A Long-term Safety Extension Study of Mavacamten (MYK-461) in Adults with Hypertrophic Cardiomyopathy Who Have Completed the MAVERICKHCM (MYK-461-006) or EXPLORER-HCM (MYK-461-005) Trials (MAVA-LTE)

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This study has been transitioned to CTIS with ID 2022-502858-14-00 check the CTIS register for the current data. primary objective:To assess the long-term safety and tolerability of mavacamten in participants with hypertrophic cardiomyopathy (HCM)...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac and vascular disorders congenital
Study type	Interventional

Summary

ID

NL-OMON54979

Source
ToetsingOnline

Brief title
MAVA-LTE

Condition

- Cardiac and vascular disorders congenital

Synonym
Heart muscle disease, inherited hart disease

Research involving

Human

Sponsors and support

Primary sponsor: MyoKardia, Inc.
Source(s) of monetary or material Support: MyoKardia Inc

Intervention

Keyword: Hypertrophic Cardiomyopathy, Mavacamten

Outcome measures

Primary outcome

Safety

• Incidence of major adverse cardiac events (death, stroke, acute myocardial infarction)

• Incidence of hospitalizations (both cardiovascular [CV] and non-CV)

• Incidence of heart failure (HF) events (includes HF hospitalizations and urgent emergency room/outpatient visits for HF)

• Incidence of atrial fibrillation/flutter (new from Screening Visit)

• Incidence of ICD discharges and resuscitated cardiac arrest

• Incidence of ventricular tachyarrhythmias (includes ventricular tachycardia, ventricular fibrillation)

• Incidence of any AE potentially linked to QT prolongation (Torsade de pointes, CV or sudden death, sustained ventricular tachycardia, ventricular fibrillation and flutter, syncope, and seizures)

• Frequency and severity of treatment-emergent AEs, treatmentemergent serious AEs, and laboratory abnormalities (including trends in NT-proBNP)

Secondary outcome

Efficacy and Pharmacodynamics

• Change from baseline in echocardiographic parameters of systolic function (eg, LVEF) and diastolic function (eg, peak velocity of early diastolic septal and lateral mitral annular motion [e*], ratio of peak velocity of early diastolic transmitral flow [E] to e* [E/e*], ratio of E to peak velocity of late transmitral flow [A] [E/A], pulmonary artery systolic pressure, left atrium size) over time

• Change from baseline in resting and post-Valsalva LVOT gradient (EXPLORER-HCM participants only)

• Change from baseline in New York Heart Association (NYHA) functional class over time

• Change from baseline in NT-proBNP over time

• Frequency of cardiac transplantation

Study description

Background summary

MyoKardia is developing mavacamten, a cardiac myosin modulator, for the treatment of patients with
symptomatic HCM, a condition with significant unmet medical need, with the goals to reduce ventricular filling pressures, improve symptoms, and increase exercise capacity. MyoKardia has designed the current study to generate long-term data in participants with symptomatic nHCM and oHCM.

Study objective

This study has been transitioned to CTIS with ID 2022-502858-14-00 check the CTIS register for the current data.

primary objective:
To assess the long-term safety and tolerability of mavacamten in participants

with hypertrophic cardiomyopathy (HCM) previously enrolled in 1 of 2 placebo-controlled trials: MAVERICK-HCM (MYK-461-006) for non-obstructive HCM (nHCM) and EXPLORERHCM (MYK-461-005) for obstructive HCM (oHCM).

Secondary objectives:
• To assess the long-term effects of mavacamten on symptoms and echocardiographic measures of cardiac function
• To assess left ventricular outflow tract (LVOT) obstruction as determined by Doppler echocardiography in the EXPLORER-LTE cohort

Study design

This is a multicenter study to evaluate the long-term safety and tolerability of mavacamten in 2 cohorts:
• Up to 60 participants with nHCM who complete MAVERICK-HCM study through Week 24 and begin Screening for this study within 90 days from the MAVERICK end of study (EOS) Visit
•Up to 250 participants with oHCM who complete EXPLORER-HCM study through Week 38 and begin Screening for this study within 90 days from the EXPLORER-HCM EOS Visit

All participants will receive active study drug (mavacamten) once daily (QD) but their status (active or placebo) in the Parent Study will remain blinded as the studies will be enrolling in parallel. All participants will undergo the same assessments and visit schedule (per cohort) to preserve the blind of study drug assignment in the Parent Study.

Screening Period (Day -28 to Day -1)
Participants in this study will be screened to ensure they continue to meet eligibility criteria. Results of assessments from the Parent Study EOS Visit may be used as screening values to confirm eligibility for this study if the participant signs the Informed Consent Form (ICF) within 28 days of the Parent Study EOS Visit.
If more than 28 days but less than 90 days has elapsed since the Parent Study EOS Visit, participants will require a full Screening Visit per protocol prior to enrollment. Once a participant signs the ICF, the screening window opens, and participants must complete the Baseline Visit (Day 1) within 28 days.
For both cohorts, the 90 day interval to begin screening may be extended if needed under special circumstances and with written approval from the MyoKardia Medical Monitor.
Participants who fail to meet all enrollment criteria may be re-screened. The MyoKardia Medical Monitor should be contacted to discuss the specific situation.

Treatment Period (Day 1 to Week 252/End of Treatment)
Participants who meet all Eligibility Criteria will undergo baseline (Day 1) assessments followed by scheduled visits through Week 104/End of Treatment

(EOT). Clinic visits will include but not be limited to clinical evaluation symptoms, adverse event (AE)/serious adverse event (SAE) assessment, electrocardiograms (ECGs), PK samples, transthoracic echocardiography (TTE), and laboratory assessments including N-terminal pro b-type natriuretic peptide (NT-proBNP).

For MAVERICK-LTE Cohort Only
• Arterial pulse wave morphology will also be performed.
• This cohort will undergo one additional visit, Week 6 for dose adjustment based on assessments made at Week 4.

For EXPLORER-LTE Cohort Only
• Dose adjustments will occur based on data from the site-read echocardiogram at Week 4, Week 8, and Week 12. Study site Investigators will not be blinded to the site-read echocardiography results from these visits. Echocardiograms will also be sent to a core laboratory for future assessment during data analysis.
• A site-read stress echocardiogram will be administered at Week 24 to evaluate the post-exercise LVOT gradient and determine whether further dose adjustment may be needed (to be discussed with the MyoKardia Medical Monitor). Participants undergoing dose adjustment at Week 24 will be asked to return 28 days later (+/- 7 days) for echocardiographic assessment of their LVOT gradient. Repeat of a subsequent post-exercise echocardiographic assessment of LVOT gradient will be at the Investigator*s discretion.
• At any visit after Week 24, if the site-read LVOT gradient with Valsalva maneuver is > 30 mm Hg and LVEF is >= 50%, then a dose increase may be considered after discussion with the MyoKardia Medical Monitor.
• PRO assessments will be performed on-site

Intervention

MAVERICK-LTE Participants
All participants will receive mavacamten immediate-release capsules to achieve 1 of 2 target drug concentrations (Group 1: ~200 ng/mL; Group 2: ~500 ng/mL). Study drug will be administered as 1 capsule QD by mouth. Group assignment and dose strength from previous study will be blinded.
Beginning on Day 1, participants who received active study drug in MAVERICK-HCM will begin receiving mavacamten at the same dose level they received at the EOT (Week 16) visit. These participants will undergo the same assessments and visit schedule as participants who received placebo in MAVERICK-HCM to preserve the blind (eg, study visits at Week 4 and Week 6).
If in the MAVERICK-HCM study at Week 16 (EOT), a participant has PK >= 1000 ng/ml, then the starting dose in this study will be:
• 5 mg if dose at EOT was 15 mg or 10 mg
• 2.5 mg if dose at EOT was 5 mg

Participants who received placebo in MAVERICK-HCM will be randomized in a 1:1 ratio to either Group 1 or Group 2. Randomization will be stratified according to current treatment with beta blocker (yes or no). They will receive a starting dose of 5 mg and undergo blinded dose adjustment through an interactive response system (IXRS) at Week 6 based on assessments made at Week 4.

EXPLORER-LTE Participants
Participants will receive mavacamten immediate-release capsules at a starting dose of 5 mg QD, for 4 weeks. Dose adjustments will occur on the day of the visit, based on results of the site-read TTE assessment. All dose adjustments will occur through IXRS, based on TTE data entered by the study site.

Study burden and risks

The following information about adverse events was obtained from studies of mavacamten in patients with HCM as of October 30, 2020.
As of 30 October 2020, more than 300 subjects with cardiomyopathy have been enrolled across completed and ongoing studies and treated with mavacamten.

Side effects that are considered to be related to taking mavacamten:

In a clinical study of subjects with obstructive HCM
• Dizziness (very common, mild or moderate, not serious)
o In the main clinical study, dizziness occurred during the treatment period in 17% of subjects treated with*mavacamten and 12% of subjects who took placebo.
• Heart failure due to systolic dysfunction (common, severe, serious)*
o Heart failure occurred during the treatment period in 2% of subjects treated with mavacamten and 2% of subjects who took placebo in the main clinical study.*
o Systolic dysfunction (measured as left ventricular ejection fraction (LVEF) <50% on echocardiography) occurred during the treatment period in 6% of subjects treated with mavacamten and 2% of subjects who took placebo in the main clinical study.*
o In clinical studies overall, heart failure and systolic dysfunction related to mavacamten have been reversible after stopping mavacamten.*

In a clinical study of subjects with nonobstructive HCM, short-lived ejection fraction reductions, or a decline in the heart*s ability to pump blood, occurred in 5 subjects (12.5%) on mavacamten and led to study drug discontinuation. All 5 subjects recovered following discontinuation of mavacamten.

Other potential risks under evaluation:
Changes in electrical activity in the heart (Prolonged QT Interval):
In studies conducted in healthy subjects, small changes in the electrical activity of the heart have been observed at higher doses of mavacamten tested.

However, other laboratory studies and other studies in animals have shown that these changes in electrical activity of the heart are not expected to result in irregular heartbeat. In addition, in patients with HCM, such changes in electrical activity (prolonged QTc interval) have not been more frequent in patients treated with Mavacamten compared to those on placebo. There has been no increase in dangerous disruption of heart rhythms associated with prolonged QTc interval in patients with HCM treated with Mavacamten. There is no information on QTc prolongation in patients with other types of heart failure.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Has completed the Parent Study through to the EOS Visit within 90 days of signing consent. (Participants who are beyond the 90 day window from EOS Visit may be included in this study

pending MyoKardia Medical Monitor approval). Participants who prematurely discontinued
from the Parent Study or the MAVA LTE study may be considered for inclusion.
2. Is able to understand and comply with the study procedures, understand the risks involved in the study, and provide informed consent according to federal, local, and institutional guidelines before the first study-specific procedure
3. Body weight is greater than 45 kg at the Screening Visit or Day 1 (Day 1 weight must be verified prior to dosing)
4. Has adequate acoustic windows to enable accurate TTEs (refer to Echocardiography Site Instruction Manual)
5. Has documented LVEF >= 50% by echocardiography core laboratory read of screening TTE at rest
6. Has safety laboratory parameters within normal limits (according to the central laboratory reference range); however, a participant with safety laboratory parameters outside normal limits may be included if he or she meets all of the following criteria:
• The safety laboratory parameter outside normal limits is considered by the Investigator to be clinically unimportant
• If there is an alanine aminotransferase or aspartate aminotransferase result, the value must be < 3× the upper limit of the laboratory reference range
• The body size-adjusted estimated glomerular filtration rate is >= 30 mL/min/1.73 m2
7. Female participants must not be pregnant or lactating and, if sexually active, must use one of the following highly effective birth control methods from the Screening Visit through 90 days after the last dose of investigational medicinal product (IMP).
• combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation or progestogen-only hormonal contraception associated with inhibition of ovulation by oral, implantable, or injectable route
of administration
• intrauterine device (IUD)
• intrauterine hormone-releasing system (IUS)
• bilateral tubal occlusion
• Female is surgically sterile for 6 months or postmenopausal for 1 year. Permanent sterilization includes hysterectomy, bilateral oophorectomy, bilateral salpingectomy, and/or documented bilateral tubal occlusion at least 6 months prior to Screening. Females are considered postmenopausal if they have had amenorrhea for at least 1 year or more following cessation of all exogenous hormonal treatments and follicle stimulating hormone (FSH) levels are in the postmenopausal range.
• In addition to the above contraceptive requirements for female

participants, male partners must also use a contraceptive (eg, barrier, condom, or vasectomy)

Exclusion criteria

1. Has persistent or permanent atrial fibrillation not on anticoagulation for at least 4 weeks prior and/or is not adequately rate-controlled
(Note: participants with persistent or permanent atrial fibrillation who are anticoagulated and adequately rate-controlled are allowed)
2. Is currently taking, or has taken within 14 days of Screening, a prohibited medication such as a cytochrome P450 (CYP) 2C19 inhibitor (eg, omeprazole), a strong CYP 3A4 inhibitor, or St. John*s Wort (see APPENDIX 2 for more details)
3. Has QTcF > 500 ms at Screening or any other ECG abnormality considered by the Investigator to pose a risk to participant safety (eg, second degree atrioventricular block type II)
4. Has documented obstructive coronary artery disease (> 70% stenosis in one or more epicardial coronary arteries) or history of myocardial infarction
5. Has known moderate or severe (as per Investigator*s judgment) aortic valve stenosis at Screening Visit
6. Has hypersensitivity to any of the components of the mavacamten formulation
7. Has participated in a clinical trial in which the participant received any investigational drug (or is currently using an investigational device) within 30 days prior to Screening, or at least 5 times the respective elimination half life (whichever is longer), except for participation in MAVERICK-HCM or EXPLORER-HCM. Prior participation in a noninterventional observational study is
allowed.
8. Has a history of syncope or a history of sustained ventricular

tachyarrhythmia with exercise between Parent Study EOS Visit and

Screening
Visit.
9. Has a history of resuscitated sudden cardiac arrest or known history

of appropriate implantable cardioverter-defibrillator (ICD) discharge for

life-threatening ventricular arrhythmia between Parent Study EOS Visit

and Screening

Visit.
(Note: history of anti-tachycardia pacing (ATP) is
allowed)
10. Currently treated with disopyramide or ranolazine (within 14 days

prior to Screening Visit) or treatment with disopyramide or ranolazine is

planned during the
study
11. Currently treated or planned treatment during the study with a

combination of beta blocker and verapamil or a combination of beta

blocker and
diltiazem
12. Has any acute or serious comorbid condition (eg, major infection or

hematologic, renal, metabolic, gastrointestinal, or endocrine

dysfunction) that, in the judgment of the Investigator, could lead to

premature termination of study participation or interfere with the

measurement or interpretation of the efficacy and safety assessments in

the
study
13. History of clinically significant malignant disease that developed

since enrollment in the Parent
Study
• Participants who have been successfully treated for nonmetastatic

cutaneous squamous cell or basal cell carcinoma or have been

adequately treated for cervical carcinoma in situ or breast ductal

carcinoma in situ (DCIS) can be included in the
study
14. Is unable to comply with the study requirements, including the
number of required visits to the clinical site
15. Is employed by or is a relative of someone employed by MyoKardia,
the Investigator, or his/her staff or family

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-01-2020
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Mavacamten
Generic name:	-

Ethics review

Approved WMO Date:	04-06-2019
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-10-2019
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-04-2020
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	30-11-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-12-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-02-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-02-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	02-08-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	31-10-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	27-01-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-05-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-07-2022
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-03-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-03-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-06-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-06-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2022-502858-14-00
EudraCT	EUCTR2018-004039-64-NL
CCMO	NL70105.028.19
Other	nog niet bekend