A multicenter, randomized, double-blind, placebo-controlled study of the effects of KW-3902 Injectable Emulsion on heart failure signs and symptoms, diuresis, renal function, and clinical outcomes in subjects hospitalized with worsening renal function and heart failure requiring intravenous therapy.

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Ethical review	Approved WMO
Status	Pending
Health condition type	Cardiac disorders, signs and symptoms NEC
Study type	Interventional

Summary

ID

NL-OMON31013

Source
ToetsingOnline

Brief title
REACH UP

Condition

- Cardiac disorders, signs and symptoms NEC
- Renal disorders (excl nephropathies)

Synonym
cardiac failure / decompensated heart failure

Research involving
Human

Sponsors and support

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

Intervention

Keyword: - Combination therapy with IV furesomide, - Heart Failure, - Worsening renal function

Outcome measures

Primary outcome

Proportion of treatment failures within 30 days (includes any one of the

following criteria):

• Death or readmission for heart failure or worsening renal function through 30

days after randomization,

OR

• Worsening symptoms and/or signs of heart failure occurring >24 hours after

the start of study drug to Day 7 or discharge, whichever occurs first, such

that there is a need for any one of the following types of *rescue therapy*:

- new diuretic initiation or a >=50% dose increase of the IV

diuretic daily

dose, or initiation or increase in dose of oral metolazone or

IV

chlorothiazide as accompanying therapy to loop diuretics,

or

- initiation of ultrafiltration

or

- initiation of an IV inotrope or an increase in the dose of

dopamine,

dobutamine, or milrinone if these were in use at the time of

randomization

or

- initiation of mechanical ventilatory (including BiPAP or CPAP)

or circulatory

support

OR

• Worsening renal impairment as defined by an increase in SCr of >=0.3 mg/dL, or

the initiation of hemofiltration or dialysis, from the time of randomization to

Day 7 or discharge, whichever occurs first.

Secondary outcome

• Number of days, during the 30 days after randomization, that the subject is

alive and out of the hospital

• Change in dyspnea and general well being as determined by Likert scale at 24

and 72 hours post-randomization

Study description

Background summary

This study is conducted to examine if administration of KW-3902IV with intravenous furesomide in patients with heart failure and renal impairment

results in an improvement of the signs and symptoms of heart failure and renal impairment.
In patients with acute heart failure diuresis is the therapeutic aim. Diuretics however frequently cause a vicious circle of deteriorating kidney function and diminishing diuretic impact. Diuretics ensure that the kidneys extract more fluid, but as a result the sodium concentrations in the kidneys raise, which result in a reduced fluid excretion (this happens automatically). KW-3902 now ensures that certain sensors which are responsible for this mechanism are being blocked. As a result the diuretic effect of the diuretics remains and improves, and the kidney function is preserved.

Study objective

The objectives of this study are to evaluate the effect of KW-3902IV, in addition to standard therapy, on the proportion of worsening heart failure and worsening renal function after initiation of therapy through Day 7 or discharge, whichever occurs first, and on the proportion of deaths or rehospitalizations for heart failure or worsening renal function over 30 days, and to estimate and compare within-trial medical resource utilization and direct medical costs between subjects treated with KW-3902IV versus placebo.

Study design

Multicenter, randomized, double-blind, parallel-group, placebocontrolled.

Intervention

Subjects will be randomized in a 1:1 ratio to one of two study arms. The specific dosing regimen and administration procedures are as follows:
• KW-3902IV 30 mg once daily (total volume 60 mL)
• Placebo once daily (total volume 60 mL)
Study drug (KW-3902IV or placebo) will be administered as a 4 hour infusion. Study drug will be administered once daily for 3 days or until discharge, whichever occurs earlier, but study drug will not be administered for less than 2 days

Study burden and risks

Patients have already been hospitalized for heart failure and get the standard of care. If they particpate in the trial the standard treatment in combination with the study treatment is continued.
- Blood samples are being taken as standard of care, each morning the study requires a blood sample is to be taken for analysis in a central laboratory (on days 1-7 and day 14). The screening values are obtained by means of the standard blood draw at admission.
- Patients are asked to complete a questionnaire on day 14, 30 (telephone

contact) and 60 (telephone contact) (lasts maximum 10 minutes)
- Patients are are asked on day 180 (telephone contact) to ascertain their vital status
- Patients are examined on a daily base (days 1-7 and day 14) (standard physical research) and 2 questions about their dyspnea and general well-being are asked to assess the primary endpoint.

Contacts

Public
NovaCardia, Inc.

12651 High Bluff Drive, Suite 200
San Diego, CA 92130
US
Scientific
NovaCardia, Inc.

12651 High Bluff Drive, Suite 200
San Diego, CA 92130
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, or a legally authorized representative is able to provide written informed consent
2. Male or female 18 years of age or greater
3. Dyspnea at rest or with minimal exertion at randomization

4. Fluid overload as manifested by at least one of the following present at randomization:
• JVP >10 cm, OR
• Pulmonary rales >=1/3 up the lung fields, not clearing with cough, OR
• >=2+ peripheral or pre-sacral edema
5. Estimated creatinine clearance (CrCl) between 20-60 mL/min using the Cockcroft-Gault equation (corrected for height in edematous subjects >=100 kg) based on a serum creatinine (SCr) value drawn within approximately 6 hours of randomization
6. Worsening renal function as manifested by one of the following present at randomization:
• An increase in SCr of at least 25% and at least 0.3 mg/dL from the time of initial presentation for this hospitalization in patients hospitalized with heart failure requiring IV diuretic therapy, OR
• A documented increase in SCr over the preceding 30 days prior to randomization of at least 40% and at least 0.3 mg/dL in patients being admitted for heart failure requiring IV therapy (these patients must be randomized within 24 hours of admission)
7. Anticipated need for IV diuretic treatment for at least 48 hours after the start of study drug
8. BNP >500 pg/mL or NT-pro-BNP >2000 pg/mL
9. Systolic blood pressure >=90 mmHg at randomization. Subjects with systolic blood pressure of 85-89 mmHg at randomization may be included if their usual systolic blood pressure measurements are consistently within 85-89 mmHg while clinically stable.

Exclusion criteria

1. Previous exposure to KW-3902
2. Pregnant or breast feeding women. Women of child bearing potential must have a negative serum pregnancy test prior to enrollment.
3. Any administration of IV radiographic contrast within 14 days of randomization or any procedures with IV radiographic contrast planned during this hospitalization
4. Administration of IV vasodilators within 6 hours of randomization (with the exclusion of nitrates, which are allowed)
5. Serum potassium <3.5 meq/L (3.0-3.4 meq/L will be allowed if adequate parenteral supplemental potassium is being administered)
6. Ongoing or planned therapy for heart failure with mechanical circulatory support (intra-aortic balloon pump, endotracheal intubation, ventricular assist device) or ventilatory support (including BiPAP or CPAP)
7. Ongoing or planned treatment with ultrafiltration, hemofiltration, or dialysis during this hospitalization
8. Rapidly progressive acute renal failure as manifested by an increase in SCr >=0.7 mg/dL in a 24-hour period
9. Evidence of acute tubular necrosis (urinary sediment, urinary sodium excretion, biopsy, etc.) or post-obstructive nephropathy or other exogenous causes of acute kidney injury, unrelated to heart failure or its treatment (contrast media, cyclosporine, other nephrotoxins)
10. Severe pulmonary disease (as evidenced by pre-admission or current oral steroid dependency, current treatment with IV steroids, or previous history of intubation for acute exacerbation)
11. Significant stenotic mitral or aortic valvular disease

12. Heart transplant recipient or admitted for cardiac transplantation or LVAD surgery
13. Any major surgery within 2 weeks prior to screening (cardiac or non-cardiac)
14. Clinical evidence of acute coronary syndrome in the 2 weeks prior to screening
15. Hgb <8 g/dL, or active bleeding requiring transfusion
16. Acute myocarditis or hypertrophic obstructive, restrictive, or constrictive cardiomyopathy. This criterion does not include restrictive patterns seen on Doppler.
17. Known hepatic impairment (total bilirubin >3 mg/dL, albumin <2.8 mg/dL, or increased ammonia levels if performed)
18. Non-cardiac pulmonary edema
19. Temperature >38°C (oral or equivalent)
20. Sepsis or active infection requiring IV anti-microbial treatment
21. Administration of an investigational drug or device or participation in another trial within 30 days before randomization
22. Current or anticipated therapy with atanazavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, or voriconazole
23. Administration of any vasopressor or inotropic drug within 72 hours of randomization (with the exception of ongoing dopamine or dobutamine at doses <=5 mcg/kg/min or milrinone at a dose of <=0.25 mcg/kg/min, which are allowed IF at a stable dose for the preceding 24 hours AND provided there has been no decrease in SCr during the prior 24 hours)
24. Inability to follow instructions or comply with study procedures
25. Allergy to soybean oil or eggs
26. History of seizure (except febrile seizure)
27. Stroke within 2 years
28. History of brain tumor of any etiology
29. Brain surgery within 2 years
30. Encephalitis/meningitis within 2 years
31. History of penetrating head trauma
32. Closed head injury with loss of consciousness (LOC) over 30 minutes within 2 years
33. History of or at risk for alcohol withdrawal seizures
34. Advanced Alzheimer*s disease
35. Advanced multiple sclerosis

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:	Prevention

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-04-2007
Enrollment:	4
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	KW-3902IV
Generic name:	[3,7-dihydro-1,3-dipropyl-8-(tricyclo[3.3.1.03,7]nonyl-1H-purine-2,6-dione]: selective adenosine A1

Ethics review

Approved WMO Date:	13-04-2007
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-06-2007
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-08-2007
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-12-2007
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	EUCTR2006-006843-29-NL
CCMO	NL16610.042.07