A multicenter, randomized, double-blind, parallel group, placebo-controlled study to evaluate the renal hemodynamic effects of RLX030 at a dose of 30 µg/kg/day or placebo infused for 24 hours in subjects with chronic heart failure (CHF).

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Primary objective(s)To assess the effects of 24 hrs i.v. infusion of RLX030 30µg/kg/day compared to placebo on renal blood flow (RBF) as measured by PAH clearance in subjects with CHF and worsening symptoms To assess the effects of 24 hrs i.v....

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

Summary

ID

NL-OMON38100

Source
ToetsingOnline

Brief title
CRLX030A2202

Condition

- Heart failures

Synonym
Chronic Heart Failure

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma AG

Intervention

Keyword: CHF, RLX030

Outcome measures

Primary outcome

To assess the effects of 24 hrs i.v. infusion of RLX030 30µg/kg/day compared to placebo on renal blood flow (RBF) as measured by PAH clearance in subjects with CHF and worsening symptoms

To assess the effects of 24 hrs i.v. infusion of RLX030 30µg/kg/day compared to placebo on glomerular filtration rate (GFR) as measured by IOTH clearance in subjects with CHF and worsening symptoms

Secondary outcome

Secondary objective(s)

To assess the effects of 24 hrs i.v. infusion of RLX030 30µg/kg/day compared to placebo on diuresis, fractional sodium and creatinine clearance in subjects with CHF and worsening symptoms

To assess the effects of 24 hrs i.v. infusion of RLX030 30µg/kg/day compared to placebo on central aortic systolic pressure (CASP), and radial arterial pulse waveform in subjects with CHF and worsening symptoms

To assess the safety and tolerability of 24 hrs i.v. infusion of RLX030 30µg/kg/day compared to placebo in subjects with CHF and worsening symptoms

To investigate the pharmacokinetics of 24 hrs i.v. infusion of RLX030 30µg/

kg/day in subjects with CHF and worsening symptoms

Exploratory objective(s)

• To explore the effects of RLX030 30µg/kg/day during and after 24 hrs i.v.

infusion compared to placebo on circulating and urinary cardio-renal biomarkers

when administered to subjects with CHF and worsening symptoms.

• To explore the effects of 24hrs i.v. infusion RLX030 30µg/kg/day compared to

placebo on renal blood flow (RBF) and redistribution of blood flow between the

cortical and medullary kidney tissue by PET / CT scanning with 15O-water in a

subset of subjects (at dedicated site only) with CHF and worsening symptoms.

Study description

Background summary

The study is designed to provide data to support the understanding of RLX030*s Mechanism of Action (MoA) through investigation of the renal hemodynamic effects at the therapeutic dose of 30 µg/kg/day as i.v. infusion for 24 hours compared to placebo in subjects with CHF, worsening symptoms and mild to moderate renal impairment (defined as estimated glomerular filtration rate (eGFR) of 30-89 mL/min/1.73 m2). To provide a better understanding of RLX030*s renal hemodynamic effects, renal blood flow and glomerular filtration will be investigated by means of paraaminohippuric acid (PAH) and iothalamate (IOTH) clearance. These data will be important for the future use of RLX030 in acute heart failure (AHF).

Study objective

Primary objective(s)
To assess the effects of 24 hrs i.v. infusion of RLX030 30µg/kg/day compared to placebo on renal blood flow (RBF) as measured by PAH clearance in subjects with CHF and worsening symptoms
To assess the effects of 24 hrs i.v. infusion of RLX030 30µg/kg/day compared to

placebo on glomerular filtration rate (GFR) as measured by IOTH clearance in subjects with CHF and worsening symptoms

Secondary objective(s)
To assess the effects of 24 hrs i.v. infusion of RLX030 30µg/kg/day compared to placebo on diuresis, fractional sodium and creatinine clearance in subjects with CHF and worsening symptoms
To assess the effects of 24 hrs i.v. infusion of RLX030 30µg/kg/day compared to placebo on central aortic systolic pressure (CASP), and radial arterial pulse waveform in subjects with CHF and worsening symptoms
To assess the safety and tolerability of 24 hrs i.v. infusion of RLX030 30µg/kg/day compared to placebo in subjects with CHF and worsening symptoms
To investigate the pharmacokinetics of 24 hrs i.v. infusion of RLX030 30µg/kg/day in subjects with CHF and worsening symptoms

Exploratory objective(s)
• To explore the effects of RLX030 30µg/kg/day during and after 24 hrs i.v. infusion compared to placebo on circulating and urinary cardio-renal biomarkers when administered to subjects with CHF and worsening symptoms.
• To explore the effects of 24hrs i.v. infusion RLX030 30µg/kg/day compared to placebo on renal blood flow (RBF) and redistribution of blood flow between the cortical and medullary kidney tissue by PET / CT scanning with 15O-water in a subset of subjects (at dedicated site only) with CHF and worsening symptoms.

Study design

This is a multicenter, double-blind, randomized, placebo-controlled study in subjects with CHF, worsening symptoms and mild to moderate renal impairment (eGFR of 30-89 mL/min/1.73 m2).
The study will consist of an up to 21 days screening period, a baseline period of approximately 24 hours and no loop diuretics administration until start of study drug and furosemide i.v. infusion, a treatment period of 24 hours, a wash-out period of 24 hour and a Study Completion evaluation approximately 4 hours after end of infusion. The duration of constant i.v. infusion with RLX030 will be 24 hours at a dose of 30µg/kg/day.
Subjects who meet the eligibility criteria at screening will have their baseline evaluations. All baseline safety evaluation results must be available prior to dosing. I.v. bolus injection followed by constant i.v. infusion of PAH and IOTH will start 3 hours before study drug infusion and last until 4 hours after the end of it. Clearance of PAH and IOTH will be determined for RBF and GFR assessments. Urine will also be collected in fractions for assessment of diuresis, sodium and creatinine clearance. CASP and radial arterial pulse waveform will be recorded using the CASPro device. Safety assessments will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, urinalysis,) adverse event and serious adverse event monitoring.

Intervention

Patients will be assigned to one of the following 2 treatment arms in a ratio of 1:1
• RLX030 30µg/kg/day as intravenous infusion for 24 hours
• Matching placebo as intravenous infusion for 24 hours

Study burden and risks

Efficacy / pharmacodynamic assessments:
• Renal blood flow (RBF) as measured by PAH clearance
• Glomerular filtration rate (GFR) as measured by IOTH clearance at the end of the 24 hours infusion are the primary variables.
The filtration fraction (FF) defined as the ratio of GFR divided by RBF in percent will be derived.

Safety assessments:
• Physical examination
• Body height
• Body weight
• Body temperature
• 12 lead ECG
• Systolic and diastolic Blood pressure (SBP, DBP) and pulse rate (PR)
• Hematology; Blood chemistry; Urinalysis
• Adverse events: from time of first administration of study drug until Study Completion. Adverse events occurring before starting study treatment but after signing the informed consent form are recorded on the Medical History/Current Medical Conditions Case Report Form.
• Serious adverse events: from time of consent until 30 days after Study Completion
• Concomitant medications/Significant non-drug therapies.

Pharmacokinetic assessments:
• Serum concentration of RLX030 during and 24 hours post infusion
• Serum anti-RLX030 antibody assessment at pre-dose

Other assessments:
• Central Aortic Systolic blood Pressure (CASP), brachial SBP, DBP, PR, mean arterial pressure (MAP) and radial arterial pulse waveform
• Urine collection intervals for total volume, sodium and creatinine clearance
• PET/CT determination of renal medullary/cortical distribution of renal blood flow (in selected site(s) in the Netherlands)

Biomarkers:
Biomarker measurements will be obtained from plasma and serum samples to determine effects relevant to heart and renal failure, cardiovascular risk, and

RLX030*s MoA and from urine samples for biomarkers of early kidney damage.
• Circulating cardio-renal biomarkers including but not limited to NT-proBNP, CTpro-ET1, hsTnT, hsCRP, TNF alpha, Il-1beta and Il-6, copeptin, aldosterone, cystatin C and other exploratory biomarkers as to be determined
• Urinary biomarkers of early kidney damage which may include cystatin C, KIM-1 and NGAL

The list may be changed or expanded further, as it is recognized that more relevant or novel biomarkers may be discovered during the conduct of this study.

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Chronic heart failure ;- On optimal standard therapy including a stable dose of loop diuretics;- Reduced systolic function (LVEF <= 45%);- BNP >= 100 pg/mL or NT-pro-BNP of >= 400 pg/mL;- NYHA Class II or III;- Worsening symptoms, e.g. fatigue and dyspnea;- Impaired renal function defined as an estimated glomerular filtration rate (eGFR) between 30-89 mL/min/1.73 m2

Exclusion criteria

- History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes;- Women of child-bearing potential unless they are using effective methods of contraception ;- Pregnant or nursing (lactating) women;- Systolic blood pressure < 110 mm Hg;- Current use of NSAIDs ;- Significant liver impairment;- Significant lung impairment;- Significant heart valve dysfunction or arrythmias;- Myocaridal infarction or acute coronary syndrome within the last 45 days;- History of hypersensitivity to iodine or shellfish

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):	01-12-2011
Enrollment:	45
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	RLX030
Generic name:	Relaxin

Ethics review

Approved WMO Date:	19-09-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-12-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-07-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-07-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-09-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-10-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-06-2014
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	EUCTR2011-001588-37-NL
CCMO	NL37640.042.11