



Clinical trial results:

A Randomized, Double blind, Placebo controlled Clinical Study to Evaluate Mavacamten (MYK-461) in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy

Summary

| | |
|--------------------------|----------------------------------|
| EudraCT number | 2017-002530-23 |
| Trial protocol | DE GB PT ES CZ BE NL PL DK FR IT |
| Global end of trial date | 06 May 2020 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 04 June 2021 |
| First version publication date | 04 June 2021 |

Trial information

Trial identification

| | |
|-----------------------|----------------------------|
| Sponsor protocol code | MYK-461-005 (EXPLORER-HCM) |
|-----------------------|----------------------------|

Additional study identifiers

| | |
|------------------------------------|-----------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03470545 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | US IND Number: 121904 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | MyoKardia, Inc. |
| Sponsor organisation address | 1000 Sierra Point Parkway, Brisbane, United States, CA 94005 |
| Public contact | Clinical Trial or Medical Inquiries, MyoKardia, Inc., medinfo@myokardia.com |
| Scientific contact | Clinical Trial or Medical Inquiries, MyoKardia, Inc., medinfo@myokardia.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 | 11 November 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 06 May 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 May 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To compare the effect of a 30-week course of mavacamten with placebo on clinical response comprising of exercise capacity and clinical symptoms in subjects with symptomatic obstructive hypertrophic cardiomyopathy (oHCM [also known as HOCM])

Protection of trial subjects:

The study was conducted in accordance with the principles stated in the Declaration of Helsinki, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines, US Title 21 Code of Federal Regulations, the European Community Directive 2001/20/EC, and all applicable laws and regulations in the countries in which the study was conducted.

The investigator (or designee) was responsible for obtaining written informed consent from each individual who participated in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. Potential subjects were informed that participation was voluntary and that they could withdraw from the study at any time for any reason. A sample informed consent form is available upon request.

Background therapy:

Most subjects were using beta-blockers (78.9% in the mavacamten group and 75.0% in the placebo group). Calcium channel blocker use (verapamil or diltiazem) was reported for 20.3% of subjects in the mavacamten group and 13.3% of subjects in the placebo group. The use of neither beta-blockers nor calcium channel blockers was reported for 3.3% of subjects in the mavacamten group and 12.5% of subjects in the placebo group.

Evidence for comparator:

There is no comparator.

| | |
|---|------------------|
| Actual start date of recruitment | 22 March 2018 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 2 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Czechia: 9 |
| Country: Number of subjects enrolled | United States: 108 |
| Country: Number of subjects enrolled | Israel: 15 |
| Country: Number of subjects enrolled | Netherlands: 7 |
| Country: Number of subjects enrolled | Poland: 32 |
| Country: Number of subjects enrolled | Portugal: 7 |
| Country: Number of subjects enrolled | Spain: 33 |

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United Kingdom: 3 |
| Country: Number of subjects enrolled | Belgium: 4 |
| Country: Number of subjects enrolled | Denmark: 7 |
| Country: Number of subjects enrolled | France: 10 |
| Country: Number of subjects enrolled | Germany: 10 |
| Country: Number of subjects enrolled | Italy: 6 |
| Worldwide total number of subjects | 251 |
| EEA total number of subjects | 125 |

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) | 166 |
| From 65 to 84 years | 85 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Subjects who met all of the inclusion criteria and none of the exclusion criteria were enrolled into the study and were randomized 1:1 to receive mavacamten (2.5, 5, 10, or 15 mg capsule) or placebo once daily for 30 weeks. The starting dose was 5 mg QD and there was a two step dose titration at weeks 8 and 14.

Pre-assignment

Screening details:

The study included a 35-day screening period (Days – 35 through – 1).

Period 1

| | |
|------------------------------|---|
| Period 1 title | Treatment period (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

Study drug was administered in a double-blind manner via the IXRS, such that subjects; investigators; and study site staff, including the pharmacist, did not know what study drugs and doses were administered. In addition, the sponsor, the central and core laboratories, and clinical site monitors were blinded to assigned treatment. Members of the pharmacovigilance team were unblinded for SUSAR reporting. The IDMC provided unblinded safety and efficacy data for periodic review.

Arms

| | |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Mavacamten |

Arm description:

One mavacamten capsule once daily by mouth for 30 weeks. The starting dose is 5 mg QD followed by two-step dose titration at Weeks 8 and 14. Four total dose strengths possible (2.5, 5, 10, and 15).

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Mavacamten |
| Investigational medicinal product code | |
| Other name | MYK-461 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

The starting dose of mavacamten was 5 mg once daily by mouth. At Week 8 and Week 14 mavacamten dose may have been up or down-titrated for individual subjects based on prespecified criteria.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

One placebo-to-match mavacamten capsule once daily by mouth for 30 weeks.

| | |
|--|----------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

A universal placebo capsule to match all strengths of mavacamten had the same appearance as mavacamten capsules but did not include the active ingredient. Placebo dose to match mavacamten capsule was administered once daily by mouth.

| Number of subjects in period 1 | Mavacamten | Placebo |
|---------------------------------------|------------|---------|
| Started | 123 | 128 |
| Completed | 119 | 125 |
| Not completed | 4 | 3 |
| Consent withdrawn by subject | 1 | 1 |
| Adverse event, non-fatal | 2 | - |
| Other | 1 | 1 |
| Death | - | 1 |

Baseline characteristics

Reporting groups

| | |
|---|------------|
| Reporting group title | Mavacamten |
| Reporting group description: One mavacamten capsule once daily by mouth for 30 weeks. The starting dose is 5 mg QD followed by two-step dose titration at Weeks 8 and 14. Four total dose strengths possible (2.5, 5, 10, and 15). | |
| Reporting group title | Placebo |
| Reporting group description: One placebo-to-match mavacamten capsule once daily by mouth for 30 weeks. | |

| Reporting group values | Mavacamten | Placebo | Total |
|---------------------------------------|------------|----------|-------|
| Number of subjects | 123 | 128 | 251 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 78 | 88 | 166 |
| From 65-84 years | 45 | 40 | 85 |
| Age continuous Units: years | | | |
| median | 60.0 | 60.0 | |
| full range (min-max) | 26 to 82 | 18 to 81 | - |
| Gender categorical Units: Subjects | | | |
| Female | 57 | 45 | 102 |
| Male | 66 | 83 | 149 |

Subject analysis sets

| | |
|--|--------------------|
| Subject analysis set title | ITT Population |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: ITT Population included all randomized subjects, regardless of whether or not they received study drug, with analyses conducted according to randomized treatment assignment. | |
| Subject analysis set title | Safety Population |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Safety Population included all randomized subjects who received at least 1 dose of study drug, with analyses conducted according to actual study drug received. | |

| Reporting group values | ITT Population | Safety Population | |
|------------------------------------|----------------|-------------------|--|
| Number of subjects | 251 | 251 | |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 166 | 166 | |
| From 65-84 years | 85 | 85 | |
| Age continuous Units: years | | | |
| median | 60.0 | 60.0 | |
| full range (min-max) | 18 to 82 | 18 to 82 | |

| | | | |
|--------------------|-----|-----|--|
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 149 | 149 | |
| Male | 102 | 102 | |

End points

End points reporting groups

| | |
|---|--------------------|
| Reporting group title | Mavacamten |
| Reporting group description: One mavacamten capsule once daily by mouth for 30 weeks. The starting dose is 5 mg QD followed by two-step dose titration at Weeks 8 and 14. Four total dose strengths possible (2.5, 5, 10, and 15). | |
| Reporting group title | Placebo |
| Reporting group description: One placebo-to-match mavacamten capsule once daily by mouth for 30 weeks. | |
| Subject analysis set title | ITT Population |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: ITT Population included all randomized subjects, regardless of whether or not they received study drug, with analyses conducted according to randomized treatment assignment. | |
| Subject analysis set title | Safety Population |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Safety Population included all randomized subjects who received at least 1 dose of study drug, with analyses conducted according to actual study drug received. | |

Primary: Composite Functional Endpoint (CFE) at Week 30 (ITT population)

| | |
|---|---|
| End point title | Composite Functional Endpoint (CFE) at Week 30 (ITT population) |
| End point description: The proportion of subjects who achieved the composite functional endpoint at Week 30 defined as: 1. An improvement of ≥ 1.5 mL/kg/min in pVO ₂ as determined by CPET and a reduction ≥ 1 NYHA class (Type 1) or 2. An improvement of ≥ 3.0 mL/kg/min in pVO ₂ with no worsening in NYHA class (Type 2) Treatment with mavacamten was superior to placebo. | |
| End point type | Primary |
| End point timeframe: At Week 30 | |

| End point values | Mavacamten | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 128 | | |
| Units: percent | | | | |
| number (not applicable) | | | | |
| Achieved CFE, (%) | 36.6 | 17.2 | | |

Statistical analyses

| | |
|---|----------------------|
| Statistical analysis title | Stratified analysis |
| Statistical analysis description: A Cochran-Mantel-Haenszel (CMH) test for categorical data was used to test the statistical significance of the composite functional endpoint rate between the mavacamten and placebo groups. | |
| Comparison groups | Mavacamten v Placebo |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0005 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.74 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.508 |
| upper limit | 5.445 |

| | |
|--|-----------------------|
| Statistical analysis title | Unstratified analysis |
| Statistical analysis description: | |
| An unstratified Pearson's Chi-square test was performed as a sensitivity analysis. | |
| Comparison groups | Mavacamten v Placebo |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0005 |
| Method | Chi-squared |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.78 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.544 |
| upper limit | 5.003 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-Emergent Adverse Events (TEAEs) were summarized for the on-treatment period (Day 1 to Week 30) and for the treatment-emergent period (Day 1 to Week 38).

Adverse event reporting additional description:

Treatment with mavacamten was well tolerated with an overall completion rate > 97%, balanced AE profile and an absence of any new safety concerns identified through 30 weeks of treatment. It is notable that the TEAE rate did not increase in the mavacamten group with 8 weeks of additional observation during study drug washout.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 21.0 |
|--------------------|------|

Reporting groups

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|-----------------------|--------------------|
| Reporting group title | Mavacamten Week 38 |
|-----------------------|--------------------|

Reporting group description:

The study drugs administered to subjects in this study were mavacamten 2.5, 5, 10, or 15 mg capsules.

| | |
|-----------------------|-----------------|
| Reporting group title | Placebo Week 38 |
|-----------------------|-----------------|

Reporting group description:

The study drug administered to subjects in this study was placebo to match mavacamten capsules.

| Serious adverse events | Mavacamten Week 38 | Placebo Week 38 | |
|---|--------------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 14 / 123 (11.38%) | 12 / 128 (9.38%) | |
| number of deaths (all causes) | 0 | 1 | |
| number of deaths resulting from adverse events | 0 | 1 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cholesteatoma | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 128 (0.78%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 128 (0.78%) | |
| 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 | | | |
| Contusion | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 123 (0.81%) | 0 / 128 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Forearm fracture | | | |
| subjects affected / exposed | 1 / 123 (0.81%) | 0 / 128 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Atrial septal defect | | | |
| subjects affected / exposed | 1 / 123 (0.81%) | 0 / 128 (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 | 3 / 123 (2.44%) | 5 / 128 (3.91%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stress cardiomyopathy | | | |
| subjects affected / exposed | 2 / 123 (1.63%) | 0 / 128 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 128 (0.78%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 123 (0.81%) | 0 / 128 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 128 (0.78%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|-----------------|-----------------|--|
| Cardiogenic shock | | | |
| subjects affected / exposed | 1 / 123 (0.81%) | 0 / 128 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 123 (0.81%) | 0 / 128 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systolic dysfunction | | | |
| subjects affected / exposed | 1 / 123 (0.81%) | 0 / 128 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 128 (0.78%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Syncope | | | |
| subjects affected / exposed | 3 / 123 (2.44%) | 1 / 128 (0.78%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 1 / 123 (0.81%) | 0 / 128 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 128 (0.78%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Sudden death | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 128 (0.78%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |

| | | | |
|---|---|-----------------|-----------------|
| Gastrointestinal disorders Abdominal pain | | | |
| | subjects affected / exposed | 1 / 123 (0.81%) | 0 / 128 (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 Vocal cord polyp | | | |
| | subjects affected / exposed | 0 / 123 (0.00%) | 1 / 128 (0.78%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders Rheumatoid arthritis | | | |
| | subjects affected / exposed | 0 / 123 (0.00%) | 1 / 128 (0.78%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Systemic lupus erythematosus | | | |
| | subjects affected / exposed | 1 / 123 (0.81%) | 0 / 128 (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 | | | |
| | Urinary tract infection | | |
| | subjects affected / exposed | 0 / 123 (0.00%) | 2 / 128 (1.56%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 2 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| | Bacterial colitis | | |
| | subjects affected / exposed | 1 / 123 (0.81%) | 0 / 128 (0.00%) |
| | occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| | Diverticulitis | | |
| | subjects affected / exposed | 1 / 123 (0.81%) | 0 / 128 (0.00%) |
| | occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| | Gastroenteritis viral | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 128 (0.78%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 1 / 123 (0.81%) | 0 / 128 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |
| Device inappropriate shock delivery | | | |
| subjects affected / exposed | 1 / 123 (0.81%) | 0 / 128 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 128 (0.78%) | |
| 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 | Mavacamten Week 38 | Placebo Week 38 | |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 108 / 123 (87.80%) | 104 / 128 (81.25%) | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 10 / 123 (8.13%) | 10 / 128 (7.81%) | |
| occurrences (all) | 10 | 10 | |
| Palpitations | | | |
| subjects affected / exposed | 7 / 123 (5.69%) | 10 / 128 (7.81%) | |
| occurrences (all) | 7 | 10 | |
| Angina pectoris | | | |
| subjects affected / exposed | 3 / 123 (2.44%) | 7 / 128 (5.47%) | |
| occurrences (all) | 3 | 7 | |
| Nervous system disorders | | | |

| | | | |
|--|-------------------------|-------------------------|--|
| Dizziness subjects affected / exposed occurrences (all) | 26 / 123 (21.14%) 26 | 17 / 128 (13.28%) 17 | |
| Headache subjects affected / exposed occurrences (all) | 15 / 123 (12.20%) 15 | 10 / 128 (7.81%) 10 | |
| Syncope subjects affected / exposed occurrences (all) | 7 / 123 (5.69%) 7 | 2 / 128 (1.56%) 2 | |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) | 7 / 123 (5.69%) 7 | 7 / 128 (5.47%) 7 | |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) | 5 / 123 (4.07%) 5 | 7 / 128 (5.47%) 7 | |
| Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) | 7 / 123 (5.69%) 7 | 3 / 128 (2.34%) 3 | |
| Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) | 18 / 123 (14.63%) 18 | 13 / 128 (10.16%) 13 | |
| Cough subjects affected / exposed occurrences (all) | 10 / 123 (8.13%) 10 | 4 / 128 (3.13%) 4 | |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 10 / 123 (8.13%) 10 | 8 / 128 (6.25%) 8 | |
| Arthralgia subjects affected / exposed occurrences (all) | 7 / 123 (5.69%) 7 | 2 / 128 (1.56%) 2 | |
| Infections and infestations | | | |

| | | | |
|-----------------------------------|-------------------|-------------------|--|
| Nasopharyngitis | | | |
| subjects affected / exposed | 15 / 123 (12.20%) | 19 / 128 (14.84%) | |
| occurrences (all) | 15 | 19 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 10 / 123 (8.13%) | 6 / 128 (4.69%) | |
| occurrences (all) | 10 | 6 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 09 August 2017 | <ul style="list-style-type: none">• Study objectives were restated for consistency and parity across objectives.• Kaplan-Meier analysis of safety was changed to a more customary analysis of incidence of safety endpoints, as the study was not powered for the former.• Type of ergometer used for exercise testing (treadmill or exercise bicycle) was included as a randomization stratification.• Pulmonary disease that limited exercise capacity or systemic arterial oxygen saturation was added as an exclusion criterion to avoid enrollment of subjects whose exercise tolerance was limited by pulmonary disease and not reflective of HCM.• Clarified that safety endpoints of CV death, atrial fibrillation that required intervention, CV hospitalization, heart failure requiring loop diuretics, syncope, and stroke would be adjudicated.• Removed reference to a separate cytochrome P450 (CYP)2C19 sampling, as CYP2C19 is included in the pharmacogenetics panel and does not require a separate sample.• Study visits were added at Weeks 16 and 20 to allow for pregnancy testing at those time points. |
| 25 January 2018 | <ul style="list-style-type: none">• The duration of treatment was extended from 24 to 30 weeks, and all endpoints were updated to be consistent with this change.• An additional opportunity for dose adjustment (dose increased, decreased, unchanged) was introduced at Week 14 (based on Week 12 assessments).• The primary efficacy endpoint was modified to include changes in NYHA class as follows:<ul style="list-style-type: none">– (1) An improvement of 1.5 mL/kg/min or more in pVO₂ as determined by cardiopulmonary exercise testing (CPET) and (2) a reduction of 1 or more class in NYHA class at the end of the Week 30 dosing period• The Patient Global Impression of Severity (PGIS), Patient Global Impression of Change (PGIC), and Work Productivity and Activity Impairment-Specific Health Problem (WPAI-SHP) questionnaires were added as exploratory endpoints, and the Canadian Cardiovascular Society Chest Pain Grade Scale was removed.• Additional safety endpoints were specified, all based on safety data collected during the study.• A CMR substudy was added for a planned 60 to 80 subjects who provided additional, specific consent and did not have an implantable ICD device or pacemaker or atrial fibrillation at screening. The primary, secondary, and exploratory objectives of the substudy were defined. In addition to main study procedures, subjects in the CMR substudy were to undergo CMR at Day 1 and Week 30.• A study drug stopping rule was included specifying that if local QTcF > 500 ms was observed at any time, study drug would be withdrawn, and subject would have an unscheduled electrocardiogram (ECG) 2 weeks later. ECG-based criteria for rechallenge/restarting study drug and permanent discontinuation of study drug were specified.• Clarified that blood samples for exploratory circulating biomarker analysis were not optional and were to be collected on Day 1 and at Week 30.• Spirometry prior to CPET was removed. |

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| 21 March 2018 | <ul style="list-style-type: none"> • Study site sonographers were permitted to read transthoracic echocardiography (TTE) results (ie, measure LVEF), while keeping other site personnel blinded so that the investigator could be notified immediately in the event of LVEF \leq 30%. • Exclusion criteria were added that prohibited the use of beta-blockers in combination with verapamil or beta-blockers in combination with diltiazem. • The requirements for triplicate ECGs and postdose ECGs were removed from the schedule of study procedures. • PK assessment was added at Week 8 visit to guide any necessary dose reduction, and PK assessments on Day 1 were removed from the schedule of study procedures. • LVEF \leq 30% was included as an adverse event of special interest (AESI), requiring reporting to MyoKardia within 24 hours. • LVEF measurement by the site sonographer was added such that the investigator could be immediately notified at the study visit if LVEF \leq 30%. • Sham unscheduled visits were included to maintain the study blind. <p>The study began enrolling on this Amendment.</p> |
| 13 November 2018 | <ul style="list-style-type: none"> • Based on FDA advice regarding the primary efficacy endpoint (09 April 2018), a second definition of clinical response for the primary endpoint was added and the endpoint was updated to: 1) An improvement of \geq 1.5 mL/kg/min in pVO₂ as determined by CPET and a reduction \geq 1 NYHA class or 2) an improvement of 3.0 mL/kg/min or more in pVO₂ with no worsening in NYHA class. • Screening period increased from 28 to 35 days to allow for potential repeat of key assessments. Rescreening requirements were added. • A list of appropriate contraceptive methods for female subjects of childbearing potential was included based on Clinical Trial Facilitation Group guidance. The statement warning that mavacamten may reduce effectiveness of hormonal contraceptives was removed based on results of the mavacamten and hormonal contraceptive drug-interaction study MYK-461-010. • Exclusion criteria were updated to allow a history of antitachycardia pacing and pulse generator changes during the trial. • Allowable QTcF interval at screening was increased from > 480 ms to > 500 ms. • Criteria for temporary study drug discontinuation based on QTcF were modified to account for QRS width and change from baseline in QTcF. These criteria are more reflective of the expected variances in QT interval and conduction abnormalities prevalent in HCM patients. • The cardiac monitoring skin patch (ie, SEEQ) was no longer available from the manufacturer, necessitating a change to a replacement continuous cardiac monitoring device (ie, Holter). |
| 04 October 2019 | <ul style="list-style-type: none"> • Kansas City Cardiomyopathy Questionnaire 23-item version (KCCQ-23) was changed from an exploratory to a secondary endpoint based on FDA feedback (09 August 2019) and to enable inclusion in product labeling. • The secondary endpoint for NYHA class was updated from a continuous to a categorical endpoint as more appropriate for the noncontinuous variable. • The endpoints of proportion of subjects with postexercise LVOT peak gradient < 50 mmHg at Week 30 and proportion of subjects with postexercise LVOT peak gradient < 30 mmHg at Week 30 were changed from secondary to exploratory endpoints. • Change from baseline to Week 30 in the HCM risk prediction model and change from baseline to Week 30 in cardiac troponin-I (cTn-I) were included as exploratory endpoints. |

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.

None reported.

Notes: