A multicenter, randomized, double-blind, placebo- controlled phase III study to evaluate the efficacy, safety and tolerability of Serelaxin when added to standard therapy in acute heart failure patients

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Primary Objective:To demonstrate that serelaxin is superior to placebo in reducing CV death in AHF patients during a follow-up period of 180 days.To demonstrate that serelaxin is superior to placebo in reducing worsening heart failure through Day...

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

Summary

ID

NL-OMON45125

Source
ToetsingOnline

Brief title
Relax-AHF-2

Condition

- Heart failures

Synonym
Acute Heartfailure

Research involving

Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Bedrijf Novartis Pharma BV (sponsor/opdrachtgever van het onderzoek)

Intervention

Keyword: Acute Heartfailure, Mortality, Serelaxin

Outcome measures

Primary outcome

Primary efficacy assessment:

Time to confirmed CV death during a follow-up period of 180 days.

Time to first occurrence of worsening of heart failure through Day5

(considering death in the 5-day period as WHF event)

Secondary outcome

Key secondary assessments:

* Time to all-cause death during a follow-up period of 180 days

* Length of total hospital stay for the index AHF hospitalization

* Time to first occurrence of the composite endpoint of CV death or

rehospitalization due to heart failure/renal failure, during a follow-up period

of 180 days.

Other secondary efficacy assessments:

* Length of ICU and/or CCU stay for the index AHF hospitalization

* Change from baseline in congestive signs and symptoms of HF through Day 5

* Change from baseline in selected biomarkers from baseline through Day 14 in a

subset of randomized patients

Study description

Background summary

Purpose:
The purpose of this study is to evaluate the efficacy, safety and tolerability of intravenous infusion of 30 *g/kg/day serelaxin administered by body weight category for 48 hours, when added to standard therapy, in approximately 6,800 acute heart failure (AHF) patients. Efficacy will be determined based on the relative reduction in CV death and other clinical outcomes through a follow-up period of 5 and 180 days, as compared to placebo.

Rationale:
The rate of mortality in AHF remains high despite contemporary standard of-care management, which has not changed significantly in the last 10 years, and represents a key unmet need for AHF patients. In the RELAX AHF trial a clinically and statistically significant 37% reduction in both CV and all-cause mortality through Day 180 were seen. Data from this study is intended to replicate the reduction in mortality in AHF patients observed in the RELAX AHF trial.

Study objective

Primary Objective:
To demonstrate that serelaxin is superior to placebo in reducing CV death in AHF patients during a follow-up period of 180 days.
To demonstrate that serelaxin is superior to placebo in reducing worsening heart failure through Day 5

Key secondary objectives:
* To demonstrate that serelaxin is superior to placebo in reducing allcause mortality during a follow-up period of 180 days
* To demonstrate that serelaxin is superior to placebo in reducing the length of total hospital stay during the index AHF hospitalization
* To demonstrate that serelaxin is superior to placebo in reducing the composite endpoint of CV death or rehospitalization due to heart failure/renal failure, during a follow-up period of 180 days

Secundary Objectives:
Efficacy
* To demonstrate that serelaxin is superior to placebo in reducing the length of ICU and/or CCU stay during the index AHF hospitalization

* To demonstrate that serelaxin is superior to placebo in relieving signs and symptoms of congestion through Day 5
* To compare serelaxin to placebo in the changes of selected biomarkers in a subset of randomized patients
Safety
* To evaluate the safety and tolerability of intravenous serelaxin in AHF patients

Study design

This is a multicenter, randomized, double-blind, placebo-controlled study.

Intervention

Intravenous infusion with placebo or serelaxin (30ug/kg/d), duration max. 48 hours.

Study burden and risks

Burden and risks of participation are the chances of side effects from the study medication and inconvenience of blood samples and infusion.

The known side effects of the study medication include: decrease of blood pressure (hypotension), prolonged or excessive uterine bleeding (which occurs irregularly and more frequently than normal) and anemia (reduction of the amount of hemoglobin/red blood cells). Note, a decrease of blood pressure (hypotension) and red blood cells (anemia) can lead to symptoms like dizziness or fainting (syncope). Treatment with Serelaxin can also be associated with low potassium levels in the blood (hypokalemia). Hypokalemia can lead to symptoms like muscle weakness, muscle cramps, and abnormal heart rhythm. Additionally, antibodies (proteins produced by the blood) have been seen after treatment with the study drug Serelaxin. To date, these antibodies have not been linked with medically significant adverse events. Furthermore (as with any protein), there is a risk of serious allergic reactions which can cause symptoms like severe decrease of blood pressure and difficulty breathing.

First phase of this study will take place during hospitalization; 10 'official study visits' and more frequent measurement of blood pressure and pulse. 4 visits take place after discharge including 1 telephonic. Total duration is estimated at 10.5 hours.
All procedures belong to standard care / therapy / diagnosis but blood draw, measuring weight, respiratory rate and bodytemperature plus performing physical examination more often than standard.

Risks and discomforts are expected to be minor and acceptable.

There is no standard therapy denies.

A therapeutic effect is expected but it is not to say with certainty that the patient will have personal benefits by participating in this study. This study may provide useful information for the future.

Contacts

Public
Novartis

Raapopseweg 1
Arnhem 6824 DP
NL
Scientific
Novartis

Raapopseweg 1
Arnhem 6824 DP
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Male or female *18 years of age, with body weight *160 kg
- Hospitalized for AHF with the anticipated requirement of intravenous therapy (including IV diuretics) for at least 48 hours, i.e. persistent dyspnea at rest or with minimal exertion at screening and at the time of randomization, despite standard background therapy for acute heart failure including the protocol required intravenous furosemide of at least 40 mg total

(or equivalent), pulmonary congestion on chest radiograph, BNP * 500 pg/mL or NT-proBNP * 2,000 pg/mL; for patients * 75 years of age or with current atrial fibrillation (at the time of randomization), BNP * 750 pg/mL or NT-proBNP * 3,000 pg/mL
- Systolic BP *125 mmHg at the start and at the end of screening
- Able to be randomized within 16 hours from presentation to the hospital, including the emergency department
- Received intravenous furosemide of at least 40 mg total (or equivalent) at any time between presentation (this includes outpatient clinic, ambulance, or hospital including emergency department) and the start of screening for the study for the treatment of the current acute HF episode. Time from presentation to start of furosemide administration should be less than 6 hours.
- Impaired renal function defined as an eGFR between presentation and randomization of * 25 and *75mL/min/1.73m2, calculated using the sMDRD equation.

Exclusion criteria

- Dyspnea due to non-cardiac causes due to non-cardiac causes such as acute or chronic respiratory disorders or infections (i.e., severe chronic obstructive pulmonary disease, bronchitis, pneumonia), which may interfere with the ability to interpret the primary cause of dyspnea.
-Known history of respiratory disorders requiring the daily use of IV or oral steroids (does not include inhaled steroids); need for intubation or the current use of IV or oral steroids for COPD.
- Patients with blood pressure > 180 mmHg at the time of randomization or persistent heart rate >130 bpm.
- Temperature >38.5°C (oral or equivalent) or sepsis or active infection requiring IV antimicrobial
treatment
- Clinical evidence of acute coronary syndrome currently or within 30 days prior to enrollment
- AHF due to significant arrhythmias, which include any of the following: sustained ventricular tachycardia, bradycardia with sustained ventricular rate <45 beats per minute, or atrial fibrillation/flutter with sustained ventricular response of >130 beats per minute
- Patients with severe renal impairment defined as pre-randomization eGFR < 25 mL/min/1.73m2 calculated using the sMDRD equation, and/or those receiving current or planned dialysis or ultrafiltration.

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):	09-12-2013
Enrollment:	125
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Serelaxin
Generic name:	Relaxin

Ethics review

Approved WMO Date:	11-10-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-10-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-01-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-02-2014

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-03-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-07-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-09-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-10-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-10-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-11-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-05-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-06-2015

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-12-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-12-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-02-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-03-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-04-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2013-001498-25-NL
ClinicalTrials.gov	NCT01870778
CCMO	NL44956.042.13