A Phase III, randomised, double blind, placebo-controlled, parallel group, efficacy, safety and tolerability trial of once daily, oral doses of empagliflozin as adjunctive to insulin therapy over 26 weeks in patients with Type 1 Diabetes Mellitus (EASE-3)

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON44650

Source
ToetsingOnline

Brief title
EASE-3

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
Diabetes, Diabetes Mellitus Type 1

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Diabetes Mellitus Type 1, Empagliflozin, SGLT-2 inhibitor

Outcome measures

Primary outcome

Primary endpoint is the change from baseline in HbA1c after 26 weeks.

Secondary outcome

- incidence rate of symptomatic hypoglycaemic adverse events (AEs) with confirmed plasma glucose < 54 mg/dL (< 3.0 mmol/L) and/or severe hypoglycaemic AEs per patient-year from Week 5 to Week 26

- incidence rate of symptomatic hypoglycaemic AEs with confirmed plasma glucose < 54 mg/dL (< 3.0 mmol/L) and/or severe hypoglycaemic AEs per patient-year from Week 1 to Week 26

- change from baseline in body weight (kg) after 26 weeks

- change from baseline in total daily insulin dose (TDID), U/kg, after 26 weeks

- change from baseline in systolic blood pressure (SBP) after 26 weeks

- change from baseline in diastolic blood pressure (DBP) after 26 weeks

Study description

Background summary

Type 1 diabetes mellitus (T1DM) accounts for 5 to 10% of all cases of diabetes mellitus. This disease is a complex disorder that requires constant attention to diet, exercise, glucose monitoring, and insulin therapy to achieve good glycaemic control. Most bodies recommend that adult patients with T1DM should obtain glycated haemoglobin (HbA1c) * 7.0%. However, most patients generally achieve HbA1c levels no lower than 8.0%. Hence, with the currently available treatment options, patients with T1DM often fail to maintain adequate blood glucose control. This may lead to acute conditions and debilitating secondary complications including heart disease, blindness and kidney failure.
Empagliflozin has the potential to provide a novel approach to the treatment of T1DM, as adjunctive therapy to insulin which may lead to a reduction of plasma glucose levels.

Study objective

The objective of this study is to assess the efficacy, safety, tolerability and pharmacokinetics (PK) of once daily oral doses of empagliflozin 2,5mg, 10mg and 25mg in patients with Type 1 diabetes mellitus (T1DM) as adjunctive to insulin therapy. Empagliflozin is being compared to placebo.

Study design

In total, 960 patients with T1DM who meet the entry criteria will be entered (randomised) in the trial.
This multi-national, randomised, placebo-controlled, double-blind, parallel group study compares three doses of empagliflozin (2.5 mg, 10mg and 25mg) to placebo in patients with T1DM as adjunctive to insulin therapy.
Patients will be enrolled (screened) in the trial once they have signed the informed consent. All patients who are suitable after screening will undergo a six week T1DM therapy optimisation period, followed by a two week open-label placebo run-in period before randomisation. Patients who successfully complete both of these periods will be randomised into the 26 week doubleblind treatment period. After the treament periode, the study will be completed by a three week follow-up period.

Intervention

Patients will start a two week placebo run-in period at visit 5.
Patients will be randomized to either Empagliflozin 2.5 mg, Empagliflozin 10 mg, Empagliflozine 25 mg or matching placebo (ratio 1:1:1:1) at visit 6.

Study burden and risks

Assuming a patient completed the trial, a patient will take part in the trial for 38 weeks. The total burden will be about 18 hours. During the clinic visits some assessments will be done (e.d. hight, weight, vital signs, ecg's, blood

samping, etc.) and the patient needs to regulary check his/hers glucose levels and if necassary keton levels and complete the electronic diary on a daily base. See section E4 for a complete description of all assessments.

During participation in this trial, a patient may experience side effects from Empagliflozin as described in section E9. Since Empagliflozin is still under investigation (phase III) new unknow side effects may occur. Due to the use of Empagliflozin the glucose value may decrease and this might lead to unawareness of diabetic ketoacidosis.

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

- Signed and dated written informed consent

- Male or female patient receiving insulin for the treatment of documented diagnosis of type 1 diabetes mellitus (T1DM) for at least 1 year
- C-peptide value of < 0.7 ng/mL (0.23 nmol/L) at visit 2
- Use of Multiple Daily Injections (MDI) of insulin or insulin pump user with total daily insulin * 0.3 and * 1.5 U/kg
- Glycated haemoglobin (HbA1c) * 7.5% and * 10.0%
- Good understanding of T1DM
- Age * 18 years
- Body Mass Index (BMI) * 18.5 kg/m2
- Estimated glomerular filtration rate (eGFR) * 30 mL/min/1.73 m2
- Women of child-bearing potential must use highly effective methods of birth control
- Compliance with trial medication administration between 80% and 120% during placebo run-in period;Further inclusion criteria apply, see protocol section 3.3.2.

Exclusion criteria

- History of type 2 diabetes mellitus, maturity onset diabetes of the young (MODY), pancreatic surgery or chronic pancreatitis
- Pancreas, pancreatic islet cells or renal transplant recipient
- T1DM treatment with any other antihyperglycaemic drug except subcutaneous basal and bolus insulin within last 3 months
- Occurrence of severe hypoglycaemia within last 3 months prior to Visit 1 and until Visit 6
- Occurence of diabetic ketoacidosis within 3 months prior to Visit 1 and until Visit 6
- Irregular sleep/wake cycle
- Acute coronary syndrome, stroke or TIA within last 3 months
- Severe gastroparesis
- Brittle diabetes
- Liver disease
- Eating disorders
- Treatment with anti-obesity drugs, weight-loss surgery or aggressive diet regimen
- Treatment with systemic corticosteroids at Visit 1 and until Visit 6
- Change in dose of thyroid hormones within last 6 weeks to Visit 1 and until Visit 6
- Cancer or treatment for cancer in the last five years
- Blood dyscrasias or any disorders causing haemolysis or unstable red blood cells
- Women who are pregnant, nursing, or who plan to become pregnant whilst in the trial
- Alcohol or drug abuse
- Intake of an investigational drug in another trial within last 30 days;Further exclusion criteria apply, see protocol section 3.3.3.

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):	15-01-2016
Enrollment:	25
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:	28-09-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	02-12-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	01-04-2016

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	06-04-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	08-07-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	20-07-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	06-09-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-10-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	28-11-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	01-12-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	08-06-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	14-06-2017

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	29-06-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	10-08-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2014-005256-26-NL
ClinicalTrials.gov	NCT02580591
CCMO	NL53615.041.15