A phase III randomised, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic Heart Failure with preserved Ejection Fraction (HFpEF).

Published: 30-01-2017
Last updated: 13-04-2024

The objective of this event-driven trial is to demonstrate superiority of empagliflozin 10 mg versus placebo in patients with symptomatic, chronic HF and preserved ejection fraction (LVEF > 40%) under stable treatment of HF symptoms.

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

Summary

ID

NL-OMON49597

Source
ToetsingOnline

Brief title
EMPEROR- PRESERVED (1245-110)

Condition

- Heart failures

Synonym
chronic Heart Failure with preserved Ejection Fraction

Research involving

Human

Sponsors and support

Primary sponsor: Boehringer Ingelheim International GmbH
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: Efficacy, Empagliflozin, Heart failure, Safety

Outcome measures

Primary outcome

The composite primary endpoint for this trial is the time to first event of

adjudicated CV death or adjudicated HHF in patients with HFpEF.

Secondary outcome

The key secondary endpoints which are part of the testing strategy, are the

following:

- Occurrence of adjudicated HHF (first and recurrent)

- eGFR (CKD-EPI)cr slope of change from baseline

Other secondary endpoints are:

- Time to first occurrence of chronic dialysis or renal transplant or sustained

reduction of *40% eGFR (CKD-EPI)cr or

a sustained eGFR (CKD-EPI)cr <15 mL/min/1.73 m2 for patients with baseline eGFR

*30 mL/min/1.73 m2

b sustained eGFR (CKD-EPI)cr <10 mL/min/1.73 m2 for patients with baseline eGFR

<30 mL/min/1.73 m2

*An eGFR (CDK-EPI)cr reduction is considered sustained, if it is determined by

two or more consecutive post-baseline central laboratory

measurements separated by at least 30 days (first to last of the consecutive eGFR values). Chronic dialysis is defined as dialysis with a frequency of twice per week or more often for at least 90 days.

* Time to first adjudicated HHF

* Time to adjudicated CV death

* Time to all-cause mortality

* Time to onset of diabetes mellitus (DM) in patients with pre-DM

* Change from baseline in clinical summary score (HF symptoms and physical limitations domains) of the KCCQ at week 52

* Occurrence of all-cause hospitalisation (first and recurrent)

Study description

Background summary

Chronic heart failure (HF) is a progressive syndrome characterised by the inability of the heart to provide adequate blood supply to meet the metabolic demand of different tissues or do it at the expense of elevated left ventricle filling pressure. HF is a prevalent disease affecting an estimated 26 million people worldwide. In the United States alone the prevalence is 5.7 million, and there are 670,000 new cases per year. HF is associated with premature mortality and frequent hospitalisation. Approximately 50% of patients who develop HF die within 5 years after diagnosis. Annually, more than 1 million patients are hospitalised with a primary diagnosis of HF. Two types of HF have been defined mainly based on the LV ejection fraction (EF) and also other structural changes in heart muscle. They consist of heart failure with reduced EF (HFrEF) *40% and heart failure with preserved EF (HFpEF) >40%.

About 25 to 45% of patients with HF have concomitant type 2 diabetes mellitus (T2DM), and nearly 15-25% have borderline DM (pre-diabetes), indicating a potential link between the HF syndromes and glucometabolic disturbances.

Empagliflozin is an orally available inhibitor of the renal dependent glucose co-transporter 2 (SGLT-2) indicated for, reduction of blood glucose in patients with T2DM by promoting urinary glucose excretion. It also reduces blood

pressure, arterial stiffness and measures of the myocardial workload, likely through various mechanisms, as well as improving other CV risk factors (uric acid, visceral fat mass, albuminuria)

Study objective

The objective of this event-driven trial is to demonstrate superiority of empagliflozin 10 mg versus placebo in patients with symptomatic, chronic HF and preserved ejection fraction (LVEF > 40%) under stable treatment of HF symptoms.

Study design

This randomised, double-blind, multi-national, parallel group trial compares empagliflozin 10 mg once daily to placebo as add-on to standard of care treatment in patients with HFpEF.

Intervention

* 4-21 days screening period
* Approximately 20-38 months double-blind treatment until the required number of adjudicated primary events is reached with empagliflozin or placebo
* Follow-up visit 30 days after end of treatment
The trial will continue until required number of adjudicated primary endpoint events have occurred to be able to comply with the objective of the trial.
Subjects will be treated with empagliflozin or placebo tablets once daily

Study burden and risks

Possible side effects:
- Hypoglycaemia
- Major hypoglycaemia (events requiring assistance)
- Urinary tract infection
- Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection
- Increased urination
- Volume depletion
- Blood creatinine increased and glomerular filtration rate decreased

Possible side effects are described in the Investigators Brochure.

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

* Patients with chronic HF diagnosed for at least 3 months before Visit 1 and currently in HF NYHA class II-IV
* Chronic HF with preserved EF defined as LVEF > 40 % per local reading (obtained by echocardiography, radionuclide ventriculography, invasive angiography, MRI or CT), and no prior measurement of LVEF * 40% under stable conditions. A historical LVEF may be used if it was measured within 6 months prior to visit 1, and more than 90 days after any myocardial infarction (as defined in exclusion criterion No.1) or the LVEF may be measured after study consent has been obtained. The LVEF must be documented in an official report prior to randomization.
* Elevated NT-proBNP > 300 pg/ml for patients without AF, OR > 900 pg/ml for patients with AF, analysed at the Central laboratory at Visit 1
* Patients must have at least one of the following evidence of HF:
- Structural heart disease (left atrial enlargement and/or left ventricular hypertrophy) documented by echocardiogram at Visit 1, OR
- Documented hospitalisation for HF (HHF) within 12 months prior to Visit 1
* Oral diuretics, if prescribed to patient according to local guideline and discretion of the Investigator, should be stable for at least 1 week prior to Visit 2 (Randomisation)
* eGFR (CKD-EPI)cr * 20 mL/min/1.73m2 at Visit 1

Exclusion criteria

* Myocardial infarction (increase in cardiac enzymes in combination with symptoms of ischaemia or newly developed ischaemic ECG changes), coronary artery bypass graft surgery or other major cardiovascular surgery, stroke or TIA in past 90 days prior to Visit 1
* Heart transplant recipient or listed for heart transplant
* Implantation of cardioverter defibrillator (ICD) within 3 months prior to Visit 1
* Implanted cardiac resynchronisation therapy (CRT)
* Cardiomyopathy based on infiltrative diseases (e.g. amyloidosis), accumulation diseases (e.g. haemochromatosis, Fabry disease), muscular dystrophies, cardiomyopathy with reversible causes (e.g. stress cardiomyopathy), hypertrophic obstructive cardiomyopathy or known pericardial constriction
* Any severe (obstructive or regurgitant) valvular heart disease expected to lead to surgery during the trial in the Investigator*s opinion
* Acute decompensated HF (exacerbation of chronic HF) requiring intravenous (i.v.) diuretics, i.v. inotropes or i.v. vasodilators, or left ventricular assist device within 1 week from discharge to Visit 1, and during screening period until Visit 2 (Randomisation)
* Atrial fibrillation or atrial flutter with a resting heart rate > 110 bpm documented by ECG at Screening
* Systolic blood pressure (SBP) * 180 mmHg at Visit 2. If SBP >150 mmHg and <180 mmHg at Visit 2, the patient should be receiving at least 3 antihypertensive drugs
* Symptomatic hypotension and/or a SBP < 100 mmHg at Visit 1 or Visit 2

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:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-04-2017

Enrollment:	103
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Jardiance
Generic name:	Empagliflozin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	30-01-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-04-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-06-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-07-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-09-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	24-10-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-11-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-01-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-03-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-06-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-06-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-08-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-09-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	17-10-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-11-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-11-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-04-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-04-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-01-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-03-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2016-002278-11-NL
CCMO	NL59667.056.17