Effect of ivabradine versus placebo on cardiac function, exercise capacity, and neuroendocrine activation in patients with Chronic Heart Failure with Preserved left ventricular Ejection Fraction;An 8-month, randomised double-blind, placebo controlled, international, multicentre study.

Published: 19-03-2013
Last updated: 24-04-2024

The primary objective of this study in patients with symptomatic chronic Heart Failure and Preserved left ventricular Ejection Fraction (HF-PEF) is to determine whether ivabradine compared to placebo could improve the diastolic function, the...

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

Summary

ID

NL-OMON41325

Source
ToetsingOnline

Brief title
CL2-16257-101

Condition

- Heart failures

Synonym
diastolic heartfailure, heartfailure with preserved ejectionfraction

Research involving
Human

Sponsors and support

Primary sponsor: Institut de Recherches Internationales Servier I.R.I.S
Source(s) of monetary or material Support: Institut de Recherches Internationales Servier (IRIS)

Intervention

Keyword: heartfailure, HF-PEF, ivabradine

Outcome measures

Primary outcome

The primary endpoints of the study are the following:

the ratio E/e*, measured on echocardiography,

the 6-minute walk test,

NT-proBNP plasma level.

Secondary outcome

The secondary objectives are:

-to evaluate the effects of ivabradine compared to placebo on:

• cardiac function and structural parameters,

• quality of life,

• NYHA classification,

• other biomarkers (including optional microRNA),

-and to evaluate the safety and tolerance profile of ivabradine compared to

placebo.

Study description

Background summary

The prevalence of Heart Failure (HF) is about 1-2% of the population in developed countries increasing to >= 10% in 70 year-old-people or more. Heart Failure with Preserved Ejection Fraction (HF-PEF) is present in half of the patients with HF. Predisposing conditions for HF-PEF are older age, female gender, diabetes, obesity, arterial hypertension and LV hypertrophy. However, the prevalence of HF-PEF is rising due to the aging of population, and no treatment has yet been shown to be effective in reducing morbidity and mortality in this population.
Recently, the SHIFT study has shown that reducing HR with ivabradine in patients with symptomatic systolic HF was associated with a significant improvement of cardiovascular outcomes: the risk for cardiovascular death or hospitalisation for worsening heart failure was reduced by 18% with ivabradine versus placebo.
The hypothesis of a beneficial effect of a specific HR-lowering drug such as ivabradine in patients with HF-PEF is based on the fact that an elevated HR decreases the diastolic filling time, increase myocardial oxygen consumption and impair coronary perfusion which may be problematic for patients with HF. A specific HR-lowering agent, without any decrease in the myocardial contractility and without conduction disturbance seems potentially of interest and will be further evaluated in this 'proof of concept' study.

Study objective

The primary objective of this study in patients with symptomatic chronic Heart Failure and Preserved left ventricular Ejection Fraction (HF-PEF) is to determine whether ivabradine compared to placebo could improve the diastolic function, the exercise capacity, and the neuroendocrine activation, over an 8-month treatment period.

Study design

This is a phase II, multicentre, international, randomised, with therapeutic benefit, double-blind, placebo-controlled, two-balanced parallel arm study,of a duration of approximative 8.5 months. There are 7 study visits planned per patient.

Intervention

Patients will receive ivabradine or placebo in addition to their usual cardiovascular treatment. Ivabradine and placebo will be administered orally b.i.d. during meals. The study medication dosis can be adapted by the

investigator, at any time during the study visits or between visits, depending on the heart rate at rest (ECG) or if signs or symptoms of bradycardia are reported.

Study burden and risks

The safety and tolerance profile of ivabradine is good (see SmPC Procoralan). The most common adverse events with ivabradine are visual symptoms (phosphenes) and bradycardia. Other possible side effects are abnormal sensation of heartbeat, irregular rapid contraction of the heart, uncontrolled bloodpressure, headache, dizziness and blurred vision. Visual symptoms are generally mild, well tolerated and transitory. Bradycardia is a dose dependent effect of ivabradine, which occurs mainly at the beginning of therapy. The dosis of the study medication can be reduced following heart rate during the study at any time, by the investigator.Patients with a heart rate below 50 bpm, will have to stop study treatment.

Contacts

Public
Servier R&D Benelux

Internationalelaan 57
Brussel 1070
BE
Scientific
Servier R&D Benelux

Internationalelaan 57
Brussel 1070
BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Male or female patients,;- Aged 50 years or older,;- Symptomatic Chronic Heart Failure of New York Heart Association (NYHA) class II or III for at least 3 months prior to selection,;- In stable clinical condition with regards to CHF symptoms for at least 4 weeks prior to selection,;- Documented sinus rhythm and HR superior or equal to 70 bpm on a resting standard 12-lead ECG at selection and inclusion,;- Left Ventricular Ejection Fraction superior or equal to 50% and E/e* >= 13 (E = early diastolic mitral flow velocity; e* = mean of mitral annular lateral and septal proto diastolic velocities) or e* lateral >= 10 cm/s and e* septal >= 8 cm/s or LAVI >= ; 34 mL/m² at selection,;- Documented NT-proBNP >= ; 300 pg/mL or BNP >= ; 100 pg/mL at selection.
-Ability to perform the 6' walk test

Exclusion criteria

- Recent (less than 3 months) myocardial infarction or coronary revascularisation,;- Scheduled coronary revascularisation,;- Severe aortic or mitral stenosis, or severe aortic regurgitation, or severe primary mitral regurgitation,;- Scheduled surgery for valvular heart disease;- Congenital heart disease,;- Previous cardiac transplantation or on list for cardiac transplantation,;- Documented permanent atrial fibrillation or other cardiac arrhythmia that interfere with the sinus node function, or recent hospitalization for atrial fibrillation or other cardiac arrhythmia that interfere with the sinus node function within the last 3 months, ;- Patients able to walk more than 450 meters within 6 minutes during the selection and the inclusion visits,;- Previous or current treatment with ivabradine.

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:	Recruitment stopped
Start date (anticipated):	16-10-2013
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Procoralan
Generic name:	ivabradine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	19-03-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-08-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-11-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-12-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-02-2014

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-04-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-05-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-07-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-10-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-03-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-04-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-04-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-04-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-05-2015

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-08-2015
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
Other	https://www.clinicaltrialsregister.eu
EudraCT	EUCTR2012-002742-20-NL
CCMO	NL43625.042.13