Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Ularitide (Urodilatin) Intravenous Infusion in Patients Suffering from Acute Decompensated Heart Failure [TRUE-AHF]

Published: 21-09-2012
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The purpose of this research study is to compare 1 dose (15 ng/kg/minute) of Ularitide with a placebo-substance, to see whether Ularitide is safe and effective for the treatment of acute decompensated heart failure.

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

Summary

ID

NL-OMON41438

Source
ToetsingOnline

Brief title
Cardiorentis TRUE-AHF ULA01

Condition

- Heart failures

Synonym
acute worsening of existing heart disease

Research involving
Human

Sponsors and support

Primary sponsor: Cardiorentis
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: - Acute decompensated heart failure (ADHF), - Intravenous (IV) ularitide infusion

Outcome measures

Primary outcome

Primary Efficacy Endpoint 1:

Improvement in a hierarchical clinical composite comprised of elements

associated with: patient global assessment using a 7-point scale of symptomatic

improvement, lack of improvement, or worsening; persistent or worsening heart

failure (HF) requiring an intervention (initiation or intensification of IV

therapy, circulatory or ventilatory mechanical support, surgical intervention,

ultrafiltration, hemofiltration or dialysis); and all-cause mortality.

Assessment of the clinical composite will be performed at 6 hour (h), 24 h and

48 h after start of IV ularitide infusion.

Patients will be classified as *improved* if the patients are moderately or

markedly improved at all 3 time points (at 6 h, 24 h and 48 h) and do not

fulfill criteria for *worse* during the first 48 hours following the start of

the study drug infusion. Patients will be classified as *worse* if (during the

48 h) they die; experience worsening HF requiring a prespecified intervention

at any time during the first 48 h; or experienced moderate or marked worsening

of their global assessment at any of the 3 time points (at 6 h, 24 h or 48 h).

Co-primary efficacy endpoint 2: evaluates freedom from cardiovascular mortality following randomization for the entire duration of the trial.

Primary Safety Endpoints:

All-cause mortality and cardiovascular rehospitalization at 30 days after start of study drug infusion.

Secondary outcome

Secondary Endpoints:

•Length of stay of index hospitalization in hours after start of study drug infusion up to 30 days.

•Length of stay in intensive care (intensive care unit [ICU] or critical care unit [CCU]) during the first 120 h following the start of the study drug infusion.

•Number of events of persistent or worsening HF requiring an intervention from the start of the study drug infusion to 120 h.

•Proportion of patients with persistent or worsening HF and requiring an intervention from the start of study drug infusion to 120 h.

•Reduction in rehospitalization for heart failure within 30 days after initial hospital discharge.

•Change of N-terminal pro-brain natriuretic peptide (NT-pro BNP) at 48 h of treatment compared to baseline.

•Time to completion of last dose of any IV drugs that can be used for the treatment of HF (e.g., diuretics, vasodilators, or positive inotropic

agents) for the first 120 h following the start of the drug infusion.

•Change in serum creatinine from baseline through 72 h.

•Combined all-cause mortality and cardiovascular rehospitalization at Day 180

after start of study drug infusion, including patients still hospitalized at

Day 30.

Study description

Background summary

This is a Prospective, randomized, placebo-controlled, double-blind, multinational, multi-center, Phase III study to evaluate the effect of a continuous intravenous (IV) ularitide infusion on the clinical status of patients (males and females between 18 and 85 years old) with ADHF. Ularitide is an investigational (experimental) drug that has not been yet approved by regulatory agencies in any country. It is a chemically synthesized form of urodilatin, a human renal natriuretic peptide that is produced in the kidneys and found primarily in urine and in very low concentrations in blood plasma.

Study objective

The purpose of this research study is to compare 1 dose (15 ng/kg/minute) of Ularitide with a placebo-substance, to see whether Ularitide is safe and effective for the treatment of acute decompensated heart failure.

Study design

Patients with ADHF who meet all inclusion and exclusion criteria will be randomized on a 1:1 basis to continuous IV infusion of either ularitide 15 ng/kg BW/min or matching placebo for 48 h. In addition, patients may receive all appropriate therapy that may include vasodilatory, inotropic, and diuretic support as clinically indicated. However, use of nesiritide, levosimendan, milrinone, or any other phosphodiesterase inhibitor is not allowed during the first 72 h following the start of the infusion.
All timepoints refer to the start of the study drug infusion at the timepoint called *0 hours* (t0). Efficacy endpoints will be assessed at 6 h, 24 h and 48 h from the start of infusion.
Safety parameters will be assessed during hospitalization and adverse events (AEs) and serious adverse events (SAEs) will be evaluated until Day 30 after the start of therapy.

All patients will be assessed through phone call follow-ups at Day 60, Day 90, Day 180 and every 90 days after start of the study treatment for the occurrence of cardiovascular rehospitalization and all-cause mortality.

Intervention

- Ularitide for injection. Ularitide, a natriuretic peptide, is lyophilized with mannitol (2.5 mg ularitide with 20 mg mannitol) in labeled 10 mL vials.
- Matching placebo, i.e., 20 mg mannitol in vials that are identical to the ularitide vials to maintain blinding.
- In addition, patients may receive all appropriate therapy that may include vasodilatory, inotropic, and diuretic support as clinically indicated. However, use of nesiritide, levosimendan, milrinone, or any other phosphodiesterase inhibitor is not allowed during the first 72 h following the start of the infusion.
- Pregnancy test at screening visit in potential childbearing females
- Routine evaluations like physical examination, check of vital signs (blood pressure, heart rate, body temperature), electrocardio¬grams (recordings of heart*s electrical activity), chest x-ray, and blood samples for routine laboratory testing will be done.
- During this study approximately 120 mL of blood will be drawn. Information like race, sex, height, weight, medical history and medications subjects are taking will be collected.
- Subject may give permission to give a blood sample to investigate biomarkers substances in their blood. This is optional and subject can participate in the rest of the study, even if they do not want to give a blood sample for biomarker research.
- Study assessments will be performed at time points 0 hour (h), 6h, 24h, 48h, 60h, 72h and 120h after start of the study treatment. Several follow up telephone calls (Day 60, Day 90, Day 180 and every 90 days after start of the study treatment until the end of trial) are planned.

Study burden and risks

Benefit:
Study investigations and monitoring could provide additional information that might improve subjects healthcare. In two previous clinical trials, Ularitide significantly reduced some clinical effects of ADHF (significantly reduced PCWP; significanlty improvement in dyspnea; a dose-dependent increase in the mean cGMP plasma concentration).

Burden and risks:
Whenever a catheter is placed in a vein, there is a risk of bruising, discomfort, bleeding or infection. Needle punctures of a vein for blood draws may cause bleeding, bruising, discomfort, infections and/or pain at the needle site; subject may experience feeling of light-headedness or dizziness.

Intravenous infusions may result in leakage of fluid into the surrounding tissues and formation of blood clots. Skin irritation can occur during an ECG from the electrodes or gel that is used. During chest x-ray, you will be exposed to a small dose of radiation.
Treatment with Ularitide may lead to the occurrence of unwanted symptoms (*side effects*) like hypotension (low blood pressure), confusion, restlessness, dyspnea, dizziness, sweating increased, weakness, headache and increased or decreased heart rate, nausea, loss of consciousness, and paleness of skin.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1) Males and females aged 18 to 85 years.
2) Unplanned hospitalization or emergency department visit for ADHF. Acute HF is defined as

including all of the following:
a) Dyspnea at rest in a recumbent sitting position (30 to 45 degrees), which has worsened within the past week.
b) Radiological evidence of HF on a chest X-ray (if an appropriate chest computerized tomography scan is done; the X-ray need not be performed).
c) Brain natriuretic peptide (BNP) >500 pg/mL or NT-pro BNP >2000 pg/mL.
3) Ability to start infusion of the study drug within 12 h after initial clinical assessment performed by a physician at the emergency room/hospital.
4) Ability to reliably carry out self-assessment of symptoms.
5) Systolic blood pressure (SBP) >=116 mmHg and <=180 mmHg.
6) Persisting dyspnea at rest despite standard background therapy for ADHF (as determined by the Investigator) which must include IV furosemide (or equivalent diuretic) at >=40 mg (or its equivalent) at any time after start of emergency services (ambulance, emergency department, or hospital). At the time of randomization, the patient must still be symptomatic. In addition, the patient should not have received an IV bolus of a diuretic for at least 2 h prior to randomization, and the infusion rates of ongoing IV infusions of medication to treat HF must not have been increased or decreased for at least 2 h prior to randomization.
7) Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local privacy regulations).

Exclusion criteria

1) Known active myocarditis, obstructive hypertrophic cardiomyopathy, congenital heart disease, restrictive cardiomyopathy, constrictive pericarditis, uncorrected clinically significant primary valvular disease.
2) Treatment with dobutamine at a dose >5 µg/kg/min or use of drugs for support of BP at the time of randomization.
3) Treatment with levosimendan, milrinone, or any other phosphodiesterase inhibitor within 7 days before randomization.
4) Treatment with nesiritide within 30 days before randomization.
5) Creatinine clearance <25 mL/min/1.73m² (as measured by the MDRD formula) at the time of screening.
6) Planned coronary revascularization procedure (percutaneous coronary intervention or coronary artery bypass grafting) within 5 days of randomization.
7) Clinical diagnosis of acute coronary syndrome meeting any 2 of the following 3 criteria:
a) Prolonged chest pain at rest, or an accelerated pattern of angina;
b) ECG changes indicative of ischemia or myocardial injury, defined as: a new ST elevation at the J point of two anatomically contiguous leads with the cut-off points: >= 0.2 mV in men >=40 years (> 0.25 mV in men < 40 years) or >= 0.15 mV in women in leads V2-V3 and/or >= 0.1 mV in other leads; or ST depression and T wave changes. New horizontal or down-sloping ST depression >= 0.05 mV in two contiguous leads; and/or new T inversion >= 0.3 mV in two contiguous leads;
c) Serum troponin >3 times upper limit of normal.
8) Clinically suspected acute mechanical cause of ADHF (e.g., papillary muscular rupture).

The diagnosis need not be confirmed by imaging or cardiac catheterization.
9) Anemia (hemoglobin <9 g/dL or a hematocrit <25%).
10) Known vasculitis, active infective endocarditis, or suspected infections including pneumonia, acute hepatitis, systemic inflammatory response syndrome, or sepsis.
11) Body temperature >=38°C just prior to randomization.
12) Acute or chronic respiratory disorder (e.g., severe chronic obstructive pulmonary disease) or primary pulmonary hypertension sufficient to cause dyspnea at rest, which may interfere with the ability to interpret dyspnea assessments or hemodynamic measurements.
13) Terminal illness other than congestive heart failure with expected survival <180 days.
14) Any previous exposure to ularitide.
15) Known allergy to natriuretic peptides.
16) Participation in an investigational clinical drug trial within 30 days prior to randomization.
17) Current drug abuse or chronic alcoholism sufficient to impair participation and compliance to study protocol.
18)Women who are breast-feeding.
19)Women of child-bearing potential (i.e. pre-menopausal women) without documentation of a negative urine/blood pregnancy assay within 12 h prior to randomization.
20) Any condition that, in the Investigator's opinion, makes the patient unsuitable for study participation.
21) Legal incapacity or limited legal capacity.
22) Patients requiring mechanical circulatory support.
23) Patients with severe hepatic impairment.

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):	30-05-2013

Enrollment:	64
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ularitide
Generic name:	urodilatin (chemical name)

Ethics review

Approved WMO Date:	21-09-2012
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-11-2012
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-12-2012
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-01-2013
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-03-2013
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-03-2013
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	22-04-2013
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	30-05-2013
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-06-2013
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-07-2013
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-10-2013
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-10-2013
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-09-2014
Application type:	Amendment
Review commission:	METC St Elisabeth Ziekenhuis (Tilburg)
Approved WMO Date:	26-09-2014
Application type:	Amendment
Review commission:	METC St Elisabeth Ziekenhuis (Tilburg)
Approved WMO Date:	06-03-2015
Application type:	Amendment
Review commission:	METC St Elisabeth Ziekenhuis (Tilburg)
Approved WMO	

Date:	08-05-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	EUCTR2010-024249-59-NL
ClinicalTrials.gov	NCT01661634
CCMO	NL41635.008.12