A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Assess the Effect of Omecamtiv Mecarbil on Exercise Capacity in Subjects with Heart Failure with Reduced Ejection Fraction and Decreased Exercise Tolerance

Published: 27-03-2019
Last updated: 12-04-2024

Primary Objective:* To evaluate the effect of treatment with omecamtiv mecarbil (OM) compared with placebo on exercise capacity as determined by cardiopulmonary exercise testing (CPET) following 20 weeks of treatment with OM or placeboSecondary...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON55869

Source
ToetsingOnline

Brief title
CY 1031 METEORIC-HF (0771/0031)

Condition

- Heart failures

Synonym
Heart Failure with Reduced Ejection Fraction

Research involving

Human

Sponsors and support

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

Intervention

Keyword: Exercise Capacity, Heart Failure with Reduced Ejection Fraction, Omecamtiv Mecarbil

Outcome measures

Primary outcome

The Primary Endpoint is change in peak oxygen uptake (pVO2) on CPET from

baseline to Week 20.

Secondary outcome

Secondary Endpoints:

* Change in total workload during CPET from baseline to Week 20

* Change in ventilatory efficiency (VE/VCO2 slope) during CPET from baseline to

Week 20

* Change in the average daily activity units measured over a 2-week period from

baseline to Week 18-20

Exploratory Endpoints:

* Change from baseline to Week 20 in oxygen uptake efficiency slope (VO2/logVE

slope), ventilatory threshold (by the V-slope method), VO2 recovery kinetics,

percent predicted pVO2, circulatory power (VO2 × systolic blood pressure [BP]),

and exercise duration

* Change from baseline in the average daily activity units at Week 6-8 and at

Week 12-14

* Change from baseline in the KCCQ Total Symptom Score and its sub-domains from

baseline to Week 20

Safety Endpoint:

* Subject incidence of reported adverse events and serious adverse events.

Study description

Background summary

Heart failure (HF) affects over 26 million people worldwide, with more than 3.5 million people newly diagnosed every year, and is a final pathway for many diseases that affect the heart (Hilfiker-Kleiner et al, 2006). Symptoms of dyspnea, fatigue, increased need to rest, low energy, and difficulty in walking or climbing, correlate with lower quality of life and higher mortality risk (Heo, 2008; Flynn, 2009; Malhotra, 2016; Swank, 2012).

Exercise intolerance, typically manifest by dyspnea and fatigue on exertion, is the predominant chronic symptom of HF and often the first symptom that prompts patients to seek medical care. Assessment of exercise capacity in daily life is widely used to classify the severity of HF, for example the New York Heart Association (NYHA) functional classification and the Canadian Cardiovascular Society functional classification. These assessments are highly prognostic of long-term outcomes. Even small improvements in exercise capacity as measured by CPET correlate with improved survival (Swank, 2012).

Few therapies have demonstrated improvements in exercise capacity. Currently, only angiotensin-converting-enzyme inhibitors (ACEis) have product labels that describe a positive effect on exercise capacity in patients with HFrEF.

This study will test the hypothesis that improving cardiac function with the cardiac myosin activator, OM, a drug therapy that directly increases myocardial contractility, will improve exercise tolerance.

Study objective

Primary Objective:
* To evaluate the effect of treatment with omecamtiv mecarbil (OM) compared

with placebo on exercise capacity as determined by cardiopulmonary exercise testing (CPET) following 20 weeks of treatment with OM or placebo

Secondary Objective:
* To evaluate the effect of treatment with OM compared with placebo on daily activity as determined by accelerometry

Exploratory Objective:
* To evaluate the relationships between exercise capacity (determined by CPET), daily activity (determined by accelerometry), and symptoms (determined by Kansas City Cardiomyopathy Questionnaire [KCCQ])

Safety Objective:
* To evaluate the safety and tolerability of OM compared with placebo, as measured by subject incidence of reported adverse events

Study design

This is a randomized, placebo-controlled, double-blind, parallel group, multicenter study in subjects with heart failure with reduced ejection fraction (HFrEF). Approximately 270 eligible subjects will be randomized in a 2:1 ratio to receive either Omecamtiv Mecarbil or placebo, respectively. Randomization will be stratified based on the respiratory exchange ratio (RER) on the baseline CPET (<1.15, *1.15) and persistent atrial fibrillation at screening (Y/N). The number of patients with persistent atrial fibrillation at screening will be capped at approximately 20% and patients with paroxysmal atrial fibrillation will be excluded.

In instances where a subject cannot complete the Week 20 CPET as planned due to COVID-19, those subjects may continue on IP until the visit can be completed for up to an additional 12 weeks (total of up to 32 weeks on IP), and only after approval from the medical monitor. Additionally, the investigator should attempt to complete the Week 20 visit with the CPET as close as safely possible to the originally planned date.

Intervention

Investigational product will be started at 25 mg orally (PO) twice a day (BID), titrated based on the Week 2 and Week 6 predose plasma concentrations to doses of 25, 37.5, or 50 mg BID and continued for a total of 20 weeks. All subjects will be managed with standard of care HF therapies consistent with regional clinical practice guidelines.

Study burden and risks

Subjects will need to visit the hospital 10 times over a period of 26-42 weeks

and will be called for phone follow up three times during this period. Procedures will include physical exams (3x), recording of vital signs (9x) and weight (5x), ECG (6x), echocardiogram (1x, if needed), cardiopulmonary exercise test (2x) and collection of blood (8x) and urine (1x) samples. Subjects will be asked to complete a questionnaire during 4 visits. During the study will be asked to wear an Actigraph watch for periods of 2 weeks at a time (4x) to measure their level of daily activity. If the amount of Omecamtiv Mecarbil (OM) in the blood reaches a very high level, subjects may develop symptoms of decreased blood supply to the heart (myocardial ischemia) or heart attack (myocardial infarction). The side effects of using OM in combination with other drugs are unknown.

Contacts

Public
Cytokinetics, Inc.

East Grand Avenue 280
South San Francisco CA 94080
US
Scientific
Cytokinetics, Inc.

East Grand Avenue 280
South San Francisco CA 94080
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* Male or female, * 18 to * 85 years of age
* History of chronic HF, defined as requiring continuous treatment with medications for HF for a minimum of 3 months before screening
* NYHA class II or III at screening
* Left ventricular ejection fraction * 35%
* On maximally tolerated HF SoC therapies consistent with regional clinical practice guidelines, if not contraindicated and according to investigator judgment of the subject*s clinical status. Beta blocker dose must be stable for 30 days prior to randomization.
* NT-proBNP level * 200 pg/mL
* Peak VO2 * 75% of the predicted normal value with RER * 1.05 on a screening CPET, confirmed by a CPET core laboratory

Exclusion criteria

* Paroxysmal atrial fibrillation or flutter documented within the previous 6 months and requiring treatment, direct-current (DC) cardioversion or ablation procedure for atrial fibrillation within 6 months, or plan to attempt to restore sinus rhythm within 6 months of randomization. Subjects with persistent atrial fibrillation and no sinus rhythm documented in the prior 6 months are permitted.
* Symptomatic bradycardia, second-degree Mobitz type II, or third-degree heart block without a pacemaker.
* Ongoing or planned enrollment in cardiac rehabilitation.
* Requires assistance to walk or use of mobility assistive devices such as motorized devices, wheelchairs, or walkers. The use of canes for stability while ambulating is acceptable if the subject is deemed capable of performing CPET.
* Major medical event or procedure within 3 months prior to randomization, including: hospitalization, surgery, renal replacement therapy or cardiac procedure. This includes episodes of decompensated HF that require IV HF treatment.
* At screening: Resting systolic BP > 140 mmHg or < 85 mmHg, or diastolic BP > 90 mmHg (mean of triplicate readings); Resting heart rate > 90 beats per minute, or < 50 beats per minute (mean of triplicate readings); Room air oxygen saturation < 90%; Hemoglobin <10.0 g/dL; Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m2 (by the modified Modification of Diet in Renal Disease equation); Hepatic impairment defined by a total bilirubin (TBL) * 2 × the upper limit of normal (ULN), or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) * 3 × ULN. Patients with documented Gilbert syndrome and TBL * 2 × ULN due to unconjugated hyperbilirubinemia, without other hepatic impairment, are permitted.

* Significant adverse finding during CPET at screening that precludes safe participation in the study, per investigator
* Male subject with a female partner of childbearing potential and not willing to inform his partner of his participation in this clinical study.
* Female subject is pregnant or breastfeeding or is planning to become pregnant or planning to breastfeed during treatment with investigational product (IP; OM or placebo) or within 5 days after the end of treatment with IP.

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):	09-07-2020
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Omecamtiv Mecarbil 25 mg tablet
Generic name:	Omecamtiv Mecarbil 25 mg tablet
Product type:	Medicine
Brand name:	Omecamtiv Mecarbil 37.5 mg tablet
Generic name:	Omecamtiv Mecarbil 37.5 mg tablet
Product type:	Medicine

Brand name:	Omecamtiv Mecarbil 50 mg tablet
Generic name:	Omecamtiv Mecarbil 50 mg tablet

Ethics review

Approved WMO Date:	27-03-2019
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-09-2019
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-12-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-12-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-11-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-11-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-06-2021

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-07-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTRTBC-NL
ClinicalTrials.gov	NCT03759392
CCMO	NL67921.100.18