A Meta-Analysis of Amputation Risk in empagliflozin studies (1245.25, 1245.110, 1245.121)

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Study Finalised

Administrative details

EU PAS number

EUPAS39461

Study ID

42437

DARWIN EU® study

No

Study countries

- [ ] Argentina
- [ ] Australia
- [ ] Austria
- [ ] Belgium

- [ ] Brazil
- [ ] Canada
- [ ] Colombia
- [ ] Croatia
- [ ] Czechia
- [ ] Denmark
- [ ] Estonia
- [ ] France
- [ ] Georgia
- [ ] Germany
- [ ] Greece
- [ ] Hong Kong
- [ ] Hungary
- [ ] India
- [ ] Indonesia
- [ ] Israel
- [ ] Italy
- [ ] Japan
- [ ] Korea, Republic of
- [ ] Malaysia
- [ ] Mexico
- [ ] Netherlands
- [ ] New Zealand
- [ ] Norway
- [ ] Peru
- [ ] Philippines
- [ ] Poland
- [ ] Portugal
- [ ] Romania
- [ ] Russian Federation

- [ ] Singapore
- [ ] South Africa
- [ ] Spain
- [ ] Sri Lanka
- [ ] Taiwan
- [ ] Thailand
- [ ] Ukraine
- [ ] United Kingdom
- [ ] United States

Study description

The primary objective of this exploratory meta-analysis is to evaluate the frequencies, incidence rates, and hazard ratios of lower-limb amputation (LLA) events (primary outcome) and of adverse events related to amputation (secondary outcome) in patients treated with empagliflozin compared with placebo in the pooled population of the long-term studies 1245.25, 1245.110, and 1245.121 (SAF-M1), in the pooled population of studies 1245.110 and 1245.121 (SAFM2), and in each of the 3 studies separately.

Study status

Finalised

Research institutions and networks

Institutions

Boehringer Ingelheim

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Institution

Multiple centres: 999 centres are involved in the study

Contact details

Study institution contact

Hristo Iliev hristo.iliev@boehringer-ingelheim.com

Study contact

hristo.iliev@boehringer-ingelheim.com

Primary lead investigator

Hristo Iliev

Primary lead investigator

Study timelines

Date when funding contract was signed

Actual: 10/05/2017

Study start date

Planned: 01/06/2021

Actual: 01/06/2021

Data analysis start date
Planned: 30/06/2021

Actual: 30/06/2021

Date of final study report
Planned: 24/08/2021

Actual: 09/08/2021

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

Boehringer Ingelheim International GmbH

Study protocol

1245-0171-ctp.pdf (415.5 KB)

Regulatory

Was the study required by a regulatory body?

Yes

Is the study required by a Risk Management Plan (RMP)?

EU RMP category 3 (required)

Methodological aspects

Study type

Study topic:

Human medicinal product

Disease /health condition

Study type:

Non-interventional study

Scope of the study:

Assessment of risk minimisation measure implementation or effectiveness

Data collection methods:

Secondary use of data

Main study objective:

Assess the risk of lower limb amputations in patients treated with empagliflozion

Study Design

Non-interventional study design

Systematic review and meta-analysis

Study drug and medical condition

Study drug International non-proprietary name (INN) or common name

EMPAGLIFLOZIN

Medical condition to be studied

Leg amputation

Additional medical condition(s)

Adverse events related to lower limb amputation

Population studied

Short description of the study population

Study 1245.25 included patients with type 2 diabetes mellitus and increased cardiovascular risk. Detailed eligibility criteria can be found in CTR 1245.25 and the key criteria are summarised below.

The key inclusion criteria were:

- Age ≥18 years, diagnosis of T2DM
- Drug-naïve or pretreated with any background therapy
- HbA1c criteria

o Patients who were drug-naïve: HbA1c of 7 to 10%

o Patients with background therapy: HbA1c of 7 to 9%

- BMI ≤45 kg/m2
- With high cardiovascular risk, defined as ≥1 of the following criteria

o History of myocardial infarction (>2 months prior to enrollment)

o Multi-vessel coronary artery disease: ≥2 major vessels or left main coronary artery

o Single-vessel coronary artery disease with no scheduled revascularization/previously unsuccessful revascularization

o Hospital discharge due to unstable angina pectoris (>2 months prior to enrollment)

o History of stroke (>2 months prior to enrollment)

o Peripheral occlusive arterial disease

The key exclusion criteria were:

- Uncontrolled hyperglycemia: fasting plasma glucose >240 mg/dl
- Severe renal impairment defined as eGFR <30 ml/min by MDRD formula
- Intake of an investigational drug in another trial within 30 days prior to intake of study medication in this trial, or participating in another trial (involving an investigational drug and/or follow-up)

Studies 1245.110 and 1245.121

Study 1245.110 will include patients with chronic heart failure with preserved ejection fraction. Study 1245.121 will include patients with chronic heart failure with reduced ejection fraction. Detailed eligibility criteria can be found in CTPs and the key criteria are summarised below.

The key inclusion criteria are:

- Age ≥18 years (Japan, age ≥20 years)
- Chronic HF NYHA class II to IV
- Ejection fraction (EF) and NT-proBNP criteria

o 1245.110: preserved EF (LVEF >40%) and elevated NT-proBNP (>300 pg/ml; >900 pg/ml for patients with atrial fibrillation)

o 1245.121: reduced EF (LVEF ≤40%) and elevated NT-proBNP (≥2500 pg/ml if EF 36 to 40%, ≥1000 pg/ml if EF 31 to 35%, ≥600 pg/ml if EF ≤30% or if EF ≤40% with documented hospitalisation for HF within 12 months prior to screening; for patients with atrial fibrillation, double the level of NT-proBNP is applied for each EF category)

- 1245.110 only: structural heart disease within 6 months or documented hospitalisation for HF within 12 months prior to screening
- 1245.121 only: stable dose of medical therapy for HF consistent with local and international cardiology guidelines

The key exclusion criteria are:

- Myocardial infarction, coronary artery bypass graft surgery or other major cardiovascular surgery, stroke or transient ischaemic attack ≤90 days before

screening

 Heart transplant recipient, or listed for heart transplant

 Acute decompensated HF

 SBP ≥180 mmHg at randomisation

 Symptomatic hypotension and/or SBP <100 mmHg at screening or randomisation

 Impaired renal function defined as eGFR (CKD-EPI)cr <20 ml/min/1.73 m2 or requiring dialysis at screening

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Age groups

- Adults (18 to < 46 years)
- Adults (46 to < 65 years)
- Adults (65 to < 75 years)
- Adults (75 to < 85 years)
- Adults (85 years and over)

Special population of interest

Other

Special population of interest, other

Type 2 diabetes mellitus patients, Chronic heart failure patients

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Estimated number of subjects

14000

Study design details

Outcomes

Lower limb amputation, Adverse events related to lower limb amputation

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Data analysis plan

This meta-analysis will be exploratory. For the primary outcome of lower limb amputation (LLA) events and for the secondary outcomeof AEs related to amputation, a Cox proportional hazards regression model for modelling the time to first event will be used, includingthe factors study, diabetes mellitus status (T1DM, T2DM, no diabetes), and treatment (all empagliflozin vs. placebo). Study is assumedas fixed effect in this meta-analysis. For treatment comparison, hazard ratios with corresponding 95% CIs as well as corresponding p-values will be presented.

Documents

Study results

1245-0171 Results summary.pdf (81.38 KB)

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data sources (types)

Other

Data sources (types), other

Randomised, placebo-controlled, double-blind, parallel-group, and event-driven clinical trials: 1245.25, 1245.110, and 1245.121

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

No