A Phase II/III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Relaxin in Subjects with Acute Heart Failure

Published: 05-10-2010
Last updated: 04-05-2024

The objectives of this phase of the study are to confirm the efficacy of IV relaxin, in addition to standard therapy, in improving symptoms of heart failure, dyspnea, and in preventing intermediate term re-admission for HF or renal failure and...

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

Summary

ID

NL-OMON36636

Source
ToetsingOnline

Brief title
RELAX-AHF

Condition

- Heart failures

Synonym
acute decompensated heart failure, heart problems

Research involving
Human

Sponsors and support

Primary sponsor: Corthera Inc.
Source(s) of monetary or material Support: Corthera;Inc.

Intervention

Keyword: acute, failure, heart, relaxin

Outcome measures

Primary outcome

The two primary efficacy endpoints for the Phase III RELAX-AHF are:

1) Area Under the Curve (AUC) representing the change in patient-reported dyspnea from baseline measured by a 100-mm Visual Analog Scale (VAS) from baseline through Day 5

2) Moderately or markedly better patient-reported dyspnea relative to the start of study drug on the 7-point Likert scale at 6, 12 and 24 hours (at all 3 timepoints)

Safety will be assessed by comparing the relaxin group to the placebo group with regard to the frequency of adverse events, and changes in vital signs, physical examination findings, AHFrelated signs and symptoms, and clinical laboratory test results (chemistry, hematology, and urinalysis). Adverse Events (AEs) and Serious Adverse Events (SAEs) are assessed through Day 5 and Day 14, respectively.

Secondary outcome

The secondary efficacy endpoints for RELAX-AHF are:

1) Days alive out of hospital through Day 60

2) Cardiovascular death or rehospitalization due to heart failure or renal

failure through Day 60

Study description

Background summary

Relaxin is believed to orchestrate many of the maternal physiological responses to pregnancy, including increases in renal function, decreases in systemic vascular resistance, and increases in cardiac output mediated largely by increased stroke volume. These effects have been replicated in numerous non-clinical studies using relaxin, which has also demonstrated the ability to prevent or reverse the effects of two potent mediators in acute heart failure, angiotensin (Ang) II and endothelin. The presence of relaxin receptors, LGR7 and LGR8, in blood vessels strongly suggests that relaxin engages these receptors when given therapeutically. Relaxin's pharmacology is believed to be mediated by activation of the endothelin type B receptor and by nitric oxide locally within blood vessels.

Relaxin has been tested in a pilot, open label, dose ranging hemodynamic study in patients with compensated CHF (Protocol RLX.CHF.001). Relaxin administration was associated with decreases in pulmonary capillary wedge pressure (PCWP) and systemic vascular resistance (SVR) and with increases in cardiac index (CI) during infusion, with a return to baseline values by 24 hr post-dosing. Administration of relaxin was also associated with decreases in serum creatinine, BUN and uric acid,consistent with its ability to increase GFR. Relaxin showed excellent safety in these patients and appeared to be most efficacious in the lower dose groups tested.

Pre-RELAX-AHF, the dose ranging Phase 2 portion of the current protocol (RLX.CHF.003), was conducted with the objective of evaluating the efficacy and safety of IV relaxin in patients hospitalized with dyspnea due to AHF, normal to high systolic blood pressure and impaired renal function. Patients were randomized to placebo or 10, 30, 100 or 250 µg/kg/day relaxin infused IV continuously for up to 48 hours, in addition to standard therapy for HF. Serial assessments of symptom relief were made through Day 14 using 2 well accepted dyspnea scales,the Likert scale and VAS. Additional measures of efficacy included AHF signs, symptoms and outcomes, length of hospital stay, days alive and out-of-hospital to Day 60, and morbidity and mortality to Day 180.

A total of 234 patients enrolled from 8 countries. The relaxin doses evaluated were 10, 30, 100, and 250 µg/kg/day compared to placebo. Baseline

characteristics were balanced among all groups. Improvement in dyspnea was greater in the active relaxin arms vs placebo, with the largest apparent effects observed at a relaxin dose of 30 µg/kg/day. Relaxin at 30 µg/kg/day also showed trends indicating benefit in in-hospital measures of HF, including greater weight loss and resolution of symptoms and signs of congestion, less IV loop diuretic use, lower incidence of in-hospital worsening heart failure and shorter length of stay. Improvements in intermediate term outcomes, including the number of days alive and out-of-hospital to Day 60 and reduced rate of HF re-admission and cardiovascular death to day 60 were also observed in the 30 µg/kg/day group. There were also positive trends in reduction of all-cause and CV mortality at Day 180.

Decreases in blood pressure were observed across all dose groups. The decreases were generally asymptomatic and manageable. There were 2 SAEs of hypotension, assessed as unrelated to study drug, following dosing with the highest relaxin dose. Relaxin administration was not associated with symptomatic renal worsening, either during or post-dosing. However, in the 250 µg/kg/day dose group, small and asymptomatic increases from baseline in serum creatinine were observed at Day 14, suggesting nascent dose limiting renal toxicity at a dose 8-times the proposed dose for the RELAX-AHF-1 study, which is 30 µg/kg/day. There were 2 SAEs of renal failure in the study, one in the placebo group and one in the 30 µg/kg/day relaxin group. The latter was believed to be possibly related to study drug by the investigator. Overall in Pre-RELAX-AHF, there were no apparent patterns of adverse events indicating safety or tolerability issues that preclude further study of 30 µg/kg/day relaxin in patients with heart failure in RELAX-AHF-1 (the Phase III portion of the study).

Study objective

The objectives of this phase of the study are to confirm the efficacy of IV relaxin, in addition to standard therapy, in improving symptoms of heart failure, dyspnea, and in preventing intermediate term re-admission for HF or renal failure and cardiovascular death in subjects hospitalized for AHF with normal to elevated blood pressure and mild to moderate renal impairment. The study*s safety objective is to assess the overall safety of IV relaxin in this patient population.

Study design

The main phase of the study (*RELAX-AHF*) is designed to confirm the efficacy and evaluate the safety of relaxin at 30 µg/kg/day, which is the optimal dose selected based on the safety and efficacy results of the Pre-RELAX-AHF phase, versus placebo infused for up to 48 hours in
subjects hospitalized with AHF. Eligible subjects will be randomized 1:1 to receive either IV placebo or relaxin. A total of up to 1160 patients will be enrolled in multiple countries in order to attain 1100 efficacy evaluable

patients.

After signing an Ethics Committee or Institutional Review Board-approved Informed Consent Form, subjects will be asked to undergo screening procedures for study eligibility. Study drug will be administered as an IV infusion for 48 hours. If at any time during dosing, the subject*s systolic blood pressure is decreased by > 40 mm Hg from baseline but is > 100 mm Hg in 2 consecutive measurements 15 min apart, the study drug infusion rate will be decreased by 50% for the remainder of the study drug administration. If at any time during dosing, the subject*s systolic blood pressure is < 100 mm Hg in 2 consecutive measurements 15 min apart, the study drug infusion will be permanently terminated. All patients will be evaluated at screening and baseline and thereafter at 6, 12 and 24 hours, daily while hospitalized through Day 4, and at Days 5, 14 and 60 for symptoms and signs of heart failure. Patient-reported AHF symptoms will be collected using both a 7-point Likert scale describing the change in symptom severity from baseline, and a 100-mm Visual Analog Scale (VAS) describing symptom severity at each point in time. These evaluations will be done at baseline (VAS only), 6, 12 and 24 hours from start of study drug infusion and then daily while hospitalized through Day 4, and at Days 5 and 14. Subjects will have clinical evaluations, including AHF symptom assessments, vitals signs,
physical examination emphasizing signs of HF, as well as an assessment of need for further IV HF treatment and worsening HF events at least daily to the earlier of Day 4 or discharge, and then at Days 5 and Days 14 and 60. Blood and urine samples will be collected at baseline and at 24 hours (Day 1) and 48 hours (Day 2) for routine safety assessments and to evaluate renal function. Blood samples will also be collected on Days 3, 4, 5, 14 and 60. Clinical and laboratory evaluations, as detailed above, will be mandatory at Days 5, 14 and 60. If the patient is discharged from the hospital prior to these visits, these evaluations will be performed as outpatient visits. Just prior to the time that the last patient enrolled in the study reaches the Day 60 follow-up, patients who have not completed the study will be contacted to ascertain an interim vital status. All patients will be contacted by phone at Day 180 to ascertain vital status. AEs will be collected through Day 5 and SAEs collected through Day 14.

Intervention

Patients will be randomized in a 1:1 fashion to receive either IV placebo or IV relaxin at 30 µg/kg/day.

Study burden and risks

Patients will be asked to provide a self-report of dyspnea and general well-being in the form of two visual analog scales at Baseline, 6 hours, 12, 24 , and 48 hours, Days 3, 4, 5, and 14. Patients will also be asked to provide

a self report of dyspnea and well-being in the form of two Likert scales at 6, 12, 24, 48 hours and Days 3, 4, 5 and Day 14. For this assessment, patients will be positioned with the head of the bed elevated at approximately 30 degrees, and oxygen will be removed for 3-5 minutes, provided the patient is able to tolerate the removal. Patients who are unable to tolerate removal of oxygen will have it readministered immediately.

Patients will have 9 blood draws for a total volume of approximately 201 mls. During screening, patients will be required to undergo a chest x-ray to determine the presence of pulmonary congestion, and an electrocardiogram.

Patients will be examined by a physician to assess dyspnea on exertion, orthopnea, edema, rales and jugular venous pulse at Baseline, 6, 12, 24, and 48 hours, and Days 3, 4, 5, 14 and 60. The physician will also evaluate the patient for worsening failure at 24 and 48 hours, and Days 3,4,5 and 14. At Day 14 and Day 60, the patient will be asked to complete the EQ-5D, a quality of life scale. At Day 180, the patient will receive a phone call to determine vital status.

Patients will undergo frequent vital sign assessments: between Baseline and 48 hours the patient will have 22 BP and heart rate assessments and temperature and respiration will be collected at Baseline, 6, 12, 24 and 48 hours. Following completion of the infusion (whether the patient receives the full 48 hours of infusion or only a partial infusion), the patient will undergo BP and heart rate measurements at 3, 6, 9, 12, 18, 24, 30, 36, 42 and 48 hours.

Relaxin has been tested in three previous studies in patients who had heart failure:
In the largest study, relaxin was given to 169 patients and placebo was given to 61 patients with AHF. There was no difference between the relaxin and placebo groups in the rate of the complications that are typically seen in patients with AHF: heart failure, hypotension, hypertension, pneumonia and cerebral vascular accident. Some patients died but there was no difference in the rate between the relaxin groups and the placebo group. More patients in the relaxin groups showed asymptomtic hypotension compared to those in the placebo group. This is not unexpected in a drug that is being used to treat patients with AHF and normal to high blood pressure. There were no cases of serious decreases in blood pressure in subjects who received 30 µg/kg/day, but there were 2 cases of serious hypotension in the highest relaxin dose group, which was 8 times higher than the one being tested in the current study. The group that received the highest dose of relaxin had some changes in their blood tests that may have indicated some worsening kidney function but these patients did not have any symptoms that needed treatment. There was one case of kidney failure in the group of patients receiving relaxin and the investigator thought that the event could have been due to relaxin. There was also one case of kidney failure in the placebo group. Small changes in laboratory values for the asymptomatic anemia were also seen in the relaxin groups.

In another study, relaxin was given to 16 patients with compensated heart failure, a less serious form of HF. In this study, relaxin was found to be safe for these patients, even at doses much higher than being studied in this trial. In this trial, patients showed some improvement of kidney and heart function during relaxin dosing, but some patients showed signs of worsening in kidney function after relaxin dosing was stopped. This worsening was only noticed in some laboratory measurements and the patients did not report any symptoms or difficulties.

In a different study, 11 patients with severe AHF were recruited. Eight patients received relaxin and three received placebo. Some of the patients developed serious complications of AHF, such as pneumonia and cardiac arrest, and 2 patients died, but these events were not unexpected in these patients and occurred equally among the patients receiving relaxin and those receiving placebo. Therefore, the doctor concluded that these serious adverse events and deaths were related to the severity of the patients* disease and not to relaxin.

Relaxin has also been tested before in 17 previous clinical trials involving 563 patients with medical conditions other than heart failure. Relaxin has never been associated with any serious side effects in studies in normal healthy male and female volunteers, patients with fibromyalgia , young women undergoing egg donation, healthy male and female subjects undergoing dental procedures or pregnant women at term. There were side effects that were common in patients who received relaxin for long periods of time (weeks or months). Since these patients will only be receiving relaxin for up to 48 hours, it is unlikely they will experience any of these side effects:
• Heavy/irregular menstrual bleeding, mild to moderate reversible anemia, diarrhea, abdominal pain, and nausea.
• Local pain, redness, swelling, irritation and infection at the site of injection
• Antibody formation. These antibodies have caused no side effects and do not appear to reduce the effects of relaxin.
• The largest clinical studies of relaxin involving 257 subjects have been in patients diagnosed with scleroderma. Six deaths, serious worsening of kidney function and hypertension were reported among patients with scleroderma that received relaxin. The doctors believed that all of the deaths were caused by scleroderma and were not related to relaxin

There is a possibility of a mild allergic reaction such as itching or skin rash, as well as anaphylaxis.

Side effects that may associated with the different procedures that patients will undergo during the study include:
• Chest x-ray: small dose of radiation
• Electrocardiogram (ECG or EKG): The electrode patches may feel cold when first applied. In rare cases, some people may develop a rash or irritation

where the patches were placed.
• IV administration: There is the possibility of discomfort and/or pain, and a very slight chance of infection at the site of the needle placement.
• Venipuncture: There is a possibility of some discomfort, pain, a small amount of bleeding or bruising and a very small possibility of infection at the site where the needle is inserted. A catheter (plastic tube) may remain in place during your hospitalization so that a needle does not have to be inserted for every blood draw. During the screening process and the whole study, up to 201 milliliters (approximately 13 * tablespoons) of blood will be drawn.
• There may be side effects not presently known associated with the use of relaxin, as well as possible side effects related to the dose used, the duration of treatment and the method of administration. Interactions between relaxin and other medications have not been studied.

Being a part of this study while pregnant may expose the unborn child to unnecessary risks. Therefore, pregnant women will be excluded from the study. Males should not father a baby while on this study because it is not known if the drugs in this study can affect an unborn baby.

Contacts

Public
Corthera Inc.

150 Industrial Road
San Carlos, California 94070
US
Scientific
Corthera Inc.

150 Industrial Road
San Carlos, California 94070
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Able to provide written informed consent
2. Male or female >=18 years of age, with body weight <= 160 kg
3. Systolic blood pressure > 125 mmHg at the start of screening and at the end of screening
4. Hospitalized for AHF. AHF is defined as including all of the following measured at any time between presentation (including the emergency department [ED]) and the end of screening:
a. Dyspnea at rest or with minimal exertion
b. Pulmonary congestion on chest radiograph
c.BNP >= 350pg/mL or NT-pro-BNP >=1400 pg/mL
5. Able to be randomized within 16 hours from presentation to the hospital, including the ED
6. Received IV furosemide of at least 40 mg (or equivalent) at any time between admission to emergency services (either ambulance or hospital, including the ED) and the start of screening for the study
7. Impaired renal function defined as an estimated glomerular filtration rate (eGFR) on admission between 30-75 mL/min/1.73 m2, calculated using the simplified Modification of Diet in Renal Disease (sMDRD) equation

Exclusion criteria

1. Pregnant or breast-feeding women (women of child bearing potential must have the results of a negative pregnancy test recorded prior to study drug administration)
2. Administration of intravenous radiographic contrast agent within 72 hours prior to screening or acute contrast-induced nephropathy at the time of screening
3. Temperature >38°C (oral or equivalent) or sepsis or active infection requiring IV anti-microbial treatment
4. Current (within 2 hours prior to screening) or planned (through the completion of study drug infusion) treatment with any IV therapies, including vasodilators (including nesiritide), positive inotropic agents and vasopressors, or mechanical support (intra-aortic balloon pump, endotracheal intubation, mechanical ventilation, or any ventricular assist device), with the exception of IV nitrates at a dose of < 0.1 mg/kg/hr if the patient has a systolic BP > 150 mmHg at screening
5. Current or planned ultrafiltration, hemofiltration, or dialysis
6. Known significant pulmonary disease
7. Known significant valvular disease (including any of the following: severe aortic stenosis [AVA < 1.0 or mean gradient >50 on prior or current echocardiogram], severe aortic regurgitation, or severe mitral stenosis)
8. Any organ transplant recipient, or patient currently listed for transplant or admitted for any

transplantation
9. Major surgery within 30 days
10. Hematocrit < 25% or blood transfusion in the prior 14 days or active, life-threatening GI bleeding or active menorrhagia or metrorrhagia
11. Major neurologic event, including cerebrovascular events, in the prior 60 days
12. Clinical diagnosis of acute coronary syndrome within 45 days prior to screening (including the present admission) as determined by both clinical and enzymatic criteria
13. Troponin >=3 times the upper limit of normal (including "borderline/intermediate") between presentation and screening.
14. AHF due to significant arrhythmias (including any of the following: ventricular tachycardia, bradyarrhythmias with ventricular rate <45 beats per minute or any second or third degree AV block or atrial fibrillation/flutter with ventricular response of >120 beats per minute)
15. Acute myocarditis or hypertrophic obstructive, restrictive, or constrictive cardiomyopathy (does not include restrictive mitral filling patterns seen on Doppler echocardiographic assessments of diastolic function)
16. Known hepatic impairment
17. Non-cardiac pulmonary edema, including suspected sepsis
18. Administration of an investigational drug or implantation of investigational device, or participation in another trial, within 30 days before screening or previous treatment with relaxin
19. Inability to follow instructions or comply with follow-up procedures
20. Known hypersensitivity to relaxin or similar substances or to any of the excipients

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):	05-02-2011

Enrollment:	42
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	The proprietary name has not been decided to date
Generic name:	relaxin

Ethics review

Approved WMO Date:	05-10-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-01-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-02-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-03-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-06-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-06-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	08-03-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-09-2013
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	EUCTR2007-004271-19-NL
ClinicalTrials.gov	NCT00520806
CCMO	NL33622.042.10