Post-authorisation safety study in patients with type 2 diabetes mellitus to assess the risk of acute liver injury, acute kidney injury and chronic kidney disease, severe complications of urinary tract infection, genital infections, and diabetic ketoacidosis among patients treated with empagliflozin compared to patients treated with DPP-4 inhibitors (PASS renal, liver injury, infection, ketoacidosis)

First published: 10/05/2016
Last updated: 18/06/2024

Study | Finalised

Administrative details

PURI
https://redirect.ema.europa.eu/resource/50541

EU PAS number
EUPAS13413

Study ID
50541

DARWIN EU® study
No

Study countries
Denmark

United Kingdom
United States

Study description
Empagliflozin (Jardiance), a highly potent and selective inhibitor of the sodium-glucose cotransporter 2 (SGLT2), was approved in Europe in May 2014 for the treatment of type 2 diabetes mellitus (T2DM) to improve glycaemic control in adults. As part of the risk management plan, Boehringer Ingelheim International GmbH (BI) has committed to conduct a post-authorisation safety study (PASS) to evaluate the liver and renal safety of empagliflozin. The study will also evaluate the risks of severe complications of urinary tract infections (UTIs), genital infections and diabetic ketoacidosis. To evaluate the association between empagliflozin use and mentioned outcomes routinely collected health information from the Clinical Practice Research Datalink (CPRD), in the United Kingdom. For the evaluation of the rarest outcomes, the Danish Population Registries in Denmark and the HealthCore Integrated Research Database (HIRD) in the United States. This PASS will be conducted through an observational cohort study among adult patients with T2DM and at least 12 months of continuous enrolment in the data source where new users of empagliflozin will be compared to new users of dipeptidyl peptidase-4 (DPP4) inhibitors. Estimations will be made on the crude and adjusted incidence rates and adjusted incidence rate ratios of the primary and secondary outcomes. The primary outcomes will be: acute liver injury (ALI) in patients without predisposing conditions, acute kidney injury, severe complications of urinary tract infection, genital infections, and diabetic ketoacidosis. The secondary outcomes will be: ALI in patients with or without predisposing conditions, chronic kidney disease, and severe genital infections.

Study status
Finalised

Research institution and networks

Institutions

RTI Health Solutions (RTI-HS)
France
Spain
Sweden
United Kingdom
United Kingdom (Northern Ireland)
United States
First published: 21/04/2010
Last updated 19/02/2024
Institution

Not-for-profit

ENCePP partner

HealthCore

First published: 01/02/2024
Last updated 01/02/2024

Institution

Clinical Practice Research Datalink (CPRD)

United Kingdom
First published: 15/03/2010
Last updated 02/07/2019

Institution

Laboratory/Research/Testing facility

ENCePP partner

Aarhus University

First published: 01/02/2024
Last updated 01/02/2024

Institution

Contact details

Study institution contact

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Study contact

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Primary lead investigator

Cristina Rebordosa

Primary lead investigator

Study timelines

Date when funding contract was signed

Planned:
31/12/2015
Actual:
09/03/2016

Study start date
Planned:
30/03/2016
Actual:
15/03/2016

Data analysis start date
Planned:
31/01/2020
Actual:
13/05/2021

Date of interim report, if expected
Planned:
15/06/2016
Actual:
20/06/2016

Date of final study report
Planned:
30/12/2022
Actual:
23/11/2022

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

Boehringer Ingelheim International GmbH

Study protocol

1245-96-protocol_v7.0_Final_redacted.pdf(1.38 MB)

1245-96-protocol_v8.0_Final_redacted.pdf(2.17 MB)

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 type list

Study topic:
Disease /health condition
Human medicinal product

Study type:
Non-interventional study

Scope of the study:
Assessment of risk minimisation measure implementation or effectiveness
Safety study (incl. comparative)

Data collection methods:
Secondary data collection

Main study objective:
To estimate, among patients with type 2 diabetes mellitus, the risk of acute liver injury, acute kidney injury and chronic kidney disease, severe complications of urinary tract infections, genital infections and diabetic ketoacidosis among patients treated with empagliflozin compared with patients treated with dipeptidyl peptidase-4 inhibitors.

Study Design

Non-interventional study design
Cohort
Other

Non-interventional study design, other
Observational study

Study drug and medical condition

Name of medicine
Jardiance
Synjardy

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

Anatomical Therapeutic Chemical (ATC) code
(A10BD20) metformin and empagliflozin
(A10BH01) sitagliptin
(A10BH02) vildagliptin
(A10BH03) saxagliptin
(A10BH04) alogliptin
(A10BH05) linagliptin
(A10BK03) empagliflozin

Medical condition to be studied
Type 2 diabetes mellitus

Additional medical condition(s)
Acute liver injury

Population studied

Short description of the study population
Patients aged 18 years or older diagnosed with type 2 diabetes received treatment with empagliflozin or DPP-4 inhibitor identified from the Clinical Practice Research Datalink (CPRD) database for the study period of August 2014 to August 2019.
Inclusion criteria:
· Be aged 18 or more years at the index date.
· Have at least 12 months of continuous registration before or at the index date. In the CPRD this means registration in a primary care practice with up-to-standard data. In Denmark, this means residency in the country. In the HIRD, this means enrolment in the health care plan.
· Have T2D ever before or at the index date: the algorithm to identify patients with T2D will be adapted to the type of data available in each data source. This algorithm may include

medication codes and will be described in the statistical epidemiological analysis plan.

Exclusion criteria:
· Patients with a confirmed diagnosis of T1D before or at the index date will be excluded from the study.
· Patients prescribed/dispensed combinations of SGLT2 inhibitors with DPP-4 inhibitors at the index date (as fixed-dose combinations such as Glyxambi® [empagliflozin and linagliptin], or as non–fixed-dose combinations of the two individual medications prescribed on the same date) will be excluded.

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

Estimated number of subjects
151184

Study design details

Outcomes
Acute liver injury, acute kidney injury, severe complications of urinary tract infection, genital infections, diabetic Ketoacidosis, acute liver injury in a subset of patients with or without predisposing factors, chronic kidney disease, severe genital infections

Data analysis plan
The following estimates and comparisons will be generated: Crude and adjusted incidence rates of each of the outcomes among empagliflozin new users and DPP-4 inhibitor new users. Incidence rates will be reported as point estimates (in cases per 1,000 person-years) and 95% confidence intervals (CIs). Summary IRRs, after adjusting for propensity score deciles, among empagliflozin new users vs. DPP-4 inhibitor new users. The adjusted IRRs for each of the primary outcomes will be the main effect estimates of interest. Adjusted incidence rates and IRRs will be calculated using analytic techniques involving stratification by categories of propensity scores. An additional analysis will further stratify the IRRs by categories of insulin use at the index date. Sensitivity analyses will be performed to evaluate the potential for other sources of bias and confounding. Meta-analytic methods

will be used to combine the IRRs obtained from the main analysis performed by all the data sources.

Documents

Study results
1245-0096_Synopsis_Redacted.pdf(437.07 KB)

Study, other information
1245-0096--protocol_revision-04_Redacted.pdf(1013.17 KB)

Study publications
Liver, renal, genitourinary and diabetic ketoacidosis risks among new users of …
Time between laboratory tests and acute liver and kidney injury diagnosis codes…

Data management

Data sources

Data source(s)
Danish registries (access/analysis)
Clinical Practice Research Datalink

Data source(s), other
HealthCore Integrated Research Database (HIRD)

Data sources (types)
Administrative data (e.g. claims)
Drug dispensing/prescription data
Electronic healthcare records (EHR)
Other

Data sources (types), other
CPRD linked data sources including: hospital episode statistics inpatient data, Office of National Statistics mortality data, multiple deprivation index data, and Townsend score data. HIRD: Commercially insured population database; Danish Population registries: nationwide hospital registries.

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