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

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Primary Objective* To compare the effect of a 30-week course of mavacamten with placebo on clinical response comprising of exercise capacity and clinical symptoms in participants with symptomatic obstructive hypertrophic cardiomyopathy (oHCM)...

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

Summary

ID

NL-OMON50292

Source
ToetsingOnline

Brief title
MYK-461-005

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: cardiomyopathy, mavacamten

Outcome measures

Primary outcome

* Clinical response defined as achieving (1) an improvement of at least 1.5 mL/kg/min or more in peak oxygen consumption (pVO2) as determined by CPET and a reduction of one or more class in NYHA Functional Classification or 2) an improvement of 3.0 mL/kg/min or more in pVO2 with no worsening in NYHA Functional Class.

Secondary outcome

* Change from baseline to Week 30 in post-exercise LVOT peak gradient
* Proportion of participants with at least 1 class improvement in NYHA functional class from baseline to Week 30
* Change from baseline to Week 30 in peak oxygen consumption (pVO2) as determined by CPET
* Change from baseline to Week 30 in participant-reported health-related quality of life as assessed by the KCCQ score
* Change from baseline to Week 30 in patient-reported severity of HCM symptoms as assessed by the HCM Symptom Questionnaire score

Study description

Background summary

MyoKardia is developing mavacamten, a cardiac myosin modulator, for the treatment of patients with symptomatic oHCM, a condition with significant unmet medical need, with the goals of improving exercise capacity, functional capacity, and symptoms including fatigue and dyspnea. This Phase 3 study is designed to evaluate the safety and efficacy of a 30-week course of mavacamten compared with placebo in participants with symptomatic oHCM.

Study objective

Primary Objective
* To compare the effect of a 30-week course of mavacamten with placebo on clinical response comprising of exercise capacity and clinical symptoms in participants with symptomatic obstructive hypertrophic cardiomyopathy (oHCM)

Secondary Objectives
* To compare the effect of a 30-week course of mavacamten with placebo on symptoms and left ventricular outflow tract (LVOT) obstruction as determined by Doppler echocardiography
* To compare the effect of a 30-week course of mavacamten with placebo on exercise capacity, clinical symptoms and Patient Reported Outcomes individually
* To assess the safety and tolerability of mavacamten
* To assess the pharmacokinetic (PK) characteristics of mavacamten

Study design

This is a Phase 3, double blind, randomized, placebo controlled, multicenter, international, parallel group study to evaluate the safety, tolerability, and efficacy of mavacamten compared with placebo (1:1) in participants with symptomatic oHCM. Approximately 220 participants will be enrolled. This includes ~80 participants (~40 per treatment group) who consent to participate in a CMR substudy at selected sites. Randomization will be stratified according to New York Heart Association (NYHA) functional classification (II or III), current treatment with * blocker (yes or no), planned type of ergometer used during the study (treadmill or exercise bicycle), and consent for the CMR substudy (yes or no). The study will comprise 3 periods as follows:

Screening period (Day -28 to Day -1):
Participants will undergo a variety of general, cardiopulmonary, laboratory, symptom, and PRO assessments over 1 to 2 days in order to assess eligibility (see Table 1 and Table 2). Key Screening tests include electrocardiogram (ECG); transthoracic echocardiography (TTE) conducted at rest, with Valsalva maneuver,

and post-exercise; as well as cardiopulmonary exercise testing (CPET).

Double-blind treatment period (Day 1 [randomization] to Week 30/end of treatment [EOT]):
The double-blind treatment period will include a two-step dose titration scheme designed to achieve safe and effective dosing for each participant based on their own response parameters. Participants who meet all eligibility criteria at Screening will first be randomized via an interactive response system in a 1:1 ratio to receive treatment with mavacamten 5 mg starting dose or matching placebo once daily (QD). Subsequently, assessments including ECG, PK (trough plasma concentrations), and TTE will be performed at each of 7 study visits, beginning at Week 4, and read by core laboratories (see also Safety Monitoring and Study Treatment sections in the Protocol synopsis and Schedule of Study Procedures in the protocol). At Week 8 and Week 14, the dose may be increased, decreased, or remain unchanged based upon results of Week 6 and Week 12 assessments, respectively. At Week 8, the dose may be increased to a maximum daily dose of 10 mg (ie, increase from 5 mg QD to 10 mg QD), and at Week 14 to a maximum daily dose of 15 mg (ie, increase from 10 mg QD to 15 mg QD). Dose increases are designed to be step wise and are not allowed to skip doses (eg, from 5 mg to 15 mg).
At Week 30/EOT, participants will complete CPET and post-exercise TTE. For any participants permanently discontinuing treatment prior to Week 30, an early termination (ET) visit should be conducted as soon as possible, including CPET and post-exercise TTE. Participants with ET will also be encouraged to complete all remaining study visits and assessments, including the Week 30 visit.

Posttreatment follow-up period (Week 30/EOT to Week 38/end of study [EOS]):
When double-blind treatment ends at Week 30, participants will be contacted by phone at Week 34 and return to the site at Week 38 for an EOS visit. At the EOS visit, specified assessments will be repeated. This posttreatment follow-up period applies only to participants who are receiving study drug after Week 22.

Intervention

Participants will receive mavacamten immediate release capsules 5 mg or matching placebo QD for the first 8 weeks of the dosing period with trough PK samples drawn at Week 4, Week 6, and Week 8. If at Week 4 the trough PK is between 700 ng/mL and 1000 ng/mL, the dose will be decreased to 2.5 mg at Week 6.
Otherwise, the dose will be adjusted (increase, decrease, or remain unchanged) at Week 8 based on Week 6 assessments and Week 14 based on Week 12 assessments. The permissible doses after dose adjustment at Week 8 will be 2.5 mg, 5 mg, 10 mg, or placebo. The permissible doses after dose adjustment at Week 14 will be 2.5 mg, 5 mg, 10 mg, 15 mg, or placebo.
For added safety, if 700 ng/mL < Week 8 PK < 1000 ng/mL then an unscheduled visit will be arranged 2 weeks later (Week 10) to reduce dose. After Week 14, assessments will continue every 4 weeks to Week 30/EOT for safety monitoring.

At any time if PK plasma concentration * 1000 ng/mL, then study drug will be temporarily discontinued.

Study burden and risks

BURDEN

See also Schedule of Study Procedures in protocol.

General procedures
ECG: 11x

Cardiopulmonary Assessments
Resting TTE: 11x
Post-exercise stress echocardiography: 4x
CPET: 3x
Cardiac monitoring skin patch: 2x
Accelerometer attached: 2x

Laboratory Assessments
Hepatitis panel and HIV test: 1x
Blood samples: 13x
Urine sample: 3x
Pregnancy test (serum): 1x
Pregnancy test (urine): 11x

Patient-reported Outcome Assessments
HCMSQ: See protocol Schedule of Patient-reported Outcome Assessments
PGIS: See protocol Schedule of Patient-reported Outcome Assessments
PGIC: 8x
WPAI-SHP: 6x
EQ-5D-5L: 6x
KCCQ-23: 6x

RISKS

Events Considered Related to Study Drug
Occurring in 2-10% of Patients Exposed to Mavacamten
* Dizziness
* Ejection fraction decreased (decreased heart function)
* Headache

Occurring in less than 2% of Patients Exposed to Mavacamten
* Asystole (heart arrest)
* Atrial Fibrillation (irregular heart beat)
* Blood creatine phosphokinase abnormal (enzyme found in the heart, skeletal

muscle, and brain)
* Brain natriuretic peptide increased (hormone secreted from brain or heart)
* Cardiac Failure (heart unable to pump sufficiently)
* Cardiac Flutter (abnormal heart rate/rhythm)
* Palpitations (noticeably rapid, strong or irregular heart beat)
* Tachycardia (fast heart rate)
* Electrocardiogram T wave inversion (electric activity of the heart)
* Electrocardiogram QT prolonged (abnormal electric activity of the heart)
* Irregular heart rate
* Diarrhea
* Nausea
* Vomiting
* Abdominal pain
* Chest pain
* Oedema peripheral (swelling)
* Asthenia (weakness)
* Upper respiratory tract infection (viral or bacterial infections of the upper portion of one*s airway, excluding the lungs)
* Muscular weakness
* Presyncope (lightheadedness)
* Lethargy (lack of energy)
* Hypoaesthesia (reduced sense of touch or sensation)
* Vasovagal reaction (fainting)
* Anxiety
* Dyspnea (shortness of breath)
* Dyspnea exertional (shortness of breath during exercise)
* Epistaxis (nose bleed)
* Hypotension (low blood pressure)
* Hypertension (high blood pressure)

Additionally, there have been two side effects causing hospitalization reported in clinical studies with HCM patients.
* One subject who received a single 144mg dose of mavacamten experienced a vasovagal reaction, otherwise known as fainting. A vasovagal reaction occurs when blood pressure drops and/or the heart slows down too much causing the person to lose consciousness. In this case, the subject*s blood pressure dropped and they experienced asystole, meaning the heart stopped for less than 1 minute. The subject*s ejection fraction (amount of blood pumping out of the heart) also decreased. The subject quickly recovered and was discharged the following day in their usual state of health.
* One subject experienced persistent atrial fibrillation, or an irregular heartbeat, requiring hospitalization for the symptoms and then underwent cardioversion. Cardioversion is a medical procedure performed to restore the heart to a normal rhythm. The atrial fibrillation started approximately two weeks after the subject received a 15mg daily dose of mavacamten.

Placebo

If you are receiving placebo there is a possibility that symptoms of your disease may return or get worse.

List of more potential side effects and risks you may experience.

Allergic Reactions
Sometimes people have allergic reactions to drugs. If you have a very bad allergic reaction, you could die. Some things that happen during an allergic reaction that could be a sign or symptom of a life-threatening allergic reaction (anaphylaxis) are:
* a rash
* having a hard time breathing
* wheezing
* a sudden drop in blood pressure (making you feel dizzy or lightheaded)
* swelling around the mouth, throat, or eyes
* a fast pulse
* sweating
You should get medical help and contact the study doctor or study staff if you have any of these or any other side effects during the study.

Other side effects
It is possible that taking the study drug along with your regular medications or supplements may change how the study drug, your regular medications, or your regular supplements work.

Risks of blood draws
Routine needle sticks for blood samples may cause pain, bruising, dizziness and rarely, infection, at the site where blood is drawn.

Risks of ECGs
You may experience some minor irritation from the adhesive (sticky pads) used for the ECG.

Risks of ultrasound for Transthoracic Echocardiogram (TTE)
When ultrasound enters the body, it heats the tissues slightly. Most people don*t notice this heating of the tissues. Even though there are no known risks of ultrasound imaging, the long-term effects of tissue heating are not known. You may experience a coolness from the gel when it is applied as the ultrasound is being taken.

Risks of the Valsalva maneuver
The risks associated with holding your breath for the Valsalva maneuver include fainting due to a low heart rate.

Risks of Exercise Stress Testing and Cardiopulmonary Exercise Testing (CPET)
Cardiopulmonary exercise testing involves stages of increasing physical effort.

Some of the risks associated with this type of testing are abnormal blood pressure, fainting, disorders of heart beat, and in very rare instances, heart attack. During the test, most people just get tired. Some get short of breath or leg pain. Some people get chest pain or discomfort. The mask, the electrodes (sticky pads) on your skin, and the pressure cuff may cause minor skin irritation. Your doctor and study staff will monitor you before and during testing to make sure you are safe. They will stop the test if he or she feels it is not safe to continue. You may stop the test at any time and should tell the doctor and other study staff if you feel very uncomfortable during the test.

Risks of wearing a Medtronic SEEQ Patch
In some people with sensitive skin, the Medtronic SEEQ device may cause skin irritations for people with known allergies or hypersensitivities to adhesives or hydrogel. It may cause mild discomfort, skin irritation, redness, itching, rash, or contact dermatitis in some individuals. The device should be removed if any pain or discomfort occurs. If skin irritation or redness persist after the device has been removed, a topical anti-inflammatory cream may be applied to the area (in consultation with your health care provider). The device is intended for single patient use and should be reapplied if it peels off or is removed.
The Medtronic SEEQ Patch cannot be used in combination with:
* Minute ventilation sensing on implantable devices should be disabled for the duration wearing the SEEQ cardiac patch
* The SEEQ cardiac patch should be removed prior to external defibrillation or an MRI scan.
* The SEEQ patch should not be applied to broken, damaged, or irritated skin
* The SEEQ patch is water resistant but not water waterproof. It should not be submerged in water. Showering is acceptable, but swimming and submersion bathing are prohibited
* No creams or lotions should be applied to the skin immediately prior to the application of the SEEQ patch.
* The SEEQ Patch must be used by individuals who are competent to wear the device during the monitoring period required for the study. If you are unable to do this you will not receive a patch and your participation in the study will end.

Risks of wearing an Accelerometer
You will fasten a wristband accelerometer to one of your arms at certain study visits. The study staff may assist as needed. The purpose of this testing is to collect data to explore the amount and type of physical activity performed before and during treatment with study drug. The wristband will be fastened during screening (at least 11 days before Day 1), and at the visit on Week 26. You will return the accelerometer at the next study visit for data upload and analysis. There is no risk to wearing the accelerometer.

Possible other risks i

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1.Able to understand and comply with the study procedures, understand the risks involved in the study, and provide written informed consent according to federal, local, and institutional guidelines before the first study specific procedure
2.Is at least 18 years old at Screening
3.Body weight is greater than 45 kg at Screening
4.Has adequate acoustic windows to enable accurate TTEs
5.Diagnosed with oHCM consistent with current AACF/AMA and ESC, ie, satisfy both criteria below (criteria

to be documented by the echocardiography core laboratory):
A.Has unexplained left ventricular (LV) hypertrophy with nondilated ventricular chambers in the absence of other cardiac (eg, hypertension, aortic stenosis) or systemic disease and with maximal LV wall thickness *15 mm (or *13 mm with positive family history of hypertrophic cardiomyopathy [HCM]), as determined by core lab interpretation and
B.Has LVOT peak gradient *50 mmHg during Screening as assessed by echocardiography at rest, after Valsalva maneuver, or postexercise (confirmed by echocardiography core laboratory interpretation)
6.Has documented left ventricular ejection fraction (LVEF) *55% by echocardiography core laboratory read of Screening TTE at rest
7. Has LVOT gradient with Valsalva maneuver at screening TTE of *30mmHg, determined by echocardiography core laboratory.
8.Has New York Heart Association (NYHA) functional Class II or III symptoms at Screening
9.Has documented oxygen saturation at rest *90% at Screening
10.Is able to perform an upright CPET and has a respiratory exchange ratio (RER) *1.0 at Screening per central reading; if the RER is between 0.91 and 1.0, the participant may be enrolled only if it is determined by the central CPET laboratory that peak exercise has been achieved in the subject (the only permitted reasons for subpeak performance are [1] a decrease in systolic blood pressure or [2] severe angina as described in the CPET Laboratory Manual)
11.Female participants must not be pregnant or lactating and, if sexually active, must be using one of the following highly effective birth control methods from the Screening visit through 3 months 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 levels are in the postmenopausal range
Male partners must also use a contraceptive (eg barrier, condom or vasectomy)

Exclusion criteria

1.Previously participated in a clinical study with mavacamten

2.Hypersensitivity to any of the components of the mavacamten formulation
3.Participated in a clinical trial in which the participant received any investigational drug (or is currently using an investigational device) within 30 days of Screening, or at least 5x the respective elimination half life (whichever is longer)
4.Infiltrative or storage disorder causing CH that mimics oHCM, such as Fabry disease, amyloidosis, or Noonan syndrome with LVH
5.Medical condition that precludes upright exercise stress testing
6.History of syncope within 6 months prior to Screening or history of sustained VT with exercise within 6 months prior
to Screening
7.History of resuscitated sudden CA (at any time) or history of appropriate ICD discharge/shock for life-threatening VA within 6 months prior to Screening
8.Has paroxysmal, intermittent AF with AF present per the investigator's evaluation of the participant's ECG at time of Screening
9.Has persistent/permanent AF not on anticoagulation for at least 4 weeks to Screening &/or not adequately rate controlled within 6 months prior to Screening
10.Current treatment (within 14 days to Screening) or planned treatment during the study with disopyramide or ranolazine
11.Current treatment (within 14 days prior to Screening) or planned treatment during the study with a combination of *-blockers and verapamil or a combination of *-blockers and diltiazem
12.Individuals on *-blockers, verapamil, or diltiazem, any dose adjustment of that medication <14 days to Screening or any anticipated change in treatment regimen using these medications during the study
13.Successfully treated with ISR (surgical myectomy or percutaneous alcohol septal ablation [ASA]) within 6 months prior to Screening or plans to have either of these treatments during the study
14.ICD placement or pulse generator change whithin 2 months prior to Screening or planned new ICD placement during study
15.Has QT interval with Fridericia correction (QTcF) >500 ms at screening or other
ECG abnormality considered by investigator to pose risk to participant safety (eg, second-degree atrioventricular block type II)
16.Documented OCAD (>70% stenosis in one or more epicardial coronary arteries) or history of MI
17.Moderate or severe (as per investigator's judgment) AVS at Screening
18.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 & safety assessments in the study

19.Has pulmonary disease that limits exercise capacity or systemic arterial oxygen saturation
20.History of malignant disease within 10 years of
Screening:
21.Has safety laboratory parameters (chemistry, hematology, coagulation, & urinalysis) outside normal limits (according to the central laboratory reference range) at Screening as assessed by the central laboratory; however, participant with safety laboratory parameters outside normal limits may be included if he or she meets all of the following criteria:
*Safety laboratory parameter outside normal limits is considered by the investigator to be clinically not significant
*If there is an alanine aminotransferase or aspartate aminotransferase result, the value must be <3 × the upper limit of the laboratory reference range
*Body size*adjusted estimated glomerular filtration rate is *30 mL/min/1.73 m2
22.Positive serologic test at Screening for infection with human immunodeficiency virus, hepatitis C virus, or hepatitis B virus
23.History or evidence of any clinically significant disorder, condition, or disease that, in the opinion of the investigator, would pose a risk to participant safety or interfere with the study evaluation, procedures, or completion
24.Currently taking, or has taken within 14 days prior to Screening, a prohibited medication, such as a cytochrome P450 (CYP) 2C19 inhibitor (eg, omeprazole or esomeprazole), a strong CYP 3A4 inhibitor, or St. John's Wort. Alternatives, such as pantoprazole, are allowed and may be discussed with the medical monitor.
25.Prior treatment with cardiotoxic agents such as doxorubicin or similar.
26.Unable to comply with the study requirements, including the number of required visits to the clinical site
27.First degree relative of personnel directly affiliated with the study at the clinical study site, any study vendor, or the study Sponsor

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel

Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	11-03-2019
Enrollment:	12
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	09-08-2018
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-12-2018
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	27-02-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-03-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Approved WMO Date:	15-07-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-07-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-03-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-03-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-05-2020
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
EudraCT	EUCTR2017-002530-23-NL

Register	ID
ClinicalTrials.gov	NCT03470545
CCMO	NL65999.028.18

Study results

Date completed: 20-04-2020

Results posted: 12-01-2021

First publication
11-11-2020