cytokinetics, Inc.
Sponsor organisation address	350 Oyster Point Blvd, South San Francisco, United States, 94080
Public contact	Medical Affairs, Cytokinetics, Inc., +1 6506242929, medicalaffairs@cytokinetics.com
Scientific contact	Medical Affairs, Cytokinetics, Inc., +1 6506242929, 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	18 December 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 December 2023
Global end of trial reached?	Yes
Global end of trial date	18 December 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of CK-3773274 on exercise capacity in patients with symptomatic obstructive hypertrophic cardiomyopathy

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:

Participants on beta-blockers, verapamil, diltiazem, or disopyramide were to have been on a stable regimen for > 6 weeks prior to randomization, which was individually optimized according to local practice.

Evidence for comparator: -

Actual start date of recruitment	01 February 2022
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Poland: 17
Country: Number of subjects enrolled	Portugal: 4
Country: Number of subjects enrolled	Spain: 32
Country: Number of subjects enrolled	Czechia: 1
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	China: 46
Country: Number of subjects enrolled	United States: 94
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	Israel: 9

Worldwide total number of subjects	282
EEA total number of subjects	115

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)	169
From 65 to 84 years	113
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study included adults with symptomatic obstructive hypertrophic cardiomyopathy (HCM) and was conducted at 82 study centers in China, Czech Republic, Denmark, France, Germany, Hungary, Israel, Italy, Netherlands, Poland, Portugal, Spain, the United Kingdom, and the United States.

Pre-assignment

Screening details:

Participants had: left ventricular (LV) hypertrophy and non-dilated LV chamber in the absence of other cardiac disease, and end diastolic LV wall thickness ≥ 15 mm in ≥ 1 myocardial segment or ≥ 13 mm in ≥ 1 wall segment; a known disease-causing gene mutation or positive family history of HCM; a Valsalva LV outflow tract gradient ≥ 50 mmHg.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Aficamten

Arm description: -

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:

Participants randomized to aficamten started at a dose of 5 mg once daily. At 2-week intervals, doses could have escalated sequentially to 10, 15, or 20 mg once daily based on echocardiography results. Participants with Valsalva LVOT-G ≥ 30 mmHg and biplane LVEF $\geq 55\%$ could escalate to the next higher dose; if these criteria were not met, the participant remained at their existing dose. The Week 6 visit was the last time a dose could have been escalated; no dose escalations were allowed after this time point. At Week 8 and later, dose reductions (to the next lower dose) occurred if echocardiography results showed that LVEF was $< 50\%$. Overall, participants were to receive aficamten for a total of 24 weeks.

Arm title	Placebo
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Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo for aficamten
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants randomized to placebo received new study drug kits on the same schedule as participants randomized to aficamten to maintain the blind during the dose titration phase.

Number of subjects in period 1	Aficamten	Placebo
Started	142	140
Completed	137	136
Not completed	5	4
Consent withdrawn by subject	2	-
Physician decision	-	1
Adverse event, non-fatal	1	2
Transportation issue due to COVID-19	-	1
Protocol deviation	2	-

Baseline characteristics

Reporting groups

Reporting group title	Aficamten
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Aficamten	Placebo	Total
Number of subjects	142	140	282
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)	85	84	169
From 65-84 years	57	56	113
85 years and over	0	0	0
Age continuous Units: years			
median	59.0	60.0	
full range (min-max)	18 to 83	23 to 84	-
Gender categorical Units: Subjects			
Female	56	59	115
Male	86	81	167
pVO2 per CPET Units: mL/kg/min			
arithmetic mean	18.4	18.6	
standard deviation	± 4.5	± 4.5	-

End points

End points reporting groups

Reporting group title	Aficamten
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Change from Baseline in pVO2 at Week 24

End point title	Change from Baseline in pVO2 at Week 24
End point description: The effect of aficamten on exercise capacity in participants with symptomatic obstructive HCM was determined through changes in peak oxygen uptake (pVO2) after 24 weeks of treatment. pVO2 was measured by cardiopulmonary exercise testing (CPET; treadmill or bicycle).	
End point type	Primary
End point timeframe: Baseline (ie, start of study drug) through Week 24	

End point values	Aficamten	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	140		
Units: mL/kg/min				
least squares mean (standard error)	1.76 (\pm 0.25)	0.02 (\pm 0.25)		

Statistical analyses

Statistical analysis title	Primary Analysis
Statistical analysis description: The primary analysis was performed using an analysis of covariance (ANCOVA) model that included terms of treatment, randomization stratification factors (beta-blocker use status and CPET modality), baseline pVO2 and baseline body weight as covariates in the Full Analysis Set.	
Comparison groups	Aficamten v Placebo
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	2.44

Variability estimate	Standard error of the mean
Dispersion value	0.36

Secondary: Change from Baseline in KCCQ-CSS at Week 24

End point title	Change from Baseline in KCCQ-CSS at Week 24
End point description: The effect of aficamten on patient health status was assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ), a patient-reported outcome designed to assess the physical limitations, symptoms, self-efficacy, social imitation, and quality of life of patients with heart failure symptoms. The KCCQ-Clinical Symptoms Score (KCCQ-CSS) is scored on a scale from 0 to 100, with higher scores indicating better physical functioning and symptoms.	
End point type	Secondary
End point timeframe: Baseline (ie, initiation of study drug) to Week 24	

End point values	Aficamten	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	140		
Units: score on a scale				
least squares mean (standard error)	11.6 (± 1.0)	4.3 (± 1.0)		

Statistical analyses

Statistical analysis title	Analysis of Change in KCCQ-CSS at Week 24
Comparison groups	Aficamten v Placebo
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	7.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.6
upper limit	10.1
Variability estimate	Standard deviation
Dispersion value	1.4

Secondary: Change from Baseline in KCCQ-CSS at Week 12

End point title	Change from Baseline in KCCQ-CSS at Week 12
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End point description:

The effect of aficamten on patient health status was assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ), a patient-reported outcome designed to assess the physical limitations, symptoms, self-efficacy, social limitation, and quality of life of patients with heart failure symptoms. The KCCQ-Clinical Symptoms Score (KCCQ-CSS) is scored on a scale from 0 to 100, with higher scores indicating better physical functioning and symptoms.

End point type	Secondary
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End point timeframe:

Baseline (ie, start of study drug) to Week 12

End point values	Aficamten	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	140		
Units: score on a scale				
least squares mean (standard error)	11.1 (± 0.9)	4.0 (± 0.9)		

Statistical analyses

Statistical analysis title	Analysis of Change in KCCQ-CSS at Week 12
Comparison groups	Aficamten v Placebo
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	7
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.5
upper limit	9.5
Variability estimate	Standard error of the mean
Dispersion value	1.3

Secondary: Proportion of Participants with ≥1 Class Improvement in NYHA Functional Class from Baseline to Week 24

End point title	Proportion of Participants with ≥1 Class Improvement in NYHA Functional Class from Baseline to Week 24
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End point description:

The effect of aficamten on New York Heart Association (NYHA) functional classification was evaluated through changes observed from baseline through 24 weeks of treatment.

End point type	Secondary
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End point timeframe:

Baseline (ie, start of study drug) to Week 24

End point values	Aficamten	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	140		
Units: % of participants				
number (not applicable)	58.5	24.3		

Statistical analyses

Statistical analysis title	Analysis 1: NYHA ≥ 1 Class Improvement at Week 24
Comparison groups	Aficamten v Placebo
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Rate difference
Point estimate	34.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	23.4
upper limit	45

Statistical analysis title	Analysis 2: NYHA ≥ 1 Class Improvement at Week 24
Comparison groups	Aficamten v Placebo
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.6
upper limit	7.6

Secondary: Proportion of Participants with ≥ 1 Class Improvement in NYHA Functional Class from Baseline to Week 12

End point title	Proportion of Participants with ≥ 1 Class Improvement in NYHA Functional Class from Baseline to Week 12
End point description: The effect of aficamten on NYHA functional classification was evaluated through changes observed from baseline through 12 weeks of treatment.	
End point type	Secondary
End point timeframe: Baseline (ie, start of study drug) to Week 12	

End point values	Aficamten	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	140		
Units: % of participants				
number (not applicable)	48.6	17.9		

Statistical analyses

Statistical analysis title	Analysis 1: NYHA ≥ 1 Class Improvement at Week 12
Comparison groups	Aficamten v Placebo
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Rate difference
Point estimate	30.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	20.6
upper limit	41

Statistical analysis title	Analysis 2: NYHA ≥ 1 Class Improvement at Week 12
Comparison groups	Aficamten v Placebo
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	4.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.6
upper limit	8.4

Secondary: Change From Baseline in Valsalva LVOT-G at Week 24

End point title	Change From Baseline in Valsalva LVOT-G at Week 24
End point description: The effect of aficamten treatment on Valsalva left ventricular outflow tract gradient (LVOT-G) was evaluated through changes from baseline to Week 24.	
End point type	Secondary
End point timeframe: Baseline (ie, start of study drug) to Week 24	

End point values	Aficamten	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	140		
Units: mmHg				
least squares mean (standard error)	-48 (± 2.4)	2 (± 2.4)		

Statistical analyses

Statistical analysis title	Analysis of Change in Valsalva LVOT-G at Week 24
Comparison groups	Aficamten v Placebo
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-50
Confidence interval	
level	95 %
sides	2-sided
lower limit	-57
upper limit	-44
Variability estimate	Standard error of the mean
Dispersion value	3.4

Secondary: Change From Baseline in Valsalva LVOT-G at Week 12

End point title	Change From Baseline in Valsalva LVOT-G at Week 12
End point description: The effect of aficamten treatment on Valsalva LVOT-G was evaluated through changes from baseline to Week 12.	
End point type	Secondary
End point timeframe: Baseline (ie, start of study drug) to Week 12	

End point values	Aficamten	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	140		
Units: mmHg				
least squares mean (standard error)	-46 (± 2.4)	3 (± 2.4)		

Statistical analyses

Statistical analysis title	Analysis of Change in Valsalva LVOT-G at Week 12
Comparison groups	Aficamten v Placebo
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-55
upper limit	-42
Variability estimate	Standard error of the mean
Dispersion value	3.4

Secondary: Proportion of Participants With Valsalva LVOT-G <30 mmHg at Week 24

End point title	Proportion of Participants With Valsalva LVOT-G <30 mmHg at Week 24
End point description: The effect of aficamten treatment on Valsalva LVOT-G was evaluated through changes from baseline to Week 24.	
End point type	Secondary
End point timeframe: Baseline (ie, start of study drug) to Week 24	

End point values	Aficamten	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	140		
Units: % of participants				
number (not applicable)	49.3	3.6		

Statistical analyses

Statistical analysis title	Analysis 1: Valsalva LVOT-G <30 mmHg at Week 24
Comparison groups	Aficamten v Placebo
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Rate difference
Point estimate	45.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	36.9
upper limit	54.4

Statistical analysis title	Analysis 2: Valsalva LVOT-G <30 mmHg at Week 24
Comparison groups	Aficamten v Placebo
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	25.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.1
upper limit	88.2

Secondary: Proportion of Participants With Valsalva LVOT-G <30 mmHg at Week 12

End point title	Proportion of Participants With Valsalva LVOT-G <30 mmHg at
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End point description:

The effect of aficamten treatment on Valsalva LVOT-G was evaluated through changes from baseline to Week 12.

End point type Secondary

End point timeframe:

Baseline (ie, start of study drug) to Week 12

End point values	Aficamten	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	140		
Units: % of Participants				
number (not applicable)	52.1	5.7		

Statistical analyses

Statistical analysis title	Analysis 1: Valsalva LVOT-G <30 mmHg at Week 12
Comparison groups	Aficamten v Placebo
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Rate difference
Point estimate	46.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	37.3
upper limit	55.5

Statistical analysis title	Analysis 2: Valsalva LVOT G <30 mmHg at Week 12
Comparison groups	Aficamten v Placebo
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	18

Confidence interval	
level	95 %
sides	2-sided
lower limit	7.8
upper limit	44.4

Secondary: Duration of SRT Eligibility During the 24-week Treatment Period for Participants Who Were SRT Eligible at Baseline

End point title	Duration of SRT Eligibility During the 24-week Treatment Period for Participants Who Were SRT Eligible at Baseline
End point description: The effect of aficamten treatment on the duration of eligibility for septal reduction therapy (SRT) was evaluated over the 24-week treatment period.	
End point type	Secondary
End point timeframe: Baseline (ie, start of study drug) to Week 24	

End point values	Aficamten	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32 ^[1]	29 ^[2]		
Units: days				
least squares mean (standard error)	35.3 (± 7.9)	113.4 (± 8.1)		

Notes:

[1] - 32 of the 142 participants in this arm were SRT eligible at baseline

[2] - 29 of the 140 participants in this arm were SRT eligible at baseline

Statistical analyses

Statistical analysis title	Analysis of duration of SRT eligibility
Comparison groups	Aficamten v Placebo
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-78.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-99.8
upper limit	-56.3
Variability estimate	Standard error of the mean
Dispersion value	10.9

Secondary: Change From Baseline to Week 24 in Total Workload During CPET

End point title	Change From Baseline to Week 24 in Total Workload During CPET
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End point description:

The effect of aficamten on intensity of exercise (based on speed, incline, participant weight, etc.) during CPET was evaluated. Workload is an indication of the energy expended during cardiopulmonary exercise testing.

End point type	Secondary
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End point timeframe:

Baseline (ie, start of study drug) to Week 24

End point values	Aficamten	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	140		
Units: watts				
least squares mean (standard error)	13.4 (± 2.1)	1.2 (± 2.1)		

Statistical analyses

Statistical analysis title	Analysis of workload at Week 24
Comparison groups	Aficamten v Placebo
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	12.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.4
upper limit	18
Variability estimate	Standard error of the mean
Dispersion value	3

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from initiation of IP through 4 weeks after the last dose of IP; as such, all serious and non-serious adverse events were treatment-emergent.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.0
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Reporting groups

Reporting group title	Aficamten
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	Aficamten	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 142 (5.63%)	13 / 140 (9.29%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia			
subjects affected / exposed	0 / 142 (0.00%)	1 / 140 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of the oral cavity			
subjects affected / exposed	0 / 142 (0.00%)	1 / 140 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	0 / 142 (0.00%)	1 / 140 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			

subjects affected / exposed	0 / 142 (0.00%)	1 / 140 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	0 / 142 (0.00%)	1 / 140 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Hypertrophic cardiomyopathy			
subjects affected / exposed	3 / 142 (2.11%)	1 / 140 (0.71%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thalassaemia			
subjects affected / exposed	1 / 142 (0.70%)	0 / 140 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 142 (0.70%)	1 / 140 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia supraventricular			
subjects affected / exposed	1 / 142 (0.70%)	0 / 140 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 142 (0.00%)	1 / 140 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 142 (0.00%)	1 / 140 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac failure congestive			
subjects affected / exposed	0 / 142 (0.00%)	1 / 140 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinoatrial block			
subjects affected / exposed	0 / 142 (0.00%)	1 / 140 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 142 (0.00%)	1 / 140 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 142 (0.70%)	0 / 140 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 142 (0.70%)	0 / 140 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 142 (0.00%)	1 / 140 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 142 (0.00%)	1 / 140 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Microcytic anaemia			
subjects affected / exposed	1 / 142 (0.70%)	0 / 140 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 142 (0.00%)	1 / 140 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 142 (0.70%)	0 / 140 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 142 (0.70%)	0 / 140 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 142 (0.70%)	0 / 140 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 142 (0.00%)	1 / 140 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 142 (0.00%)	1 / 140 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Aficamten	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	105 / 142 (73.94%)	96 / 140 (68.57%)	

Vascular disorders Hypertension subjects affected / exposed occurrences (all)	11 / 142 (7.75%) 11	3 / 140 (2.14%) 3	
Congenital, familial and genetic disorders Hypertrophic cardiomyopathy subjects affected / exposed occurrences (all)	3 / 142 (2.11%) 3	3 / 140 (2.14%) 3	
Cardiac disorders Palpitations subjects affected / exposed occurrences (all) Angina pectoris subjects affected / exposed occurrences (all)	10 / 142 (7.04%) 12 3 / 142 (2.11%) 4	4 / 140 (2.86%) 5 7 / 140 (5.00%) 12	
Nervous system disorders Headache subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all)	11 / 142 (7.75%) 12 6 / 142 (4.23%) 6	10 / 140 (7.14%) 13 2 / 140 (1.43%) 2	
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Chest pain subjects affected / exposed occurrences (all) Chest discomfort subjects affected / exposed occurrences (all) Asthenia subjects affected / exposed occurrences (all)	3 / 142 (2.11%) 3 6 / 142 (4.23%) 13 5 / 142 (3.52%) 7 4 / 142 (2.82%) 6	7 / 140 (5.00%) 9 2 / 140 (1.43%) 2 3 / 140 (2.14%) 3 0 / 140 (0.00%) 0	
Ear and labyrinth disorders			

Vertigo subjects affected / exposed occurrences (all)	1 / 142 (0.70%) 1	4 / 140 (2.86%) 4	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	6 / 142 (4.23%) 6	4 / 140 (2.86%) 4	
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	4 / 142 (2.82%) 4	0 / 140 (0.00%) 0	
Diarrhoea subjects affected / exposed occurrences (all)	2 / 142 (1.41%) 2	4 / 140 (2.86%) 4	
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	8 / 142 (5.63%) 8	8 / 140 (5.71%) 8	
Cough subjects affected / exposed occurrences (all)	5 / 142 (3.52%) 6	1 / 140 (0.71%) 1	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	4 / 142 (2.82%) 4	2 / 140 (1.43%) 2	
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	9 / 142 (6.34%) 13	12 / 140 (8.57%) 16	
COVID-19 subjects affected / exposed occurrences (all)	8 / 142 (5.63%) 8	9 / 140 (6.43%) 11	
Nasopharyngitis subjects affected / exposed occurrences (all)	5 / 142 (3.52%) 5	6 / 140 (4.29%) 7	
Urinary tract infection			

subjects affected / exposed	4 / 142 (2.82%)	1 / 140 (0.71%)	
occurrences (all)	4	1	
Bronchitis			
subjects affected / exposed	0 / 142 (0.00%)	4 / 140 (2.86%)	
occurrences (all)	0	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 March 2023	Protocol Amendment 03: Added endpoints to evaluate eligibility for septal reduction therapy and updated pVO2 inclusion criterion. Added option to increase the sample size based on pVO2 variability and missing data rate.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.
The length of the study was relatively short and did not permit assessment of longer-term cardiovascular outcomes. Ethnic diversity was limited.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/38739079>