A Double-blind, Randomized, Placebo-controlled, Multicenter, Dose Escalation Study to Select and Evaluate an Oral Modified Release Formulation of Omecamtiv Mecarbil in Subjects with Heart Failure and Left Ventricular Systolic Dysfunction

Published: 08-01-2013
Last updated: 24-04-2024

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

Summary

ID

NL-OMON39652

Source
ToetsingOnline

Brief title
COSMIC-HF 20110151

Condition

- Heart failures

Synonym
Failure of the left ventricle, Heart failure

Research involving
Human

Sponsors and support

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

Intervention

Keyword: AMG423, Heart Failure, Left Ventricular Systolic Dysfunction, Omecamtiv Mecarbil

Outcome measures

Primary outcome

Primary Endpoints:

Dose Escalation Phase:

* Maximum observed concentration (Cmax), time at which Cmax is attained (Tmax), minimum observed concentration (Cmin) and area under the curve until 12 hours after investigational product (IP) administration (AUC12h) of omecamtiv mecarbil following dose on day 7

Expansion Phase:

* Cmax and concentration prior to IP administration (Cpredose) of omecamtiv mecarbil at weeks 2, 8,12, 16 and 20 following chronic oral BID dosing

Secondary outcome

Secondary Endpoints:

* Changes from baseline in SET, stroke volume, left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), and HR at week 20

* Change from baseline in NT-proBNP at week 20

Safety Endpoints:

* Subject incidence of adverse events

* Changes from baseline in laboratory values and vital signs

* Changes from baseline electrocardiogram (ECG)

PK Endpoints:

* PK parameters of omecamtiv mecarbil metabolites

Study description

Background summary

Systolic heart failure is a clinical syndrome marked by impaired cardiac contractility. Omecamtiv mecarbil (AMG 423) is a novel small molecule that increases cardiac contractility by directly activating myosin in the heart muscle. In contrast to currently available inotropes, AMG 423 achieves its effects without increasing myocyte calcium transients, myocardial oxygen uptake or heart rate.

Study objective

The primary objectives of this study are to select an oral modified release (MR) formulation and dose of omecamtiv mecarbil for in subjects with HF and left ventricular systolic dysfunction and to characterize itspharmacokinetics (PK) after 20 weeks of treatment.

Study design

This study consists of a dose escalation phase to select 1 of 3 oral omecamtiv mecarbil formulations studied in 2 dose escalation cohorts, followed by an expansion phase to evaluate 20 weeks of administration of the selected omecamtiv mecarbil formulation at 2 dose levels, compared with placebo. In each of the dose escalation cohorts, approximately 40 subjects will be randomized to receive 1 of the 3 formulations of omecamtiv mecarbil BID (25-mg BID cohort 1; 50-mg BID cohort 2) or placebo BID for 7 days. If necessary to achieve an effective plasma concentration in subjects with HF, a third cohort may be added to test some or all of the omecamtiv mecarbil formulations at the dose of 75 mg BID before proceeding to the expansion phase. In the expansion phase, approximately 450 subjects will be randomized into 1 of 3 treatment groups to receive the selected formulation of omecamtiv mecarbil at 1 of 2 dose levels, or placebo. It is expected that the dose levels in the expansion phase will be 25 mg and 50 mg BID. Dose levels of 50 mg and 75 mg BID may be selected if a

third dose escalation cohort at 75 mg BID is conducted. Treatment in the expansion phase is for 20 weeks. PK and safety data will be reviewed in a Dose Level Review Meeting (DLRM) before enrollment into the next cohort is initiated.

In total, up to approximately 570 subject in 125 centers will be randomized. The Netherlands will only participate in cohort 2 (and 3 if applicable) and in the expansion phase.

With protocol amendment #4 a titration step has been added to the 50 mg arm in the expansion phase. The total treatment duration has therefore been amended from 12 weeks to 20 weeks, with an end of study visit at week 24.

Protocol amendment #4:
Subjects randomized to omecamtiv mecarbil 50 mg BID target dose will initiate administration at 25 mg BID until week 8. These subjects will start administration at 50 mg BID at the week 8 visit only if the week 2 predose omecamtiv mecarbil plasma concentration is < 200 ng/mL. Subjects with week 2 predose PK >= 200 ng/mL, or for which a week 2 PK value is not available in time for dose adjustment, will continue administration at 25 mg BID until the end of study participation. Subjects randomized to placebo or to 25 mg BID will receive the assigned IP throughout the study.

Intervention

Dose escalation phase cohort 1: 25 mg BID omecamtiv mecarbil (1 of the 3 oral formulations) or placebo 7 days
Dose escalation phase cohort 2: 50 mg BID omecamtiv mecarbil (1 of the 3 oral formulations) or placebo 7 days
Dose escalation phase cohort 3: 75 mg BID omecamtiv mecarbil (1 of the 3 oral formulations) or placebo 7 days
Enrollment expansion phase: 25 or 50 mg BID omecamtiv mecarbil (1 formulation) or placebo 20 weeks

Study burden and risks

The following procedures will be performed according to the ''Schedule of Assessments'' (protocol page 39 and 41): physical examination, vital signs, ECG, and blood sampling in both escalation phase and expansion phase. Moreover a serum pregnancy will be done at the screening and end of study visit in both phases. In the expansion phase echocardiograms will also be performed at screening, week 12 and 20. In the expansion phase PROs/ClinROs will need to be completed at certain visits.

In the escalation phase patients will need to come to the hospital 10 times. In the expansion phase patients will need to come to the hospital 8 times. In

between, patients will be contacted by phone. The visits on day 1 and 7 of the escalation phase and on week 2 and 12 of the expansion phase will take the whole day. Patients may stay over for the night.

For adverse events of AMG423, please see question E9.

Contacts

Public
Amgen

Minervum 7061
Breda 4817 ZK
NL
Scientific
Amgen

Minervum 7061
Breda 4817 ZK
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Dose Escalation Cohorts:;4.1.1 Subject has provided informed consent.;4.1.2 Male or female >= 18 years and <= 85 years of age at the time of informed consent.;4.1.3 History of chronic HF, defined as requiring treatment for HF for a minimum of 4 weeks prior to screening.;4.1.4 Treated for HF with stable, optimal pharmacological therapy. In general, optimal treatment will include a beta-blocker and an ACE inhibitor and/or an angiotensin receptor blocker at

doses shown to be efficacious in HF trials, unless not tolerated. Stable medical therapy is defined as having no new HF drug class introduced or uptitrated >= 4 weeks prior to randomization.;4.1.5 LVEF <= 40% (echocardiogram, radionuclide ventriculography, cardiac magnetic resonance imaging, or contrast ventriculography) within 18 months prior to randomization and without an intervening value greater than 40%.;4.1.6 NT-proBNP >= 200 pg/mL (>= 1200 pg/mL if the subject has atrial fibrillation at presentation) at screening; (Note: enrollment of subjects with atrial fibrillation will be limited to up to approximately 20% of planned enrollment in each cohort).;Expansion Phase:;4.1.7 Subject has provided informed consent.;4.1.8 Male or female >= 18 years and <= 85 years of age at the time of informed consent.;4.1.9 History of chronic HF, defined as requiring treatment for HF for a minimum of 4 weeks prior to screening.;4.1.10 Treated for HF with stable, optimal pharmacological therapy. In general, optimal treatment will include a beta-blocker and an ACE inhibitor and/or an angiotensin receptor blocker at doses shown to be efficacious in HF trials, unless not tolerated. Stable medical therapy is defined as having no new HF drug class introduced or uptitrated >= 4 weeks prior to randomization.;4.1.11 NYHA class II or III symptoms.;4.1.12 LVEF <= 40% by centrally read screening echocardiogram.;4.1.13 Acceptable echocardiographic image quality of screening echocardiogram per central echo core laboratory;4.1.14 NT-proBNP >= 200 pg/mL (23.60 pmol/L) (>= 1200 pg/mL (141.60 pmol/L) if the subject has atrial fibrillation at presentation) at screening; (Note: enrollment of subjects with atrial fibrillation will be limited to up to approximately 20% of planned cohort enrollment).

Exclusion criteria

Dose Escalation Cohorts and Expansion Phase:;4.2.1 Cardiac resynchronization therapy (CRT) or ICD implantation within 30 days prior to enrollment.;4.2.2 NYHA class IV.;4.2.3 Hospitalization for any reason within 30 days prior to randomization.;4.2.4 Likely to receive within 3 months after randomization, in the opinion of the Investigator, planned revascularization, implantation of ICD or CRT, ventricular assist device, continuous or intermittent inotropic therapy, hospice care, or cardiac transplant.;4.2.5 Severe uncorrected valvular heart disease.;4.2.6 Hypertrophic obstructive cardiomyopathy, active myocarditis, or constrictive pericarditis, or clinically significant congenital heart disease.;4.2.7 Acute myocardial infarction, unstable angina or persistent angina at rest within 30 days prior to randomization .;4.2.8 Chronic antiarrhythmic therapy, with the exception of amiodarone. ;4.2.9 Routinely scheduled outpatient IV infusions for HF (eg, inotropes, vasodilators [eg, nesiritide], diuretics) or routinely scheduled ultrafiltration.;4.2.10 Systolic BP > 160 mm Hg or < 90 mm Hg, or diastolic BP > 90 mm Hg, or HR > 110 beats per minute (bpm) or HR < 50 bpm at screening.;(Full list in protocol)

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:	Recruitment stopped
Start date (anticipated):	22-04-2014
Enrollment:	21
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	08-01-2013
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-05-2013
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-06-2013

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-06-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-08-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-09-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-09-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-01-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-01-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-03-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	20-06-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-06-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-08-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-08-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-11-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2012-000327-40-NL
CCMO	NL42744.056.12
Other	Nog niet beschikbaar