A multicentre, randomised, double-blind, 90-day superiority trial to evaluate the effect on clinical benefit, safety and tolerability of once daily oral EMPagliflozin 10 mg compared to placebo, initiated in patients hospitalised for acUte heart faiLure (de novo or decompensated chronic HF) who have been StabilisEd (EMPULSE)

Published: 10-12-2019
Last updated: 10-04-2024

The main objective of this study is to assess whether in-hospital administration of empagliflozin results in improvement in HF-related outcomes in patients hospitalised for acute heart failure (de novo or decompensated chronic HF) and after initial...

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

Summary

ID

NL-OMON49418

Source
ToetsingOnline

Brief title
EMPULSE

Condition

- Heart failures

Synonym
heart disease, heart insufficiency

Research involving
Human

Sponsors and support

Primary sponsor: Boehringer Ingelheim
Source(s) of monetary or material Support: De opdrachtgever Boehringer Ingelheim

Intervention

Keyword: Heart Failure, Phase III, SGLT-2 inhibitor

Outcome measures

Primary outcome

Clinical benefit, a composite of death, number of heart failure events (HFEs)

(including hospitalisations for heart failure (HHFs), urgent heart failure

visits and unplanned outpatient visits), time to first HFE and change from

baseline in Kansas City Cardiomyopathy Questionnaire - Total Symptom Score

(KCCQ-TSS) after 90 days of treatment.

See protocol section 2.1.2

Secondary outcome

* Proportion of patients with a clinically meaningful improvement in KCCQ-TSS

of * 10 points after 90 days of treatment

* Change from baseline in KCCQ TSS after 90 days of treatment

* Change from baseline in log-transformed N-Terminal Pro-Brain * Natriuretic

Peptide (NT-proBNP) level over 30 days of treatment (area under the curve (AUC)).

* Days alive and out of hospital from study drug initiation until 30 days after initial hospital discharge

* Days alive and out of hospital from study drug initiation until 90 days after randomisation

* Time to first occurrence of cardiovascular (CV) death or HFE until end of trial visit

* Occurrence of HHF until 30 days after initial hospital discharge

* Occurrence of chronic dialysis or renal transplant or sustained reduction of *40% estimated glomerular filtration rate (eGFR) Chronic Kidney Disease Epidemiology Collaboration Equation ((CKD-EPI)cr)

* Diuretic effect as assessed by weight loss per mean daily loop diuretic dose after 15 days of treatment

* Diuretic effect as assessed by weight loss per mean daily loop diuretic dose after 30 days of treatment

See protocol section 2.1.3

Study description

Background summary

Heart failure (HF) is one of the most prevalent chronic diseases associated with high mortality and morbidity. Over 22 million people around the world suffer from chronic heart failure (CHF). Patients with HF are at high risk of mortality and morbidity, 50% die within 5 years of their diagnosis of HF and a

large number are re-hospitalised for exacerbation of HF symptoms. Heart failure is the most frequent cause of hospital admission among patients 65 years or older, and there are over 1 million hospitalised patients each year with HF as a primary diagnosis.

Empagliflozin is an orally available inhibitor of the renal dependent sodium glucose cotransporter 2 (SGLT-2), promoting urinary glucose excretion. Empagliflozin is indicated for reduction of blood glucose in patients with Type 2 Diabetes Mellitus (T2DM), and for cardiovascular (CV) death risk reduction in patients with T2DM and established CV disease.Empagliflozin also reduces blood pressure, arterial stiffness and measures of myocardial workload, likely through various mechanisms, as well as improving other CV risk factors (e.g. uric acid, visceral fat mass, albuminuria.

Other trials with empagliflozin are performed to assess mortality and morbidity, functional capacity and safety of empagliflozin in patients with chronic heart failure under stable conditions (i.e. after hospital discharge). Due to its mode of action (MOA), empagliflozin is expected to potentially alleviate congestive symptoms seen in patients shortly after initial stabilisation of acute cardiac decompensation helping to improve heart failure (HF)-related outcomes within several weeks after discharge from hospital. In-hospital initiation of different therapies is one of the best predictors of long-term adherence to medications and long-term improved prognosis.

See protocol section 1

Study objective

The main objective of this study is to assess whether in-hospital administration of empagliflozin results in improvement in HF-related outcomes in patients hospitalised for acute heart failure (de novo or decompensated chronic HF) and after initial stabilisation.
Secondary objectives are to further assess whether it is safe to start empagliflozin in patients admitted to hospital in this setting.

See protocol section 2

Study design

Randomised, double-blind, parallel-group, placebo controlled, multinational and multicentre study.

See protocol section 3.1

Intervention

Patient will receive:
* empagliflozin, dose 10 mg q.d. oral
or
* placebo, q.d. oral

Duration of treatment 90 days

See protocol section 4

Study burden and risks

Empagliflozin is currently indicated for reduction of blood glucose in patients with T2DM, and for CV death risk reduction in patients with T2DM and established CV disease.

The safety profile of empagliflozin has been well established in over 15000 patients with T2DM treated in clinical studies (of which more than 10000 were treated with empagliflozin) with maximum treatment duration of 4 years. Empagliflozin was tested in over 4600 patients
with T2DM and high CV risk for median treatment duration of 2.6 years [P15-09840]. In addition, approximately 550 healthy volunteers were exposed to empagliflozin (up to 800 mg single dose and up to 50 mg multiple dosing). Based on the mode of action of empagliflozin, which is independent of insulin and potential concomitant T2DM, it is not expected that the safety profile in patients without T2DM would be different to that in patients with T2DM.

Because of the mode of action, blockade of the SGLT2 transporter by empagliflozin leads to glucosuria in patients with and without diabetes, although with less average daily glucose excretion in non-diabetic patients. Therefore, it is considered likely that the tolerability of empagliflozin in non-diabetic patients will be as favourable as in those with T2DM.

Available data from completed and ongoing trials do not indicate safety concerns for nondiabetic CHF patients, other than those already described for patients with T2DM.

See protocol section 1.4

Contacts

Public
Boehringer Ingelheim

Comeniusstraat 6
Alkmaar 1817MS
NL
Scientific
Boehringer Ingelheim

Comeniusstraat 6
Alkmaar 1817MS
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Currently hospitalised for the primary diagnosis of acute heart failure (de novo or decompensated chronic HF), regardless of ejection fraction (EF). Patients with a diagnosis of hospitalized heart failure must have HF symptoms at the time of hospital admission
2. Evidence of left ventricular ejection fraction (LVEF, either reduced or preserved EF) as per local reading preferably measured during current hospitalisation or in the 12 months prior to randomisation
3. Patients must be randomised after at least 24 hours and no later than 5 days after admission, as early as possible after stabilization and while still in hospital
4. Patients must fulfil the following stabilisation criteria (while in the hospital):
- SBP *100mm Hg and no symptoms of hypotension in the preceding 6 hours,
- no increase in i.v. diuretic dose for 6 hours prior to randomisation,
- no i.v. vasodilators including nitrates within the last 6 hours prior to randomisation
- no i.v. inotropic drugs for 24 hours prior to randomisation.
5. Elevated NT-proBNP * 1600pg/mL or BNP *400 pg/mL according to the local lab,

for patients without atrial fibrillation (AF); or elevated NT-proBNP * 2400pg/mL or BNP *600 pg/mL for patients with AF, measured during the current hospitalization or in the 72 hours prior to hospital admission,. For patients treated with an angiotensin receptor neprilysin inhibitor (ARNI) in the previous 4 weeks prior to randomisation, only NT-proBNP values should be used
6. HF episode leading to hospitalisation must have been treated with a minimum dose of 40 mg of i.v. furosemide (or equivalent i.v. loop diuretic defined as 20 mg of torasemide or 1 mg of bumetanide)

Exclusion criteria

1. Cardiogenic shock
2. Current hospitalisation for acute heart failure primarily triggered by pulmonary embolism, cerebrovascular accident, or acute myocardial infarction (AMI)
3.Current hospitalisation for acute heart failure not caused primarily by intravascular volume overload;
4. Below interventions in the past 30 days prior to randomisation or planned during the study:
- Major cardiac surgery, or TAVI (Transcatheter Aortic Valve Implantation), or PCI, or Mitraclip
- All other surgeries that are considered major according to investigator judgement
- Implantation of cardiac resynchronisation therapy (CRT) device
- cardiac mechanical support implantation
- Carotid artery disease revascularisation (stent or surgery)
5. Acute coronary syndrome / myocardial infarction, stroke or transient ischemic attack (TIA) in the past 90 days prior to randomisation
6. Heart transplant recipient, or listed for heart transplant with expectation to receive a transplant during the course of this trial (according to investigator judgement), or planned for palliative care for HF, or currently using left ventricular assist device (LVAD) or intra-aortic balloon pump (IABP) or any other type of mechanical circulatory support, or patients on mechanical ventilation, or patients with planned inotropic support in an outpatient setting
7. Haemodynamically significant (severe) uncorrected primary cardiac valvular disease planned for surgery or intervention during the course of the study (note: secondary mitral regurgitation or tricuspid regurgitation due to dilated cardiomyopathy is not excluded unless planned for surgery or intervention during the course of the study)
8. Impaired renal function, defined as eGFR < 20 mL/min/1.73 m2 as measured during hospitalization (latest local lab measurement before randomisation) or requiring dialysis
9. Type 1 Diabetes Mellitus (T1DM)
10. History of ketoacidosis, including diabetic ketoacidosis (DKA)

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):	25-06-2020
Enrollment:	38
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	10-12-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-03-2020
Application type:	First submission

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-08-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-08-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-09-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-10-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-05-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-06-2021
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	EUCTR2019-002946-19-NL
CCMO	NL72059.042.19