A multicenter, double blind, randomized, parallel group, placebo-controlled study to evaluate the hemodynamic responses to intravenous RLX030 infusion in subjects with acute heart failure.

Published: 08-06-2012
Last updated: 26-04-2024

Primary objective(s)• To assess the effects of RLX030 compared to placebo on hemodynamic variables (PCWP, CI) during the first 8 hours administered as i.v. infusion over 20 hours in subjects with Acute Hart FailureSecondary objective(s)• To assess...

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

Summary

ID

NL-OMON37099

Source
ToetsingOnline

Brief title
CRLX030A2201

Condition

- Heart failures

Synonym
Acute Heart Faillure

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: acute heart failure, CRLX030A2201, Relaxine, RLX030

Outcome measures

Primary outcome

- Pulmonary capillary wedge pressure (PCWP)

- Right atrial pressure (RAP)

- Systolic and diastolic pulmonary artery pressure (PAP)

- Pulmonary oxygen saturation (pO2) and

- Cardiac output (CO)

Secondary outcome

a.Non-invasive measurement of central aortic systolic pressure and

radial arterial pulse waveform

b.Pharmacokinetics

c.Total urine volume

d.Safety and tolerability

e.Sodium and creatinine excretion

Study description

Background summary

Relaxin is a naturally occurring peptide hormone with a molecular weight of 5963 Daltons. Three human relaxin genes have been identified (H1, H2, and H3). The protein product of the gene H2, is further described here and referred to

as RLX030. RLX030 is produced by
recombinant DNA technology in a bacterial expression system and is identical in amino acid sequence and structure to the mature, naturally-occurring human relaxin-2. In men, relaxin is expressed locally in the prostate and at very low levels in circulation. Relaxin circulates in
women at low levels in the luteal phase of the menstrual cycle but is elevated in pregnancy. It is believed to mediate many of the maternal physiological responses to pregnancy including increases in renal function (Davison and Noble 1981), decreases in systemic vascular
resistance (Capeless and Clapp 1989), and increases in cardiac output mediated largely by increased stroke volume (Capeless and Clapp 1989). Triggering similar hemodynamic and adaptive changes as seen in pregnancy could potentially be beneficial in the treatment of
patients with acute heart failure (AHF). RLX030 has been evaluated in approximately 21 clinical trials in 7 indications over the last 20 years.

RLX030 is foreseen to be administered as a 48-hour continuous intravenous (i.v.) infusion of 30 µg/kg/day on top of standard of care, to improve the signs and symptoms of AHF (mainly dyspnea), and, ultimately, reduce heart failure re-hospitalizations and cardiovascular death.
The Phase 3 trial (RELAX-AHF) with 30 µg/kg/day and placebo i.v. as a 48 hour infusion is currently ongoing. The results of the Phase 2 Pre-RELAX-AHF (part of RLX.CHF.003) showed the following potential benefits of RLX030 at doses of 10, 30, 100 and 250 µg/kg/day as 48-hour i.v. infusion compared to placebo in patients with acute heart failure: rapid and sustained relief of dyspnea, trends for greater relief from signs and symptoms of fluid overload, a lower incidence of worsening heart failure, lower use of i.v. loop diuretics and other vasodilator therapy and a shortened length of hospital stay. Additionally there were outcome benefits up to Day 60, including improved cardiovascular mortality and fewer rehospitalizations for heart failure or renal failure and greater number of days alive and out-ofhospital (Teerlink et al 2009).

RLX030 activity is mediated through binding to its cognate receptor, RXFP1 (or LGR7), localized in small renal and mesenteric arteries and in the thoracic aorta in mice and rats of both sexes, as well as in human blood vessels. The pharmacological effects of relaxin include
increased production of nitric oxide, inhibition of endothelin-1, inhibition of angiotensin II, increased production of vascular endothelial growth factor (VEGF), and local up-regulation of matrix metallo-proteinases (MMP). These effects lead to arterial vasodilation, increased
arterial compliance, and may have favorable effects on renal hemodynamics.

Since RLX030 works indirectly through multiple pathways with short- and long-term effects on hemodynamics, it may be particularly well-suited for therapeutic treatment of heart failure,
with acute and sustained effects, as well as a favorable benefit-risk profile.
The current study is designed to provide data to support the understanding of

RLX030*s Mechanism of Action (MoA) through effects on hemodynamics in patients with AHF at the therapeutic dose,
information about the on-set and off-set of effects and population pharmacokinetics.

Study objective

Primary objective(s)
• To assess the effects of RLX030 compared to placebo on hemodynamic variables (PCWP, CI) during the first 8 hours administered as i.v. infusion over 20 hours in subjects with Acute Hart Failure

Secondary objective(s)
• To assess the onset and offset of the hemodynamic effects during and following the end of the i.v. infusion of RLX030 over 20 hours compared to placebo when administered to subjects with Acute Hart Failure.
• To investigate the population pharmacokinetics of RLX030 during and after i.v. infusion over 20 hours in subjects with Acute Hart Failure.
• To assess the effects of 20 hours i.v. infusion of RLX030 on diuresis and calculated creatinine clearance when administered to subjects with Acute Hart failure
• To assess the effects of 20 hours i.v. infusion of RLX030 on central aortic systolic pressure (CASP), and radial arterial pulse waveform compared to placebo in subjects with Acute Hart Failure.
• To assess the tolerability of 20 hours i.v. infusion of RLX030 compared to placebo when administered to subjects with Acute Hart Failure

Study design

This is a multicenter, double-blind, randomized, placebo-controlled study in subjects with AHF. The study will consist of a one to three day(s) screening period, a baseline period, a treatment period of 20 hours infusion, a wash-out period after stop of infusion. Discharge from hospital is possible from approximately 44 hours after start of the study drug infusion if medically capable of doing so per Investigator*s discretion. Study Completion evaluation is done 30 (±3) days after start of the study drug infusion.

Subjects who meet the clinical and laboratory eligibility criteria at screening will have a Swan-Ganz catheter inserted and the hemodynamic eligibility criterion will be assessed. If also this criterion is met the baseline evaluations are performed. All baseline safety evaluation results must be available prior to dosing.

During the study the hemodynamic parameters RAP, PAP, PCWP and CO will be measured repeatedly. At the same time points, blood pressure and CASP will be measured. Blood samples will be taken at intervals for PK estimation and for

assessment of selected biomarkers.
Urine will be collected for assessment of diuresis, natriuresis, creatinine clearance, and for assessment of selected biomarkers and urinary albumin creatinine ratio (UACR).

Safety assessments will include physical examinations, ECGs, vital signs, investigator assessments of signs and symptoms, standard clinical laboratory evaluations (hematology, blood chemistry, urinalysis), adverse event and serious adverse event monitoring.

The study will be conducted in two sequential parts:
• In part 1 the dose of 30 µg/kg/day, currently used in the ongoing phase 3 trial, will be compared to placebo.

• After completion and statistical evaluation of part 1 the study may, optionally, continue with a Part 2 to investigate additional dose(s) or dose regimen(s) of RLX030 compared to placebo using the same study design. The dose(s) or dose regimen(s) in part 2 will be defined in an amendment and selected based on the results obtained with 30 µg/kg/day.

Intervention

Swan-Ganz Catheterization

Study burden and risks

This study will be conducted in subjects with acute heart failure requiring hospitalization for management of AHF and central hemodynamic monitoring. Inclusion and exclusion criteria will ensure that the appropriate subjects will be included in this study.

Currently available treatment options in AHF consist of primarily diuretics in almost all subjects supplemented by vasodilators or inotropic agents in selected subsets. In patients with preserved or elevated BP, vasodilators are recommended at an early state for AHF patients by
the European Society of Cardiology (ESC) guidelines. In this study all patients will receive study medication on top of standard of care which must include loop diuretics. Therefore patients will receive standard treatment of care for this indication. RLX030 will be administered at a dose that has proven symptom improvement in the Phase 2b study and is currently in Phase 3 of development. However, patients might not have an additional medical benefit from participating in the study over standard treatment of care.

Overall, RLX030 has demonstrated an acceptable safety profile and was well-tolerated in clinical with stable congestive HF (CHF) and AHF. Risks involved with RLX030 administration include hypotension, increase in serum

creatinine, meno-/metrorrhagia, and anemia as a result of menometrorrhagia or hemodilution. As with any protein, there is a possibility of allergic reactions. Antibody formation to RLX030 has occurred in 39% of subjects receiving RLX030 only after systemic exposure via the SC route of administration. To date, the antibodies have been associated with no apparent adverse events. There is no evidence that the antibodies are inhibitory nor is there evidence of any long-term sequelae. Chronic HF patients dosed i.v. with RLX030 for 24 hr at a dose of up to 960 µg/kg/day for 24 hours in study RLX.CHF.001 did not develop anti-RLX030 antibodies. Because of the i.v.route and short treatment duration, antibody formation is highly unlikely.

Risks associated with invasive hemodynamic monitoring by puncture of an access vein and insertion of a Swan-Ganz catheter may include complications such as bleeding, and pneumothorax. Through stimulation of the myocardium atrial and ventricular arrhythmias can occur which are generally without hemodynamic relevance and self-limiting. Risks also include thrombosis which may be limited by heparinization. The risk of infections will be limited by sterile procedures. Pulmonary infarction has also been reported. The incidence of complications arising from pulmonary artery catheters has been reported to be between 5 and 10% in two randomized controlled studies with hematoma being most frequent (4%) (Binanay et al 2005a; Binanay et al 2005b).

The 20 hours i.v. infusion requiring an indwelling catheter could potentially lead to discomfort, development of hematoma or in rare cases of phlebitis.

The risk to subjects in this trial will be minimized by adherence to the inclusion/exclusion criteria, close clinical monitoring in a hospital setting, strict adherence to standard catheterization practice including training of staff and provision of manuals for study procedures, stopping rules for the individual subject and a Data Monitoring Committee (DMC) for the entire study.

Contacts

Public
Novartis

Novartis Campus- Forum 1 1
Basel 4056
CH
Scientific
Novartis

Novartis Campus- Forum 1 1
Basel 4056

CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Patients admitted to hospital or who require admission to hospital for management of acute heart failure with shortness of breath at rest or minimal exertion
- stabilized within 2 days after admission
- normal or elevated systolic blood pressure
- elevated pulmonary capilary wedge pressure measured by Swan-Ganz catheterization

Exclusion criteria

- severe renal impairment
- significant liver impairment
- significant lung impairment
- significant heart valve dysfunction or arrythmias
- myocardial infarction or acute coronary syndrome within th elast 45 days

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):	01-07-2012
Enrollment:	10
Type:	Anticipated

Medical products/devices used

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

Ethics review

Approved WMO Date:	08-06-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-07-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-08-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-08-2012
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-10-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-10-2012
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	EUCTR2011-000833-35-NL
ClinicalTrials.gov	NCT01543854
CCMO	NL40880.042.12