Double-Blind, Placebo-Controlled, Multicenter Acute Study of Clinical Effectiveness of Nesiritide in Subjects with Decompensated Heart Failure

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

Summary

ID

NL-OMON31659

Source
ToetsingOnline

Brief title
ASCEND-HF

Condition

- Heart failures

Synonym
Heartfailure, weakness of the heart

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag

Source(s) of monetary or material Support: de opdrachtgever van het onderzoek (Zie ook B6)

Intervention

Keyword: Acute, Effectiveness, Heartfailure, Nesiritide

Outcome measures

Primary outcome

The study has two co-primary hypotheses:

· Nesiritide administered in addition to standard care is superior to placebo administered in addition to standard care in the reduction of the composite endpoint of HF rehospitalization and all-cause mortality from randomization through Day 30 in subjects with ADHF, and

· Nesiritide administered in addition to standard care is superior to placebo administered in addition to standard care in relieving dyspnea symptoms, as measured by self-assessed Likert scale at 6 or 24 hours after study drug initiation, in subjects with ADHF

Secondary outcome

The secondary objectives of this study are to evaluate the effect of treatment with nesiritide, compared with placebo, when each is administered in addition to standard care in ADHF, in:

· Improving subject self-assessed overall well-being at 6 or 24 hours after study drug initiation

· Increasing the number of days alive and outside of the hospital from randomization through Day 30

· Reducing the composite of cardiovascular rehospitalization and cardiovascular

mortality from randomization through Day 30

- the effect on persistent or worsening of heart failure from randomization

through index hospitalization (amendment INT-1).

Study description

Background summary

Heart and bloodvessel diseases are one of the major causes of death in the western world. Heartfailure is a serious disease. Other medications are available for the treatment of heart failure. Some of these medications include diuretics, oxygen, ACE inhibitors, Angiotension II receptor blockers (ARBs), beta blockers, inotropes, digoxin, and nitrates. In this trial, it will be investigated whether nesiritide can be a valuable contribution to the current therapy for ADHF.

Study objective

The primary objective of this study is to evaluate whether treatment with nesiritide improves patient outcomes (as measured by reduction in the composite of HF rehospitalization and all-cause mortality through 30 days after randomization [Day 30]) or HF symptoms (as measured by subject self-assessed Likert dyspnea scale at 6 and 24 hours after study drug initiation) compared with placebo when each is administered in addition to other standard therapies in subjects with ADHF.

Study design

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter study evaluating the efficacy and safety of nesiritide administered in addition to standard care compared with placebo administered in addition to standard care in subjects with ADHF. The co-primary endpoints are: 1) the composite of HF rehospitalization and all-cause mortality from randomization through Day 30 and 2) subject self-assessed symptoms of dyspnea at 6 or 24 hours after study drug initiation. To be eligible, subjects must be hospitalized with a primary diagnosis of ADHF, or experience ADHF while already hospitalized for another reason. Once all inclusion criteria are met and exclusion criteria are ruled out, subjects will be randomly assigned to 1 of 2 treatment groups, nesiritide or placebo, blocked by site. Approximately 7,000 subjects (3,500 per treatment group) will be enrolled in this study.
The study will be divided into a screening phase, a double-blind treatment phase, and a follow-up phase including a Day-30 visit and a Day-180 telephone

contact. A pharmacogenomic blood sample (10 mL) will be collected from subjects who give separate written informed consent for this component of the study (where local regulations permit). Participation in pharmacogenomic research is optional.

Intervention

Treatment with i.v. nesiritide or placebo, added to treatment with standard care. Nesiritide will be administered for a period of at least 24 hours up to a maximum of 168 hours (7 days), at the investigator*s discretion.

Study burden and risks

Burden for the patient: patients will be included during hospitalisation with diagnosis of ADHF. During the hospitalisation, several assessments will be done like assessment of the vital signs, physical examination, blooddraws. In addition, the patients will be asked to complete questionnaires about their dyspnea, general well-being and quality of life. After discharge from the hospital, the patient will be asked to come back to the hospital for one more time (day 30 after randomization). On Day 180, there will be a telephone call to assess the patient's (survival) status at that time.
Risks:Nesiritide works by lowering the blood pressure. In some patients (11%) the blood pressure is lowered too much. Bloodpressure will be closely monitored and when the blood pressure is decreased too much, the study doctor will reduce or stop the dose of study drug.
Reduced kidney function is often seen in heart failure patients and has been reported in 5% of nesiritide treated patients. The study doctor will closely watch kidney function during this study.
Other side effects which might happen are headache, dizziness and nausea. Events that were reported less frequently (at least 1% of patients) were slow heart rate, vomiting, sweating, itching, or rash.
Nesiritide has not been studied in a trial designed to specifically evaluate the risk of death associated with its use. In seven nesiritide clinical trials, through 30 days, 5.5% in the nesiritide treatment group died as compared with 4.3% in the group treated with other standard medications. In five clinical trials, through 180 days, 21.5% in the nesiritide treatment group died as compared with 20.7% in the group treated with other medications. At present, there is not enough information to know if there is an increased risk of death after treatment with nesiritide compared with the treatment with other standard medications.
The patient will be screened extensively before randomisation and willl be closely monitored during the trial. In case of hyposention, guidance on the study medication is given in the protocol (pag. 37-38 of the protocol).
Risks of blooddrawing and use of an IV catheter are minimal.

Contacts

Public
Janssen-Cilag

Dr. Paul Janssenweg 150
5026 RH Tilburg
Nederland
Scientific
Janssen-Cilag

Dr. Paul Janssenweg 150
5026 RH Tilburg
Nederland

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Men or women 18 years of age or older
- Hospitalized for the management of ADHF or diagnosed with ADHF within 48 hours after being hospitalized for another reason
- Diagnosis of ADHF must meet the following definition:
- Dyspnea at rest or dyspnea with minimal activity
AND at least 1 of the following signs:
- Tachypnea with respiratory rate >20 breaths per minute, OR
- Pulmonary congestion/edema with rales or crackles/crepitations at least one-third above lung base
AND at least 1 of the following objective measures:
- Chest x-ray with pulmonary congestion/edema, OR
- B-type natriuretic peptide ³400 pg/mL or NT-proBNP ³1,000 pg/mL at presentation, OR

- Pulmonary capillary wedge pressure >20 mmHg, OR
- Ejection fraction <40% measured by any modality (echocardiography, nuclear testing, cardiac MRI, ventricular angiography) within 12 months before randomization without intervening revascularization or cardiac surgery

Exclusion criteria

- Hospitalized for more than 48 hours before randomization
- Likely to be discharged from the hospital in 24 hours or less
- At high risk for hypotension:
- Baseline SBP <100 mmHg or
- Systolic blood pressure <110 mmHg with i.v. nitroglycerin or another i.v. vasodilator used at baseline
- Persistent, uncontrolled hypertension (SBP >180 mmHg)
- Have any of the following cardiovascular disease parameters:
- Echocardiogram (ECG) with new ST elevation >1 mm in 2 consecutive leads
- Acute coronary syndrome as primary diagnosis
- A coronary catheterization or other coronary intervention is planned within 48 hours
- History of cardiac valvular stenosis, restrictive cardiomyopathy, hypertrophic obstructive cardiomyopathy, or pericardial tamponade
- PCWP =<20 mmHg within 6 hours before randomization (only if measured)
- Have a left ventricular assist device
- Medication History:
- Received first i.v. treatment of diuretics, vasodilators or inotropes for HF more than 24 hours before randomization
- Treated with levosimendan or milrinone within 30 days before randomization or anticipated need for one of these medications during the current hospitalization
- Treated with i.v. nitroglycerin, i.v. dobutamine <5 mg/kg/min or another i.v. vasoactive medication, the dosage of which is not stable for 3 hours before randomization
- Treated with dobutamine >= 5 mg/kg/min. at the time of randomization
- Had prior therapy with nesiritide in the past 30 days, or anticipate the need for open-label nesiritide during the current hospitalization
- Known allergic reaction or hypersensitivity to nesiritide
- Laboratory abnormalities (when laboratory values are available)
- Troponin level >5 times the upper limit of normal (ULN)
- Creatine kinase - MB (CK-MB) levels >3 times ULN
- BNP or NT-proBNP is within normal limits (i.e., BNP <100 pg/mL or NT-proBNP <125 pg/mL for subjects <75 years old; NT proBNP <425 pg/mL for subjects >=75 years old)
Comorbid Diseases
- Chronic or intermittent renal support therapy (hemodialysis, ultrafiltration, or peritoneal dialysis)
- Significant chronic or acute lung disease that might interfere with the ability to interpret the dyspnea assessments
- Serious comorbid disease in which the life expectancy of the subject is less than 6 months
- Anemia

- Active gastrointestinal bleeding

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:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-12-2007
Enrollment:	75
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Natrecor
Generic name:	Nesiritide

Ethics review

Approved WMO Date:	10-12-2007
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-04-2008

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-07-2008
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	EUCTR2007-001670-84-NL
ClinicalTrials.gov	NCT00475852
CCMO	NL20006.042.07