A Phase 3, Multi-Center, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy and Safety of CK-3773274 in Adults with Symptomatic Hypertrophic Cardiomyopathy and Left Ventricular Outflow Tract Obstruction

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Primary• To evaluate the effect of CK-3773274 on exercise capacity (VO2) in patients with symptomatic oHCMSecondary• To evaluate the effect of CK-3773274 on patient health status• To evaluate the effect of CK-3773274 on New York Heart Association (...

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

Summary

ID

NL-OMON54001

Source
ToetsingOnline

Brief title
Cytokinetics CY 6031

Condition

- Congenital cardiac disorders

Synonym
Hypertrophic cardiomyopathy and Left Ventricular Outflow Tract Obstruction; thickened heart muscle

Research involving
Human

Sponsors and support

Primary sponsor: Cytokinetics, Inc
Source(s) of monetary or material Support: The study sponsor as listed in question B6/B7

Intervention

Keyword: CK-3773274, Double blind/placebo, Hypertrophic cardiomyopathy / Left Ventricular Outflow Tract Obstruction, Phase 3

Outcome measures

Primary outcome

The primary endpoint of the study is change in pVO2 by CPET from baseline to

Week 24.

Secondary outcome

• Change in Kansas City Cardiomyopathy Questionnaire - Clinical Summary Score

(KCCQ-CSS) from baseline to Week 12 and Week 24

• Proportion of patients with >=1 class improvement in NYHA Functional Class

from baseline to Week 12 and Week 24

• Change in post-Valsalva LVOT-G from baseline to Week 12 and Week 24

• Proportion of patients with post-Valsalva LVOT-G <30 mmHg at Week 12 and Week

24

• Change in total workload during CPET from baseline to Week 24

Study description

Background summary

CK-3773274, a small molecule allosteric inhibitor of cardiac myosin, is being developed as a chronic oral treatment for patients with HCM. CK-3773274 is designed to reduce the hypercontractility that underlies the pathophysiology of HCM in the cardiac sarcomere. The intended pharmacologic effect is reduction in force produced by the cardiac sarcomere resulting in less LVOT obstruction and improved diastolic function in patients with oHCM.
CK-3773274 has been studied in a Phase 1 study of healthy adult participants and a Phase 2 study of patients with oHCM. This Phase 3 trial will assess the efficacy and safety of CK-3773274 in patients with oHCM.

Study objective

Primary
• To evaluate the effect of CK-3773274 on exercise capacity (VO2) in patients with symptomatic oHCM

Secondary
• To evaluate the effect of CK-3773274 on patient health status
• To evaluate the effect of CK-3773274 on New York Heart Association (NYHA) Functional Classification
• To evaluate the effect of CK-3773274 on post-Valsalva left ventricular outflow tract gradients (LVOT-G)
• To evaluate the effect of CK-3773274 on exercise capacity(total workload)
• To evaluate the effect of CK-3773274 on duration of eligibility for septal reduction therapy

Safety
• To evaluate the safety and tolerability profile of CK-3773274 in patients with symptomatic oHCM

For exploratory objectives, please refer to the protocol.

Study design

This is a Phase 3, randomized, placebo-controlled, double-blind, multi-center trial in patients with symptomatic oHCM. Approximately 270 eligible patients will be randomized in a 1:1 ratio to receive CK-3773274 or placebo.
IP will be administered orally once daily with or without food. IP doses will be individually titrated. The primary endpoint of pVO2 will be measured by CPET at screening and at end of treatment (Week 24). If applicable, patients will continue taking background HCM medications consistent with regional clinical practice guidelines during the trial.

Intervention

Subjects will receive CK-3773274 or placebo. CK-3773274 is administered as an

oral 5 mg tablet at doses of 5-20 mg per day.

Study burden and risks

Risks and side effects observed with CK-3773274
CK-3773274 has the potential to reduce heart pumping function too much. This has been observed in a few study subjects with no other side effect and improved after the study medicine dose was reduced or discontinued. Since CK-3773274 is a research medicine, there may be other risks that are unknown. All medicines have the potential risk of an allergic reaction, which if not treated promptly, could become life threatening.

Risks from study procedures
Risks and discomforts that subjects may experience from the study procedures include:

Electrocardiogram (ECG):
Occasionally there may be some minor skin irritation from the adhesive tabs of the wire electrodes.

Echocardiogram:
The technician will spread gel on the subject*s chest and then press a device known as a transducer firmly against the skin. The subject may feel some mild discomfort during the process.

Cardiopulmonary exercise test (CPET):
As during any moderate exercise, the subject will become tired and short of breath; this is normal. It is likely that the subject*s heart rate and blood pressure will increase during exercise. In rare instances, abnormal changes may occur such as fainting, irregular heartbeat and low blood pressure. In very rare instances heart attack may occur as in any other strenuous activity. Every effort will be made to minimize any possible risks by constant monitoring of heart rate, heart rhythm and blood pressure. Trained medical personnel provide surveillance during testing and may stop the test at any time. Trained medical personnel and equipment are available to deal with unusual situations, should they arise.

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

Males and females between 18 and 85 years of age, inclusive, at screening.
• Body mass index <35 kg/m^2.
• Diagnosed with HCM per the following criteria: * Has LV hypertrophy and non-dilated LV chamber in the absence of other cardiac disease and
* Has an end-diastolic LV wall thickness as measured by the echocardiography core laboratory of: • >=15 mm in one or more myocardial segments OR
• >=13 mm in one or more wall segments and a known-disease-causing gene mutation or positive family history of HCM
• Has resting LVOT-G >=30 mmHg and post-Valsalva LVOT G >=50 mmHg during screening as determined by the echocardiography core laboratory.
• LVEF >=60% at screening as determined by the echocardiography core laboratory.
• NYHA Functional Class II or III at screening.
• Hemoglobin >=10g/dL at screening.
• Respiratory exchange ratio (RER) >=1.05 and pVO2 <=90% predicted on the screening CPET per the core laboratory.
• Patients on beta-blockers, verapamil, diltiazem, or disopyramide should have been on stable doses for >6 weeks prior to randomization and anticipate remaining on the same medication regimen during the trial. Patients treated with disopyramide must also be concomitantly treated with a beta blocker and/or

calcium channel blocker

Exclusion criteria

• Known or suspected infiltrative, genetic or storage disorder causing cardiac hypertrophy that mimics oHCM (eg, Noonan syndrome, Fabry disease, amyloidosis).
• Significant valvular heart disease (per investigator judgment).
* Moderate-severe valvular aortic stenosis.
* Moderate-severe mitral regurgitation not due to systolic anterior motion of the mitral valve.
• History of LV systolic dysfunction (LVEF <45%) or stress cardiomyopathy at any time during their clinical course.
• Inability to exercise on a treadmill or bicycle (eg, orthopedic limitations).
• Has been treated with septal reduction therapy (surgical myectomy or percutaneous alcohol septal ablation) or has plans for either treatment during the trial period.
• Documented paroxysmal atrial fibrillation during the screening period.
• Paroxysmal or permanent atrial fibrillation requiring is only excluded IF:
- rhythm restoring treatment (eg, direct-current cardioversion, atrial fibrillation ablation procedure, or antiarrhythmic therapy) has been required <=6 months prior to screening. (This exclusion does not apply if atrial fibrillation has been treated with anticoagulation and adequately rate-controlled for >6 months.)
-rate control and anticoagulation have not been achieved for at least 6 months prior to screening
• History of syncope or sustained ventricular tachyarrhythmia with exercise within 6 months prior to screening.
• Has received prior treatment with CK-3773274 or mavacamten.
Exclusion Criteria for CMR sub-study
• Inability to tolerate CMR.
• Has an implantable cardioverter-defibrillator (ICD).
• Has a cardiac pacemaker.

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:	Recruitment stopped
Start date (anticipated):	04-01-2023
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Not applicable
Generic name:	aficamten

Ethics review

Approved WMO Date:	22-03-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-07-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-03-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-04-2023
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-12-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-12-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2021-003536-92-NL
ClinicalTrials.gov	NCT05186818
CCMO	NL79139.078.22