



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 |
|-----------------------|---------|

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 |
|------------------|---------|

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 |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 (\pm 2.4) | 3 (\pm 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 |
|-----------------|---|

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 |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|-----------------|------------|

Dictionary used

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|-----------------|--------|
| Dictionary name | MedDRA |
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| Dictionary version | 26.0 |
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Reporting groups

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| Reporting group title | Aficamten |
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Reporting group description: -

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| 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 | | | |

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|---|-----------------|-----------------|--|
| 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 | |

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| 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 | |

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| 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%) | |

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| 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 | | | |

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| 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 | | | |

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|-----------------------------|-----------------|-----------------|--|
| 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.

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| The length of the study was relatively short and did not permit assessment of longer-term cardiovascular outcomes. Ethnic diversity was limited. |
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Notes:

Online references

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