A Randomized, Double-blind, Placebo-controlled Clinical Study to Evaluate Mavacamten in Adults with Symptomatic Non-obstructive Hypertrophic Cardiomyopathy

Published: 21-11-2022
Last updated: 05-10-2024

This study has been transitioned to CTIS with ID 2023-506352-24-00 check the CTIS register for the current data. Primary Objectives: • To assess the efficacy of a 48-week course of mavacamten compared to placebo on patient- reported health status (...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Congenital cardiac disorders
Study type	Interventional

Summary

ID

NL-OMON56426

Source
ToetsingOnline

Brief title
Mavacamten in non-obstructive HCM

Condition

- Congenital cardiac disorders
- Cardiac and vascular disorders congenital

Synonym
Symptomatic hardening of the left ventricle, Symptomatic Nonobstructive Hypertrophic Cardiomyopathy

Research involving

Human

Sponsors and support

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

Intervention

Keyword: Symptomatic Nonobstructive Hypertrophic Cardiomyopathy

Outcome measures

Primary outcome

Primary endpoints:

• Change from baseline in KCCQ-23 CSS at Week 48

• Change from baseline in pVO2 at Week 48

Secondary outcome

Secundary endpoints:

• Change from baseline in VE/VCO2 slope to Week 48

• Proportion of participants with at least 1 class of NYHA improvement from baseline to Week 48

• Proportion of participants with (1) pVO2 >= 1.5 mL/kg/min and NYHA improvement >= 1; or (2) pVO2 >= 3 mL/kg/min and NYHA no worsening, from baseline to Week 48

• Change from baseline in NT-proBNP to Week 48

• Change from baseline in cTn-T to Week 48

• Change from baseline in HCMSQ-SoB domain to Week 48

• Time to first MACE-plus events defined as any CV death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure, or

hospitalization for arrhythmias or appropriate ICF therapy

Study description

Background summary

The efficacy of medications commonly used to treat symptomatic patients with nHCM (beta blockers, verapamil, and diltiazem) can be limited by side effects and bradycardia. Accordingly, safer and more effective treatments to reduce symptoms and increase functional capacity for patients with nHCM have been identified as unmet medical needs by the recent American College of Cardiology/American Heart Association (ACC/AHA) Joint Committee on Clinical Practice Guidelines. The Sponsor believes mavacamten has the potential to meet this unmet need. In contrast to currently available therapies, mavacamten is a first-in-class, selective, and reversible modulator of cardiac myosin that targets the underlying pathophysiology of the disease.
Dyspnea and fatigue are the most common symptoms reported by patients with nHCM. Dyspnea associated with nHCM can be attributed to reduced LV compliance characteristic of HCM. The formation of an excessive number of myosin-actin crossbridges that persist during diastole in patients with HCM decreases diastolic compliance. Reduced LV compliance increases left ventricular filling pressure (LVFP) which increases LA pressure causing exudation of fluid into pulmonary tissue. The accumulated pulmonary fluid causes dyspnea, especially with exertion. Mavacamten can reduce dyspnea by increasing LV compliance through reducing the number of crossbridges that persist during diastole. Increased LV compliance reduces the increased LVFP that causes dyspnea.
Beta blockers and non-dihydropyridine calcium channel blockers are often used to treat patients with symptomatic nHCM but unlike mavacamten, neither targets the abnormal crossbridge formation that underlies the disease. Therapy with these drugs can be limited by adverse reactions.
Data from clinical studies with mavacamten suggest that mavacamten could provide a safe potential treatment option to reduce symptoms and improve exercise capacity in patients with nHCM.

Study objective

This study has been transitioned to CTIS with ID 2023-506352-24-00 check the CTIS register for the current data.

Primary Objectives:
• To assess the efficacy of a 48-week course of mavacamten compared to placebo on patient- reported health status (symptoms and physical limitations)
• To assess the efficacy of a 48-week course of mavacamten compared to placebo on exercise capacity

Secundary Objectives:
• Evaluate the effects of mavacamten on exercise capacity as measured by VE/VCO2
• Evaluate the effects of mavacamten on NYHA classification
• Evaluate the effects of mavacamten on the composite of NYHA and pVO2
• Evaluate the effects of mavacamten on cardiac biomarkers of wall stress
• Evaluate the effects of mavacamten on cardiac biomarkers of myocardial injury
• Evaluate the effects of mavacamten on patient- reported shortness of breath
• Evaluate the effects of mavacamten on composite of cardiovascular events

Study design

CV027031 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 in participants with symptomatic nHCM. The study will randomize approximately 420 participants at 180 sites in a 1:1 ratio to mavacamten and placebo. Randomization will be stratified by New York Heart Association (NYHA) class (II or III), type of exercise (treadmill or exercise bicycle), region (Asia, North America, Europe, and Rest of the World), and beta blocker use at baseline (Yes/No). All participants are planned to be on double-blind study treatment from the time the first participant is randomized until the last randomized participant completes 48 weeks of study treatment. To participate in the study, participants must have: 1) New York Heart Association (NYHA) Functional Classification II or III and Kansas City Cardiomyopathy Questionnaire-23 Clinical Summary Score (KCCQ-23 CSS) <= 80 2) Increased cardiac wall stress (increased N-terminal pro B-type natriuretic peptide/B-type natriuretic peptide according to thresholds specified in the protocol) 3) Cardiac wall thickness >= 15 mm (or >= 13 mm if family history) 4) Left ventricular ejection fraction (LVEF) >= 60% 5) Left ventricular diastolic dysfunction (E/e* > 14 OR left atrial volume index > 34 mL/m2) OR myocardial damage as indicated by elevated cardiac troponin > 99th percentile of the upper limit of normal of the assay used by the analyzing laboratory 6) Left ventricular outflow tract gradient < 30 mm Hg at rest and < 50 mm Hg after provocation (Valsalva and post exercise). Cardiac medications cannot be initiated, discontinued, or dose adjusted within 2 weeks prior to screening and up to the day of randomization. At Week 48 after study treatment, the effects of mavacamten compared to placebo on health status (symptoms and physical limitations) will be assessed by change from baseline in KCCQ-23 CSS and the effect on exercise capacity by change from baseline in peak oxygen consumption (pVO2). The 2 primary endpoints were selected to assess the symptoms and functional limitation reported most frequently as troublesome by participants with nHCM: exertional dyspnea, fatigue, and limited exercise capacity.

Intervention

Study Intervention for CV027031
Medication
Potency IP/Non-IP/AxMP
Mavacamten 1 mg, 2.5 mg, 5 mg, 10 mg, and
15
mg IP
PBO matching mavacamten oral capsule
NA IP

Study burden and risks

Overall, the benefit/risk profile of mavacamten is positive and warrants further evaluation in the population of nHCM that carries a high unmet medical need. This study has been designed with appropriate measures in place to monitor and minimize any potential health risks to participating patients. Taking into account the clinical experience with mavacamten to date and the extent of monitoring and precautions included in the study protocol, participation in this study should represent an acceptable risk to patients who meet the inclusion/exclusion criteria and consent to participate in the study.
An independent Data Monitoring Committee (DMC) will be responsible for safeguarding the interests of the study participants by reviewing safety data throughout the study. The DMC and Sponsor will evaluate the risk/benefit profile of the study on an ongoing basis. This evaluation will be based on all available data, with particular attention to: (i) AEs or other safety trends in this or any other clinical study of BMS-986427 whose character, severity, and/or frequency suggest that participants would be exposed to an unreasonable and significant risk of illness or injury; (ii) new data suggesting unreasonable and significant risk of illness or injury.
If such evaluation suggests that the risk/benefit profile of the study has become unfavorable to participants, the Sponsor will pause enrollment and/or treatment until further evaluation of data, and interaction with the appropriate Health Authority(ies) can take place on potential actions. Such actions may include (but are not limited to) study continuation, substantial amendment, or termination of the study.

Contacts

Public

Myokardia, Inc.

Sierra Point Parkway 1000
Brisbane, CA 94005

US
Scientific
Myokardia, Inc.

Sierra Point Parkway 1000
Brisbane, CA 94005
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Participants must be at least 18 years old or local age of majority at the time of signing the informed consent 2. Female participants must adhere to highly effective contraceptive methods or have documented proof that they are not of childbearing potential 3. No additional contraceptive measures are required to be used for male participants 4. Diagnosis of HCM consistent with current American College of Cardiology Foundation/American Heart Association and European Society of Cardiology guidelines. 5. Peak LVOT pressure gradient < 30 mmHg at rest and < 50 mmHg with provocation (Valsalva maneuver and stress echocardiography) 6. CPET: Documented oxygen saturation at rest >90% at Screening. Able to perform an upright cardiopulmonary stress test (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 if the central CPET laboratory determines that peak exercise has been achieved. Participants with subpeak performance may not be enrolled as described in the CPET Laboratory Manual. 7. New York Heart Association (NYHA) Class II or III 8. NT-proBNP>=200 pg/mL or BNP>=70 pg/mL 9. LVEF >=60 % as determined by the echocardiography central laboratory 10. KCCQ-23 CSS Score <= 85 at screening

Exclusion criteria

Medical Conditions - Known infiltrative or storage disorder causing cardiac hypertrophy that mimics nHCM such as Fabry disease, amyloidosis, or Noonan syndrome with LV hypertrophy
Note: Investigators should not screen participants who have comprehensive Echo features suggestive of amyloidosis, including
abnormal global longitudinal strain in the setting of an appropriate clinical picture which could include low voltage on ECG and severely elevated NT-proBNP or BNP
- History of unexplained syncope within 6 months prior to screening - History of sustained ventricular tachyarrhythmia (> 30 seconds) within 6 months prior to Screening - Paroxysmal or persistent (non-permanent) AF detected at the time of screening. Permanent AF is allowed if the participant is anticoagulated and the investigator considers the heart rate adequately controlled - CV diseases or treatments that in the opinion of the investigator increase the unpredictability of or change the participants' clinical course. - Acute heart failure from 4 weeks prior to screening up to randomization - Coronary artery disease requiring intervention, including myocardial infarction (increase in cardiac enzymes in combination with symptoms of ischemia or new ischemic ECG changes), coronary artery bypass graft surgery, or other major CV surgery, stroke, or transient ischemic attack in the past 90 days - Women who are breastfeeding or pregnant. Prior/Concomitant Therapy - Any adjustments of beta-blockers, verapamil, or diltiazem within 2 weeks prior to Screening and up to the day of randomization - Concomitant use of strong inhibitors of cytochrome P450 (CYP) 2C19 Note: Use should be discontinued for a minimum of 5 elimination half-lives prior to first dose of study intervention. Other Exclusion Criteria - Any other serious condition that in the opinion of the investigator could prevent participation in the study and follow-up, including active infection with COVID-19 from 4 weeks prior to screening up to randomization - Completed a study with an investigational device < 30 days prior to screening or an investigational drug <5 half-lives prior to screening
- Participants who have completed a study with mavacamten or aficamten
--Enrolled in another study and receiving any investigational treatment (device or drug) other than the study intervention given in this study

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:	Recruiting
Start date (anticipated):	31-08-2023
Enrollment:	31
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Mavacamten
Generic name:	Mavacamten

Ethics review

Approved WMO Date:	21-11-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-06-2023
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-07-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-07-2023

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-08-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-10-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-12-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-12-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-01-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	CTIS2023-506352-24-00
EudraCT	EUCTR2021-005329-26-NL
ClinicalTrials.gov	NCT05582395
CCMO	NL82368.091.22