Post-authorisation safety study to assess the risk of urinary tract malignancies in relation to empagliflozin exposure in patients with type 2 diabetes: a multi-database European study (PASS DiabCancer)

First published: 16/12/2016

Last updated: 31/10/2025

Study Finalised

Administrative details

EU PAS number

EUPAS16424

Study ID

48643

DARWIN EU® study

No

Study countries

Finland

Sweden

United Kingdom

Study description

Jardiance (empagliflozin), a highly potent and selective inhibitor of the sodium-glucose cotransporter 2 (SGLT-2), was approved in Europe in May 2014 for the treatment of type 2 diabetes mellitus (T2D) to improve glycaemic control in adults. Synjardy (empagliflozin/metformin HCl) was approved in Europe in May 2015.

As part of the risk management plan, Boehringer Ingelheim International GmbH (BI) has committed to conduct a post-authorisation safety study (PASS) to evaluate safety of empagliflozin regarding urinary tract malignancies in incident users of empagliflozin compared to incident users of dieptidyl peptidase-4 (DPP-4) inhibitors and incident users of SGLT-2 inhibitors.

The inclusion of renal cancer as a potential risk was based on preclinical toxicology findings and clinical cases of bladder cancer observed with other SGLT-2 inhibitors.

This PASS will be conducted using routinely collected health information from the UK, Finland, and Sweden, through an observational cohort study among adult patients with type 2 diabetes mellitus and at least 12 months of continuous enrollment in the UK CPRD, Finland or Swedish national registries. New users of empagliflozin will be compared to new users of dipeptidyl peptidase-4 (DPP-4) inhibitors and to new users of other SGLT-2 inhibitors. Estimations will be made on the crude and adjusted incidence rates and adjusted incidence rate ratios of the primary and secondary outcomes. Primary outcomes are urinary tract cancers, bladder cancer, and renal cancer. Secondary outcomes include non-renal, non-bladder urinary tract cancers.

Study status

Finalised

Research institutions and networks

Institutions

IQVIA

United Kingdom

First published: 12/11/2021

Last updated: 22/04/2024

Institution | Non-Pharmaceutical company | ENCePP partner

Contact details

Study institution contact

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Study contact

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Primary lead investigator

Hoti Fabian

Primary lead investigator

Study timelines

Date when funding contract was signed

Actual: 05/04/2016

Study start date

Planned: 15/11/2016

Actual: 16/11/2016

Data analysis start date

Planned: 01/12/2020

Actual: 24/05/2022

Date of interim report, if expected

Planned: 31/03/2021

Actual: 13/03/2017

Date of final study report

Planned: 30/04/2024

Actual: 24/04/2024

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

Boehringer Ingelheim International GmbH

Study protocol

ER-9521_protocol_1245-0097_version3.pdf (969.84 KB)

1245-0097 Final protocol v8.0_Redacted.pdf (2.68 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:

Safety study (incl. comparative)

Data collection methods:

Secondary use of data

Main study objective:

The main objective of the study is to estimate, among patients with type 2 diabetes mellitus, the risk of all urinary tract cancers and those of bladder and

renal cancers also separately in patients initiating empagliflozin compared to patients initiating a DPP-4 inhibitors.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

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

EMPAGLIFLOZIN

Anatomical Therapeutic Chemical (ATC) code

(A10BD20) metformin and empagliflozin

metformin and empagliflozin

Medical condition to be studied

Type 2 diabetes mellitus

Population studied

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)

Estimated number of subjects

56100

Study design details

Outcomes

The primary outcomes of interest for this study are urinary tract cancers, bladder cancer, and renal cancer. The secondary outcome of interest for this study is non-renal, non-bladder urinary tract cancers (referred to as other urinary tract cancers). Non-renal, non-urinary bladder urinary tract cancers include ureter and urethra cancers.

Data analysis plan

The main data analyses will be conducted in two stages: (i) construction of the propensity score (PS)-matched cohorts (for each comparison) (ii) estimating the effect of exposure to empagliflozin on the outcomes using adjusted hazard ratio compared to those exposed to DPP-4 inhibitor or SGLT-2 inhibitor and their respective incidence rates.

Patients starting combination of empagliflozin and metformin (fixed-dose or free combination) will be compared with patients starting combination of another DPP-4 inhibitor or SGLT-2 inhibitor and metformin.

Incidence rates (crude and adjusted) will be presented for each exposure group and stratified by relevant variables using the Poisson regression approach.

Relative risks will be presented as hazard ratios adjusted for relevant variables using the Cox’s proportional hazards model with the time-varying covariate approach.

The adjusted hazard ratios and incidence rates will be presented along with

95% confidence intervals for the risk estimate

Documents

Study results

1245-0097_Synopsis.pdf (246.17 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 source(s)

Clinical Practice Research Datalink

Sweden National Prescribed Drugs Register / Läkemedelsregistret

Data source(s), other

Hospital Episode Statistics, Cancer Registry, ONS mortality statistics United Kingdom, National Patient Register, Swedish Cancer Registry, Cause of Death Register, National Diabetes Register Sweden, Finnish prescription register, Care register for health care (HILMO), Register of primary health care visits

(AvoHILMO), Finnish cancer register, Regional EMR records Finland

Data sources (types)

Administrative healthcare records (e.g., claims)

Disease registry

Drug prescriptions

Electronic healthcare records (EHR)

Other

Pharmacy dispensing records

Data sources (types), other

Population-wide registers in Sweden and Finland contain information e.g. on medication purchases, hospitalisations, cancers and deaths. UK CPRD contains the anonymised longitudinal medical records managed by GPs working the NHS primary care setting.

Use of a Common Data Model (CDM)

CDM mapping

Yes

Data quality specifications

Check conformance

Yes

Check completeness

Yes

Check stability

Yes

Check logical consistency

Yes

Data characterisation

Data characterisation conducted

Yes