A multi-center, randomized, double-blind, placebo-controlled, dose-finding study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of CK-3773274 in adults with symptomatic hypertrophic cardiomyopathy

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Primary objectives:To determine the safety and tolerability of CK-3773274 in patients with symptomatic HCMSecondary objectives:- To describe the concentration-response relationship of CK-3773274 on the resting and post-Valsalva LVOT-G on...

Ethical review	Approved WMO
Status	Pending
Health condition type	Myocardial disorders
Study type	Interventional

Summary

ID

NL-OMON52672

Source
ToetsingOnline

Brief title
0771/0032 (Cytokinetics CY 6021)

Condition

- Myocardial disorders

Synonym
Hypertrophic Cardiomyopathy; 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: CK3773274, Double blind/placebo, Hypertrophic Cardiomyopathy, Phase 2

Outcome measures

Primary outcome

- Patient incidence of reported adverse events (AEs)

- Patient incidence of reported serious adverse events (SAEs)

- Patient incidence of left ventricular ejection fraction (LVEF) <50%

Secondary outcome

- Slope of the relationship of the plasma concentration of CK-3773274 to the

change from baseline in the resting LVOT-G

- Slope of the relationship of the plasma concentration of CK-3773274 to the

change from baseline in the post-Valsalva LVOT-G

- Change from baseline in resting and post-Valsalva LVOT-G over time as a

function of dose

- Change from baseline in resting and post-Valsalva LVOT-G to Week 10

- Slope of the relationship of the plasma concentration of CK-3773274 to the

change from baseline in the resting LVEF

- Observed maximum plasma concentration (Cmax) and trough plasma concentration

(Ctrough) for CK-3773274 during dosing

Study description

Background summary

This is the first patient study of CK-3773274, a small molecule, allosteric inhibitor of cardiac myosin being developed as a chronic oral treatment for patients with hypertrophic cardiomyopathy (HCM).

Hypertrophic Cardiomyopathy
HCM results from pathogenic genetic mutations, often affecting the genes encoding the proteins of the cardiac sarcomere, such as myosin (Maron B J 2018). Histologic features include myofibrillar disarray, myocyte hypertrophy and interstitial fibrosis. Clinically, HCM is characterized by left ventricular (LV) hypertrophy unexplained by loading conditions and a nondilated LV with preserved or increased ejection fraction (Gersh 2011). Imaging studies of patients with HCM show hypertrophied LV walls, enhanced ventricular contractility, normal end-diastolic LV volume, reduced end-systolic volume, impaired diastolic compliance and often left atrial enlargement (Marian 2017). From population-based insurance claims and national health system data, the prevalence of clinically identified individuals with HCM in the US and EU is approximately 1:2000 and 1:3195 (Maron M S 2016; Husser 2018; Magnusson 2017; Pujades-Rodriguez 2018).

Approximately 70% of patients with phenotypic HCM will demonstrate an element of LVOT obstruction (Maron M S 2006). The mechanisms for developing obstruction are well defined and involve a complex interplay between alterations in ventricular flow between asymmetric septal hypertrophy and the mitral valve leaflets. The result is abnormal systolic contact with the mitral valve leaflets (most commonly the anterior leaflet) and the development of an LVOT gradient (LVOT-G). By nature, oHCM is a dynamic condition with variable systolic gradients. In the setting of reduced afterload or reduced preload, symptoms change depending on the gradient and often worsen during exertion. Additional clinical manifestations of HCM include an elevated risk for ventricular fibrillation and sudden cardiac death; heart failure syndrome due to diastolic dysfunction; chest pain due to microvascular ischemia; palpitations and stroke due to atrial fibrillation; syncope and presyncope due to either ventricular arrhythmias or an abnormal blood pressure response to exercise; and, in a minority of patients, progression to systolic heart failure.

Contemporary management strategies for oHCM have resulted in the majority of patients achieving normal or near-normal longevity and improved morbidity; however, there has been little progress with the development of novel pharmacotherapies. Current medical treatment consists of beta-blockers, verapamil, diltiazem and disopyramide as recommended in the 2014 European Society of Cardiology and in the 2011 American College of Cardiology Foundation

/ American Heart Association guidelines for the diagnosis and management of HCM. For patients with advanced symptomatic disease unresponsive to medications, septal reduction therapies (surgical myectomy or percutaneous alcohol ablation of the septum) can provide effective LVOT-G reduction (Elliott 2014; Gersh 2011; Ponikowski 2016). A subgroup of patients, who have been resuscitated from sudden cardiac death or who are at risk of sudden cardiac death, may undergo placement of an implantable cardioverter defibrillator (ICD) (Kristensen 2014). For those patients with HCM with end-stage disease who have both significant systolic impairment and diastolic dysfunction, cardiac transplantation may be the only treatment option (Gersh 2011). Disease-related mortality is most often attributable to sudden cardiac death, heart failure, and embolic stroke.

The remaining 30% of patients with HCM do not have LVOT obstruction, either at rest or with physiologic provocation (ie Valsalva maneuver or exercise) and are categorized as nHCM. Of note, patients with nHCM experience a higher burden of life-threatening ventricular arrhythmias (sustained ventricular tachycardia or ventricular fibrillation) compared to patients with resting or latent obstruction but have a similar risk of developing heart failure and all-cause mortality compared to patients with resting oHCM. Treatment options for patients with nHCM are limited and while there may be some benefit of beta-blockers and calcium channel blockers, the evidence for these therapies is minimal. Patients with severe heart failure symptoms may require heart transplantation.

Mutations in over a dozen genes encoding sarcomere-associated proteins cause HCM. MYH7 and MYBPC3, encoding β-myosin heavy chain and myosin-binding protein C, respectively, are the two most common genes involved, together accounting for approximately 50% of the HCM families (Elliott 2014). Mechanistically, mutations in HCM appear to increase the net power generation in the sarcomere in vitro (Chuan 2012; Sommese 2013; Spudich 2016; Toepfer 2019). The findings in these studies are consistent with the underlying myocardial pathophysiology of the LV in patients with HCM being hypercontractile with diminished compliance (Wilson 1967).

These nonclinical investigations have enhanced our understanding of the molecular pathogenesis of HCM and have stimulated efforts designed to identify cardiac myosin modulators that can target the underlying mechanism of hypercontractility in obstructive HCM.

CK3773274
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 that seems to drive the disease, improving diastolic function and also reducing LVOT obstruction in those

patients with oHCM.

CK-3773274 has been studied in a Phase 1 study of healthy adult participants. This Phase 2 study will be the first investigation of CK-3773274 in patients with HCM.

Study objective

Primary objectives:
To determine the safety and tolerability of CK-3773274 in patients with symptomatic HCM

Secondary objectives:
- To describe the concentration-response relationship of CK-3773274 on the resting and post-Valsalva LVOT-G on echocardiogram over 10 weeks of treatment in patients with oHCM (Cohorts 1, 2, 3 only)
- To describe the dose response relationship on LVOT-G (resting and Valsalva) of CK-3773274 in patients with symptomatic oHCM (Cohorts 1, 2, 3 only)
- To evaluate the concentration-response relationship of CK-3773274 on resting left ventricular ejection fraction (LVEF) over 10 weeks of treatment in patients with HCM.
- To evaluate the plasma concentrations of CK-3773274 in patients with HCM

For exploratory objectives refer to the protocol.

Study design

This is a Phase 2, multi-center, dose finding study in patients with symptomatic HCM. Four sequential cohorts will be enrolled. The first two cohorts will enroll patients with oHCM randomized 2:1 to CK-3773274 or placebo. Patients in Cohorts 1 and 2 will receive up to three escalating doses of CK-3773274 or placebo based on echocardiographic guidance. Cohort 3 will enroll patients with oHCM whose background HCM therapy includes disopyramide (patients on disopyramide are excluded from Cohorts 1, 2, and 4). Cohort 4 will enroll patients with nHCM. In the third and fourth cohorts, all patients will be assigned CK-3773274 and will receive up to three escalating doses of CK-3773274 based on echocardiographic guidance. Overall, the treatment duration will be 10 weeks with a 4-week follow-up period after the last dose.

Intervention

In Cohorts 1 and 2, subjects will receive CK-3773274 or placebo. In Cohorts 3 and 4, subjects will receive CK-3773274. CK-3773274 is administered as an oral tablet at doses of 5-30 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:

Heart Monitoring Device:
An ambulatory monitoring device (about the size of a deck of cards) will be used to monitor your heartbeat. The small device attaches to your chest with an adhesive bandage. You may be asked to shave a part of your chest prior to placing the device, which may cause irritation. In rare instances, the adhesive bandage may cause skin irritation. Also, wearing the device may be uncomfortable, such as during sleep. You may take a shower while wearing the device.

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.

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 at Screening.
Body weight is >=45 kg at Screening.
Diagnosed with HCM per the following criteria:
• Has LV hypertrophy with non-dilated LV chamber in the absence of other cardiac disease.
• Has minimal wall thickness >=15 mm (minimal wall thickness >=13 mm is acceptable with a positive family history of HCM or with a known disease-causing gene mutation).
Adequate acoustic windows for echocardiography.

For Cohorts 1,2 and 3 has LVOT-G during screening as follows:
• Resting gradient >=50 mmHg
OR
• Resting gradient >=30 mmHg and <50 mmHg with post-Valsalva LVOT G >=50 mmHg
LVEF >=60% at screening.
New York Heart Association (NYHA) Class II or III at Screening.
Patients on beta-blockers, verapamil, diltiazem, or ranolazine should have been on stable doses for >4 weeks prior to Randomization and anticipate remaining on the same medication regimen during the study.
For Cohort 3: Patients must be taking disopyramide. Patients should have been on stable disopyramide doses for >4 weeks prior to screening and anticipate remaining on the same medication regimen during the study.
For Cohort 4 has resting and post-Valsalva LVOT-G <30 mmHg at the time of screening.
For Cohort 4 has elevated NT-proBNP >300 pg/mL at the time of screening.

A full listing can be found in Protocol section 5.

Exclusion criteria

- Aortic stenosis or fixed subaortic obstruction.
- Known infiltrative or storage disorder causing cardiac hypertrophy that mimics HCM (eg, Noonan syndrome, Fabry disease, amyloidosis).
- History of LV systolic dysfunction (LVEF <45%) at any time during their clinical course.
- Documented history of current obstructive coronary artery disease (>70% stenosis in one or more epicardial coronary arteries) or documented history of myocardial infarction.
- Has been treated with septal reduction therapy (surgical myectomy or percutaneous alcohol septal ablation) or has plans for either treatment during the study period (Cohorts 1, 2, and 3 only). Patients having undergone septal reduction therapy > 12 months prior to screening who remain symptomatic from nHCM, and who meet all other criteria for inclusion, may be enrolled in Cohort 4.
- For Cohorts 1, 2 and 4: Has been treated with disopyramide or antiarrhythmic drugs that have negative inotropic activity within 4 weeks prior to screening. For Cohort 3, use of disopyramide is required.
- Paroxysmal atrial fibrillation or flutter documented during the Screening period.
- Paroxysmal or permanent atrial fibrillation requiring rhythm restoring treatment (eg, direct-current cardioversion, ablation procedure, or antiarrhythmic therapy) <=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.)
- History of syncope or sustained ventricular tachyarrhythmia with exercise within 6 months prior to Screening.
- Has received prior treatment with CK3773274 or is currently receiving mavacamten.
- For Cohort 4: has any documented history of LVOT-G >= 30 mmHg at rest, with Valsalva, or with exercise (for subjects who have had prior septal reduction therapy, this exclusion criteria only applies to gradients detected following septal reduction therapy).

Study design

Design

Study phase: 2

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	17-06-2022
Enrollment:	6
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	CK-3773274
Generic name:	CK-3773274

Ethics review

Approved WMO Date:	20-01-2020
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-05-2020
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-12-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	11-01-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-04-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-08-2022
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	EUCTR2019-002785-12-NL
CCMO	NL71785.078.19

Study results

Results posted: 30-01-2024

First publication
20-11-2023