A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate the Safety and Efficacy of IV Infusion Treatment With Omecamtiv Mecarbil in Subjects With Left Ventricular Systolic Dysfunction Hospitalized for Acute Heart Failure

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

Summary

ID

NL-OMON37556

Source
ToetsingOnline

Brief title
ATOMIC-AHF

Condition

- Heart failures

Synonym
acute heartfailure, shortness of breath

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Acute Heart Failure, efficacy, Omecamtiv Mecarbil, safety

Outcome measures

Primary outcome

The primary endpoint is dyspnea symptom response by 7-point Likert scale. Minimally, moderately or markedly better by 7-point Likert scale at 6 hours after investigational product initiation, AND moderately or markedly better at 24 and 48 hours after investigational product initiation without worsening heart failure or death from any cause by 48 hours.

Secondary outcome

* Death from any cause or worsening heart failure within 7 days of initiation of investigational product
* Worsening heart failure within 7 days of initiation of investigational product
* Dyspnea AUC (baseline to day 6 or discharge, whichever comes first) as measured by subject self-assessed Numerical Rating Scale (NRS)
* Dyspnea by 7-point Likert scale at each scheduled assessment
* PGA response (minimally, moderately or markedly better by subject self-assessed 7-point Likert scale at 6 hours after investigational product initiation, AND moderately or markedly better at 24 and 48 hours after investigational product initiation)

* PGA at each scheduled assessment

* Change from baseline in NT-proBNP at each scheduled assessment

* Length of initial hospital stay

* Days alive out of hospital until day 30

Study description

Background summary

Omecamtiv mecarbil (AMG 423, CK-1827452) is a novel small molecule that increases cardiac contractility by selectively and directly activating the enzymatic domain of cardiac myosin heavy chain, the force-generating motor protein of the cardiac sarcomere.
An unmet need exists for more effective and safe strategies to treat acute heart failure. Although available inotropes improve hemodynamics, their use has been associated with clinical liabilities and increased mortality that severely restrict their use. In contrast to currently available inotropes, omecamtiv mecarbil does not raise intracellular calcium, which can increase heart rate and myocardial oxygen consumption, and cause arrhythmias.
This study is conducted to gather information on the safety and efficacy of three increasing dose levels of omecamtiv mecarbil. It is expected that at least 1 dose level of omecamtiv mecarbil IV will be well tolerated and will result in improvement of dyspnea in subjects with left ventricular systolic dysfunction hospitalized for acute heart failure.

Study objective

The primary objective of the study is to evaluate the effect of 48 hours of intravenous (IV) omecamtiv mecarbil compared with placebo on dyspnea in subjects with left ventricular systolic dysfunction hospitalized for acute heart failure.

Secondary:
* To assess the safety and tolerability of 3 dose levels of IV omecamtiv mecarbil compared with placebo in subjects with left ventricular systolic dysfunction hospitalized for acute heart failure
* To evaluate the effects of 48 hours treatment with IV omecamtiv mecarbil on additional measures of dyspnea, patient global assessment (PGA), change in N-terminal pro brain-type natriuretic peptide (NT-proBNP) and short-term clinical outcomes
* To characterize pharmacokinetics of omecamtiv mecarbil, including metabolites

M1 and M3, following IV infusion and to evaluate the relationship between omecamtiv mecarbil plasma concentration and echocardiographic parameters in subjects with acute heart failure

Study design

This is a multicenter, randomized, double-blind, placebo-controlled study with 3 dose cohorts enrolled sequentially in order of ascending dose strength of omecamtiv mecarbil.
In each cohort, subjects are randomized 1:1 to omecamtiv mecarbil or placebo. The safety risk to study subjects will be evaluated on an ongoing basis through regular review of unblinded data by an independent Data Monitoring Committee (DMC). Before proceeding to the next higher dose strength, the safety, tolerability, and PK data of omecamtiv mecarbil at the lower dose(s) will be evaluated by the DMC which will issue a recommendation whether to proceed or whether to make any changes. Subjects will be enrolled within 24 hours after their initial IV furosemide (or alternative IV loop diuretic) dose.
Randomization will be stratified by region and by planned participation in the pharmacokinetic/pharmacodynamic (PK/PD) substudy (see below). Omecamtiv mecarbil or placebo will be infused IV over 48 hours (4 hours loading infusion, followed by 44 hours maintenance infusion). Subjects will remain hospitalized for at least 24 hours after termination of the IV infusion. Evaluations are scheduled at 2, 4, and 6 hours, once at 12 to 18 hours and then daily until discharge or 7 days after initiation of investigational product (study day 8), whichever is earlier, and on the day of discharge from inpatient treatment. Active study participation of an enrolled subject concludes with an end-of-study visit at day 30. For a mortality analysis, the investigator will obtain the vital status of the subject at month 6 and, if deceased, will obtain the date and reported cause of death. All subjects will be invited to participate in a biomarker and pharmacogenetic substudy. At a number of sites, subjects will be invited to participate in a PK/PD substudy with additional blood sampling for PK analysis and with echocardiography imaging.

Intervention

Treatment with IV omecamtiv mecarbil

Study burden and risks

Risk: Adverse effects of study medication and procedures
Burden: Maximum duration of 1 month follow up after 6 months. Up to 8 visits (most of the procedures are performed while the patient is hospitalized for acute heart failure).
1x 48 hours IV (dose depending on the patient's cohort, 384 ml in total).
Follow up 4 hours after infusion rate adjustments, after 24 hours infusion bag replacement.

Physical examination 2x, vital signs 12x
8x blood, approximately 160 ml, plus 70 ml for PKPD substudy
Pregnancy test (if applicable) 2x
ECG 6x, plus 3x for PKPD substudy
Questionnaires 8x

Contacts

Public
Amgen

Minervum 7061
Breda 4800 DH
NL
Scientific
Amgen

Minervum 7061
Breda 4800 DH
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Current hospitalization for a primary reason of worsening heart failure (determined by the investigator) and requiring IV therapy for heart failure
- History of chronic heart failure (defined as requiring treatment for heart failure for a minimum of 30 days before hospitalization)
- History of left ventricular ejection fraction (LVEF) * 40% (echocardiogram, radionuclide

ventriculography, cardiac magnetic resonance imaging, or contrast ventriculography) and without an intervening value of > 40%.
- Dyspnea due to heart failure, at rest or with minimal exertion, within 24 hours after their initial IV furosemide (or alternative IV loop diuretic) dose and at least 2 hours after having received a total of * 40 mg IV
furosemide (or equivalent dose of an alternative IV loop diuretic).
- Brain-type natriuretic peptide (BNP) * 400 pg/mL or NT-proBNP * 1600 pg/mL during screening (BNP * 600 pg/mL or NT-proBNP * 2400 pg/mL if the subject has atrial fibrillation at presentation)
- If participating in the PK/PD substudy, subject must currently be in sinus rhythm.

Exclusion criteria

Various heart failure and other cardiovascular exclusions apply, including, but not limited to, receiving IV vasopressor (excluding dopamine * 5 mcg/kg/min), inotropic or mechanical circulatory (eg, intra-aortic balloon pump counterpulsation) support between admission and randomization, a pulmonary artery catheter, endotracheal mechanical ventilation, evolving acute coronary syndrome, or within 30 days prior to enrollment any of the following: cardiac resynchronization therapy (CRT) or implantable cardioverter defibrillator (ICD) implantation, hospitalization for acute coronary syndrome, coronary revascularization, transient ischemic attack or stroke, sustained ventricular arrhythmia, or major surgery. In addition, subjects are excluded if likely to receive within 30 days after randomization: planned revascularization, ICD or CRT, ventricular assist device, continuous inotropic therapy, intermittent out-patient inotropic therapy, hospice care, or cardiac transplant. Subjects cannot have severe aortic or mitral stenosis or heart failure primarily due to valvular heart disease.
Other exclusions are blood pressure (BP) > 160/100 mm Hg, systolic BP (SBP) < 90 mm Hg, or heart rate (HR) > 110 or < 60 bpm, estimated glomerular filtration rate (eGFR) calculated by the Modification of Diet in Renal Disease (MDRD) equation < 20 mL/min/1.73m2 during screening, severe non-cardiovascular disease that is expected to reduce life expectancy to less than 1 year, any major organ transplant (eg, lung, liver, heart, bone marrow, renal), receiving renal replacement therapy by dialysis, total bilirubin * 2 times the upper limit of normal (ULN) or alanine aminotransferease (ALT) or aspartate aminotransferase (AST) * 5 times ULN during screening. Subjects cannot be receiving or have received chemotherapy and/or radiation therapy for treatment of a malignancy within 6 months prior to randomization or clinical evidence of current malignancy.

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):	05-06-2012
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Omecamtiv mecarbil
Generic name:	Omecamtiv mecarbil

Ethics review

Approved WMO Date:	10-10-2011
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	07-02-2012
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	08-03-2012

Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	26-03-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	04-04-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	17-04-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	16-05-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	01-06-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	11-07-2012

Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	12-02-2013
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	22-03-2013
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	09-04-2013
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2010-021003-24-NL
ClinicalTrials.gov	NCT01300013
CCMO	NL38091.098.11