A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Assess the Efficacy and Safety of Omecamtiv Mecarbil on Mortality and Morbidity in Subjects With Chronic Heart Failure With Reduced Ejection Fraction

Published: 08-11-2016
Last updated: 31-12-2024

Primary Objective:- to evaluate the effect of treatment with omecamtiv mecarbil (OM) compared with placebo on the time to cardiovascular (CV) death of first HF event, whichever occurs first, in subjects with chronic HF with reduced ejection fraction...

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

Summary

ID

NL-OMON50612

Source
ToetsingOnline

Brief title
20110203 - GALACTIC HF

Condition

- Heart failures

Synonym
Heart failure, insufficient pump function of the heart

Research involving

Human

Sponsors and support

Primary sponsor: Amgen
Source(s) of monetary or material Support: Amgen

Intervention

Keyword: Heart failure, Omecamtiv Mecarbil (AMG 423), Placebo, Reduced ejection fraction

Outcome measures

Primary outcome

Primary Endpoint:

- composite of time to CV death or first HF event, whichever occurs first

An HF event is defined as the presentation of the subject for an urgent, unscheduled clinic/office/ED visit, or hospital admission, with a primary diagnosis of HF, where the patient exhibits new or worsening symptoms of HF on presentation, has objective evidence of new or worsening HF, and receives initiation or intensification of treatment specifically for HF (Hicks et al, 2015). Changes to oral diuretic therapy do not qualify as initiation or intensification of treatment.

Secondary outcome

Secondary Endpoints:

* time to CV death

* change in Kansas City Cardiomyopathy Questionnaire Total Symptoms Score (KCCQ TSS) from baseline to Week 24

* time to first HF hospitalization

* time to all-cause death

Study description

Background summary

Omecamtiv Mecarbil is a promising new oral therapeutic agent for HFrEF patients targeting myocardial contractility. Current recommended pharmacological therapies for chronic HF aim at blocking/controlling the physiological compensatory mechanism. Therapeutic options to directly improve myocardial contractility for these patients are lacking.

The early post-discharge period following a HF hospitalization carries particular high risk for poor clinical outcomes and is known as the *vulnerable phase* (Greene et al, 2015). To help assess effects of omecamtiv mecarbil during this period, the study will enroll some subjects that are in the hospital transitioning from initial treatment to discharge. The total population in this study allows assessment of omecamtiv mecarbil treatment effect and safety in a more representative population of chronic HFrEF patients.

Omecamtiv mecarbil is a novel small molecule classified as a cardiac myosin activator that increases cardiac contractility by selectively and directly activating the enzymatic domain of the cardiac myosin heavy chain, the force-generating motor protein of the cardiac sarcomere, without increasing cardiac myocyte intracellular calcium (Teerlink et al, 2011; Malik et al, 2011). Omecamtiv Mecarbil increases the left ventricular systolic ejection time (SET) without changing the velocity of contraction (dP/dt) or increasing the heart rate.

The salutary effects of omecamtiv mecarbil were achieved without noticeable effect upon myocardial oxygen uptake, blood pressure, or coronary blood flow (Shen et al, 2010; Malik et al, 2011).

Study objective

Primary Objective:
- to evaluate the effect of treatment with omecamtiv mecarbil (OM) compared with placebo on the time to cardiovascular (CV) death of first HF event, whichever occurs first, in subjects with chronic HF with reduced ejection fraction (HFrEF) receiving standard of care (SoC) therapy

Secondary Objectives:

- to evaluate the effects of OM on time to:
CV death
HF hospitalization
all-cause death

- to evaluate the effects of treatment with OM on change in patient-reported outcomes (PROs)

Safety Objective:
- to evaluate the safety of OM as measured by subject incidence of reported adverse events, including serious adverse events of ventricular arrhythmias requiring treatment and positively adjudicated major cardiac ischemic events (fatal and nonfatal myocardial infarction, unstable angina hospitalization, and coronary revascularization) (Hicks et al, 2015)

Study design

This is a randomized, placebo-controlled, double-blind, parallel group, multicenter, CV outcomes study for oral omecamtiv mecarbil in subjects with HFrEF, including subjects with ongoing or history of HF hospitalization.

Approximately 8000 eligible subjects will be randomized in a 1:1 ratio to receive either omecamtiv mecarbil or placebo.

Randomization will be stratified by randomization setting (currently hospitalized for HF or recently and not currently hospitalized for HF) and region (5 strata: US and Canada; Latin America; Western Europe, South Africa, and Australasia; Eastern Europe including Russia; Asia).

Approximately 25% or more of the total planned enrollment will include subjects who are hospitalized at randomization. Enrollment of subjects with atrial fibrillation will be limited to 20% of each enrollment setting.

The study is event-driven and will conclude when approximately 1590 CV death events have occured.

The primary hypothesis is that when added to Standard of Care, omecamtiv mecarbil is well tolerated and superior to placebo in reducing the risk of CV death or HF events in subjects with chronic heartfailure (Outcome study).

Intervention

50% of the patients will be randomized to omecamtiv mecarbil, 50% to placebo (1:1 ratio).
Omecamtiv mecarbil (OM) or placebo will be administered orally twice a day (BID) in the morning and evening and can be taken under fasted or fed

conditions. Subjects randomized to OM will initiate administration at 25 mg BID. At study visit Week 2 (steady-state for initial dose), a blood sample will be collected from all subjects to determine pharmacokinetic (PK) predose level. The results will be blinded to investigators.

For subjects randomized to OM, the predose plasma concentration at Week 2 will guide the dose adjustment at Week 4 as follows:

* Subjects with plasma concentration < 200 ng/mL will start administration of 50 mg BID.

* Subjects with plasma concentration * 200 and < 300 ng/mL will start administration of 37.5 mg BID.

* Subjects with plasma concentration * 300 and < 1000 ng/mL will maintain the administration of 25 mg BID.

* Subjects with plasma concentration * 1000 ng/mL will start administration of placebo BID.

* At study visit Week 6, a predose plasma concentration will be collected from all subjects to confirm plasma concentration achieved while subjects are receiving their targeted dose and assess if potential changes to the dose should be made. The results will be blinded to investigators.

* A new investigational product supply will be provided to all subjects at the Week 4 and Week 8 study visits regardless of randomized treatment group and outcome of the PK assessment in order to maintain the blind.

Further tests/procedures (as stated in the 'Schedule of Assessments' (page 38-40 of the protocol):
- Medical/Surgical History: 1 time during screening
- Vital Signs, Weight: 1 time during screening, thereafter at each visit and 1 time at End of Study
- Reporting side (adverse) effects: continuously
- Placebo run-in: 1 time during screening
- Dosing instructions: day 1, week 4, week 8, week 12, week 24, week 36, week 48 en after week 48 every 16 weeks
- Compliance assessment: week 2, week 6, week 24, week 48, week 96
- ECG: 1 time at day 1, 1 time at week 48, 1 time at week 96, 1 time at End of Study
- Physical Examination: 1 time during screening, 1 time at End of Study
- Pregnancy Exam: 1 time during screening
- Blood tests: during screening, at day 1, week 2, week 6, week 24, week 48, week 96 and at End of Study
- Urinalysis: 1 time at day 1, 1 time at End of Study
- Biomarker Discovery/Future Research: at day 1, week 6, week 24 and at End of

Study
- Omecamtiv mecarbil level test: week 2, week 6, week 24, week 48, week 96
- Patient reported outcomes: as of day 1 at each visit till (incl.) End of Study
- Omecamtiv mecarbil dispensation and tablet count: at day 1 (dispensation only), week 4, week 8 and week 12, thereafter at each visit till (incl.) End of Study (only tablet count)

Study burden and risks

Please see question E9 for risks associated with participation.
Please see question E2 with regard to extent of the burden as well as 'intervention' in section K2.

Contacts

Public
Amgen

Minervum 7061
Breda 4817 ZK
NL
Scientific
Amgen

Minervum 7061
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NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Subject has provided informed consent
- Male or female, * 18 to * 85 years of age
- History of chronic HF
- LVEF * 35%
- NYHA class II to IV
- Managed with HF SoC therapies consistent with regional clinical practice guidelines
- Current hospitalization with primary reason of HF or prior HF hospitalization, or urgent HF admission to emergency department (ED) within 1 year prior to screening
- BNP level * 125 pg/mL or an NT-proBNP level * 400 pg/mL at most recent screening assessment (for subjects with atrial fibrillation, the cut off levels are: BNP * 375 pg/mL or NT proBNP * 1200 pg/mL)

Exclusion criteria

- Inability to swallow study medication tablet
- Receiving mechanical hemodynamic support or mechanical ventilation * 7 days prior to randomization
- Receiving IV inotropes or IV vasopressors * 3 days prior to randomization
- Receiving IV diuretics or IV vasodilators, or supplemental oxygen therapy * 12 hours prior to randomization
- Acute coronary syndrome, stroke, or transient ischemic attack, major cardiac surgery, percutaneous coronary intervention, or valvuloplasty within the 3 months prior to randomization
- Severe uncorrected valvular heart disease, or hypertrophic obstructive cardiomyopathy, active myocarditis, constrictive pericarditis, or clinically significant congenital heart disease
- Routinely scheduled outpatient intravenous infusions for HF (eg, inotropes, vasodilators, diuretics) or routinely scheduled ultrafiltration
- Systolic blood pressure > 140 mmHg or < 85 mmHg, or diastolic blood pressure > 90 mmHg, or heart rate > 110 beats per minute, or < 50 beats per minute at screening
- Estimated glomerular filtration rate (eGFR) < 20 mL/min/1.73m2

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):	23-06-2017
Enrollment:	180
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	N/A
Generic name:	Omecamtiv Mecarbil

Ethics review

Approved WMO Date:	08-11-2016
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	03-02-2017
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-06-2017
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-06-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-09-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-11-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-11-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-12-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-12-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-12-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-01-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-01-2018
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-01-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	29-01-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-02-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-02-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-03-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-03-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-03-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-04-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-05-2018
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-06-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-06-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-07-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-08-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-08-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	29-01-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-02-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-05-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-05-2019
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-08-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-08-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-01-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-02-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-07-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-07-2020
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	EUCTR2016-002299-28-NL
ClinicalTrials.gov	NCT02929329
CCMO	NL58631.028.16

Study results

Date completed: 07-08-2020

Results posted: 06-10-2021

First publication
16-04-2021