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 pVO2 as determined by CPET and a reduction ≥ 1 NYHA class (Type 1) or 2. An improvement of ≥ 3.0 mL/kg/min in pVO2 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 categorial 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

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

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

21 March 2018	• 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 ≤ 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 ≤ 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 ≤30% • Sham unscheduled visits were included to maintain the study blind. The study began enrolling on this Amendment.
13 November 2018	• 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 ≥ 1.5 mL/kg/min in pVO2 as determined by CPET and a reduction ≥ 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	• 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: