Safety and efficacy of TRC4186 in the treatment of stable heart failure associated with HbA1c >= 6.5 % or type 2 diabetes receiving oral hypoglycaemic therapy (with or without additional insulin) as an add-on to conventional treatment for heart failure

Published: 28-07-2009
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The objectives are to evaluate the safety and efficacy of TRC4186 and to define the recommended dose level for further pivotal studies.

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

Summary

ID

NL-OMON33519

Source
ToetsingOnline

Brief title
Not applicable

Condition

- Heart failures
- Diabetic complications

Synonym
diabetes, heart failure

Research involving
Human

Sponsors and support

Primary sponsor: Torrent Pharmaceuticals Ltd.
Source(s) of monetary or material Support: pharmaceutical industry

Intervention

Keyword: AGE breaker, efficacy, heart failure, safety

Outcome measures

Primary outcome

The primary efficacy parameters are the *Physical dimension of Minnesota Living with Heart Failure Questionnaire (MLHFQ)* and the *Oxygen uptake efficiency slope*.

Secondary outcome

Secondary parameters are NT-proBNP levels, peak VO2, NYHA classification, change in diuretic dosage, Impedance cadiography (ICG) parameters, conventional and tissue Doppler echocardiography, VAS scale *Oxygen Cost Diagram*.

Study description

Background summary

Patients of CHF with diabetes are a high risk population with compromised prognosis due to increased accumulation of AGEs (Advanced Glycosylation Endproducts) which cause macro-and micro-vascular complications. The Investigational Medicinal Product (IMP) TRC4186 retards the progression of and reverses diabetic macro-and micro-vascular complications by reducing AGEs burden in various target tissue. Thus improving the endothelial and myocardial function in animal models of diabetes. Its safety has been ascertained in pre-clinical and clinical studies. Therefore, TRC4186 could offer a potentially effective therapy for the complications of diabetes.

Study objective

The objectives are to evaluate the safety and efficacy of TRC4186 and to define the recommended dose level for further pivotal studies.

Study design

This is a randomised, double-blind, multinational, multi-centre, placebo-controlled, parallel-group study.

Intervention

During a period of 14 months patients have to attend the study site for 9-13 ambulant visits. Then blood samples, in total 240 ml, for safety assessments will be collected. Other measurements like ECG, ICG or spiroergometry are non-invasive.

Study burden and risks

Based on preclinical studies patients with symptoms of congestive heart failure (CHF) on antihypertensive medication may experience a fall in blood pressure. Additionally, observed effects of the proposed study drug may be similar to events associated with the use of Losartan (hypotensive pharmaceutical).
As this is a clinical research trial and despite the careful control and the exclusion of any risk factors throughout the study, it cannot be excluded that unforeseen effects occur from treatment with TRC4186.

Since this a first study in patients with CHF and impaired glucose tolerance participants may benefit from study treatment and are otherwise, e.g. placebo group, under close supervision by the investigational site, and appropriate measures can be initiated early.

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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. Male and female subjects aged >= 45 years. Female and male subjects must be of non-childbearing potential or non-fertile potential, i.e. surgically
sterile (bilateral oophorectomy, hysterectomy, bilateral tubal ligation, vasectomy) or post-menopausal for at least one year. Male subjects of fertile potential must use an effective method of birth control.
2. Subjects with stable chronic heart failure for 3 months (NYHA class II - III) according to the criteria given in Appendix I and on stable medication for at least 6 weeks.
3. Subjects with established Type 2 diabetes mellitus (i.e. receiving oral therapy with or without insulin) or an
impaired glucose tolerance (HbA1c should be 6.5% -10.0% at screening)
4. Subjects with NT-proBNP (N-terminal fragment of the a brain natriuretic peptide (BNP)) >= 600 pg/mL
(subjects with atrial fibrillation NT-proBNP >= 1200 pg/mL)
5. Subjects receiving a loop, thiazide or thiazide like diuretic (Metolazone, Chlorthalidon, Indapamide and
Xipamide) for treating heart failure (HF)
6. Subjects able to undergo cardiopulmonary exercise testing
7. Subjects able to communicate well with the investigator and to comply with the requirements of the entire
study
8. Subjects willing to give written informed consent (prior to any study-related procedures being performed) and
able to adhere to the study restrictions and assessments schedule.

Exclusion criteria

1. CHF caused by myocarditis, cor pulmonale, congenital heart disease, constrictive pericarditis, or hypertrophic
or restrictive cardiomyopathy
2. Significant important hemodynamic disease in the investigators opinion, e.g. mitral regurgitation and/or
planned for surgery
3. Acute coronary syndrome or coronary revascularization within 3 months
4. Angina as the symptom limiting treadmill/bicycle exercise
5. Evidence of myocardial ischemia in ECG during CPET
6. Presence of a left ventricular (LV) aneurysm
7. History of symptomatic or sustained ventricular fibrillation or ventricular tachycardia unless treated with a
defibrillator
8. Second-degree or third-degree heart block (unless treated with a pacemaker), LBBB and patients receiving
CRT
9. Left ventricular assist device (or an activated minute ventilation pacemaker)
10. Gross obesity (body mass index (BMI) > 40 kg/m2)
11. Pulmonary function (FEV1) less than 60 % of predicted or requiring long-term corticosteroids
12. Type I diabetes
13. Severe joint disease or peripheral arterial disease sufficient to impede exercise testing
14. History of systemic and other vascular inflammatory disease
15. Uncontrolled hypertension (systolic blood pressure >= 160 mmHg under antihypertensive treatment)
16. Screening liver enzyme test (AST or ALT) exceeding 3 times the upper limit of normal range or hepatic
impairment of Child-Pugh class C
17. Serum creatinine > 1.6 mg /dl or glomerular filtration rate (eGFR) < 40 ml/min
18. Hemoglobin < 10.5 mg%.
19. Gastrointestinal disorder that could interfere with study drug absorption
20. Medical history of Chronic hepatitis B, C
21. Medical history of HIV seropositivity
22. Pregnancy or nursing females
23. Any cancer disease, except non-invasive skin cancer (e. g. actinic keratosis or basal cell carcinoma), or any
other condition that may preclude full participation in the study or that limit survival
24. Prior history of radiation and chemotherapy for malignancies
25. Known hypersensitivity to any ingredient of the study medication
26. Current participation (including prior 30 days) in any other therapeutic clinical trial
27. Unwilling or unable to comply with protocol

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	15-08-2009
Enrollment:	15
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	not applicable
Generic name:	not applicable

Ethics review

Approved WMO Date:	28-07-2009
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-02-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	31-08-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-10-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-08-2012
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	EUCTR2008-006237-27-NL
CCMO	NL28020.042.09