Protocol CKI-302 KW-3902IV in the treatment of subjects with acute heart failure syndrome
A multicenter, randomized, double-blind, placebo-controlled study of the effects of KW-3902 injectable emulsion on heart failure signs and symptoms and renal function in subjects with acute heart failure syndrome and renal impairment who are hospitalized for volume overload and require intravenous diuretic therapy

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To evaluate the effect of KW-3902IV in addition to IV loop diuretic therapy on heart failure signs and symptoms, persistent renal dysfunction, morbidity and mortality, and safety in subjects hospitalized with acute heart failure syndrome, volume...

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

Summary

ID

NL-OMON31606

Source
ToetsingOnline

Brief title
PROTECT-2

Condition

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

Synonym
acute cardiac failure / acute decompensated heart failure

Research involving
Human

Sponsors and support

Primary sponsor: NovaCardia, Inc. (a wholly owned subsidiary of Merck & Co., Inc.)
Source(s) of monetary or material Support: NovaCardia;Inc. (a wholly owned subsidiary of Merck & Co.;Inc.)

Intervention

Keyword: - Acute Heart Failure, - Combination therapy with IV furesomide, - Preserve/protect kidney function

Outcome measures

Primary outcome

A categorical outcome of:

- treatment success,

- patient unchanged, or

- treatment failure

(definitions see protocol pages 30 and 31).

Secondary outcome

- Time to death or rehospitalization for cardiovascular or renal causes through

Day 60.

- Proportions of subjects with persistent renal impairment as defined by a SCr

increase of >=0.3 mg/dL from randomization to Day 7, confirmed at Day 14, or the

initation of hemofiltration or dialysis through Day 7.

(page 31 of protocol)

Study description

Background summary

This study is conducted to examine if administration of KW-3902IV with intravenous loop diuretics in patients with acute 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

To evaluate the effect of KW-3902IV in addition to IV loop diuretic therapy on heart failure signs and symptoms, persistent renal dysfunction, morbidity and mortality, and safety in subjects hospitalized with acute heart failure syndrome, volume overload, and renal impairment.
To estimate and compare within-trial medical resource utilization and direct medical costs between patients treated with KW-3902IV and placebo.

Study design

Multicenter, randomized, double-blind, parallel-group, placebo controlled.

Intervention

Four treatment arms were evaluated in a double-blind fashion during the pilot phase.
1. Placebo
2. KW-3902; 10mg
3. KW-3902; 20mg
4. KW-3902; 30mg
Based on the pilot phase data the doses 10 mg and 20 mg of KW-3902IV were dropped for the main phase of the study. In the main phase of the study, two

treatment arms will be evaluated in double-blind fashion:
1. Placebo
2. KW-3902IV; 30 mg
Study drug (placebo or KW-3902 30 mg IV) will be administered each day as a 4-hour infusion for 3 days. The infusion will begin as soon as possible following randomization, preferably in the morning hours and continue at approximately the same time each day for 3 days or until discharge, if earlier. Study drug must be administered at least 15 hours after the conclusion of the previous study drug administration.
To ensure blinding, all study drug doses will be administered in the same total dose volume.

Study burden and risks

Patients have already been hospitalized for acute 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 and 60 (telephone contact) (lasts maximum 10 minutes)
- 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

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

See also pages 46 and 47 of protocol
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. History of heart failure of at least 14 days duration for which diuretic therapy has been prescribed
4. Hospitalized for AHFS requiring IV diuretic therapy. AHFS is defined as dyspnea at rest or with minimal exertion and signs of fluid overload manifested by at least one of the following at time of randomization:
• JVP >8 cm, or
• Pulmonary rales >=1/3 up the lung fields, not clearing with cough, or
• >=2+ peripheral edema, or pre-sacral edema,
5. Eligible for randomization within 24-hours of presentation to the hospital (including time spent in the emergency department). Study drug infusion should start as soom as possiblefollowing randomization, preferably in the morning hours.
6. Anticipated need for IV furosemide >=40 mg/day (or equivalent dose of IV loop diuretic) for at least 24 hours after start of study drug
7. Impaired renal function defined as a creatinine clearance on admission between 20-80 mL/min using the Cockcroft-Gault equation for estimating creatinine clearance (corrected for height in edematous or obese subjects >=100 kg)
8. Systolic blood pressure >=95 mmHg (subjects with a systolic blood pressure of 90 - 94 mmHg at randomization may be included if their usual systolic blood pressure measurements are consistently within this range while clinically stable)

Exclusion criteria

See also pages 47-49 of protocol

9. Pregnant or breast feeding women. Women of child bearing potential must have a negative urine or serum pregnancy test prior to enrollment.
10. Acute contrast induced nephropathy
11. Temperature >38°C (oral or equivalent) or sepsis or active infection requiring IV anti-microbial treatment
12. Serum potassium <3.5 mEq/L (3.0-3.4 mEq/L will be allowed if parenteral supplemental potassium is being administered)
13. Ongoing or planned IV therapy for AHFS with positive inotropic agents, vasopressors, vasodilators, or mechanical support (intra-aortic balloon pump, endotracheal intubation, ventricular assist device) with the exception of IV nitrates
14. BNP <500 pg/mL or NT-pro-BNP <2000 pg/mL
15. Ongoing or planned treatment with ultrafiltration, hemofiltration, or dialysis
16. Severe pulmonary disease (as evidenced by pre-admission or current oral steroid dependency, current treatment with IV steroids, or previous history of CO2 retention or intubation for acute exacerbation)
17. Significant stenotic valvular disease (severe aortic stenosis, mitral stenosis)
18. Heart transplant recipient or admitted for cardiac transplantation
19. Clinical evidence of acute coronary syndrome in the 2 weeks prior to screening
20. AHFS due to significant arrhythmias (ventricular tachycardia, bradyarrhythmias with slow ventricular rate [<45 beats per minute] or atrial fibrillation/flutter with a rapid ventricular response of >120 beats per minute)
21. Acute myocarditis or hypertrophic obstructive, restrictive, or constrictive cardiomyopathy. This criterion does not include restrictive patterns seen on Doppler.
22. Known hepatic impairment (total bilirubin >3 mg/dL, albumin <2.8 mg/dL, or increased ammonia levels if performed)
23. Non-cardiac pulmonary edema, including suspected sepsis
24. Administration of an investigational drug or device, or participation in another trial, within 30 days before randomization
25. Current or anticipated therapy with atanazavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, or voriconazole
26. Systolic blood pressure >160 mmHg at randomization
27. Inability to follow instructions or comply with follow-up procedures
28. Allergy to soybean oil or eggs or benzodiazepines
29. History of seizure (except febrile seizure)
30. Stroke within 2 years
31. History of or current brain tumor of any etiology
32. Brain surgery within 2 years
33. Encephalitis/meningitis within 2 years
34. History of penetrating head trauma
35. Closed head injury with loss of consciousness (LOC) over 30 minutes within 2 years
36. History of drug or alcohol abuse or at risk for alcohol withdrawal seizures
37. Advanced Alzheimer*s disease
38. Advanced multiple sclerosis
39. Hgb <8 g/dL, or Hct <25%, or the need for a blood transfusion
40. Previous exposure to KW-3902

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:	Recruitment stopped
Start date (anticipated):	01-12-2006
Enrollment:	60
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]: selectieve adenosine A1

Ethics review

Approved WMO Date:	17-11-2006
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-05-2007
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)
Approved WMO Date:	11-02-2008
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-03-2008
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-03-2008
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-05-2008
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-08-2008
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-10-2008
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	EUCTR2006-001637-18-NL
ClinicalTrials.gov	NCT00354458
CCMO	NL14535.042.06