Post-authorization safety study (PASS) to assess the risk of acute pancreatitis in type 2 diabetes mellitus (T2DM) patients newly initiating empagliflozin compared to other oral non-incretin/non-sodium glucose co-transporter-2 inhibitors (SGLT2)-containing glucose lowering agents

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Study Finalised

Administrative details

EU PAS number

EUPAS44267

Study ID

49733

DARWIN EU® study

No

Study countries

United States

Study description

Empagliflozin is an oral hypoglycaemic agent belonging to the sodium glucose co-transporter-2 inhibitor (SGLT2i) class, which promotes renal excretion of glucose and lowers elevated blood glucose levels in patients with T2DM. Pancreatitis is defined as an important potential risk in the risk management plan (RMP) for empagliflozin. This post-authorization safety study (PASS) is voluntarily performed to assess the risk of acute pancreatitis in patients with T2DM newly initiating empagliflozin compared to the initiators of other oral non-incretin/non-SGLT2i–based hypoglycaemic agents. Studies have shown that the risk of acute pancreatitis is higher in patients with T2DM and established cardiovascular disease (eCVD) than those without these disorders. In the past ten years, numerous studies assessed the association between pancreatitis and hypoglycaemic agents in the United States (US), Canada, United Kingdom (UK), Denmark, and in Asia. Certain diabetes drug classes, for instance incretin-containing medications (including dipeptidyl peptidase 4 inhibitors (DPP-4i, such as sitagliptin, saxagliptin, linagliptin, alogliptin) and glucagon-like peptide-1 receptor agonists (GLP-1 RA, such as exenatide, liraglutide, lixisenatide, dulaglutide, semaglutide)), have been associated with the risk of developing acute pancreatitis. Results have varied from protective to null associations to 2-3-fold elevated risk of acute pancreatitis depending on the design, population, treatments and comparators studied. A voluntary PASS was designed to investigate the risk of acute pancreatitis in new users of empagliflozin compared to the new users of other oral non-incretin/non-SGLT2i-containing hypoglycaemic agents. Comparison groups in this study are selected based on clinical guideline recommendations and current real-world patterns of use for oral hypoglycaemic agents.

Study status

Finalised

Contact details

Study institution contact

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Primary lead investigator

Study timelines

Date when funding contract was signed

Planned: 12/10/2018

Actual: 12/10/2018

Study start date

Planned: 20/12/2021

Actual: 20/12/2021

Date of final study report

Planned: 31/01/2023

Actual: 20/02/2023

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

Boehringer Ingelheim International GmbH

Study protocol

1245-0201_CTP_final-rule_Redacted.pdf (2.33 MB)

Regulatory

Was the study required by a regulatory body?

No

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

Not applicable

Methodological aspects

Study type

Study type list

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

Disease epidemiology

Safety study (incl. comparative)

Data collection methods:

Secondary use of data

Main study objective:

The objective of the study is to compare the incidence rate of acute pancreatitis in T2DM patients initiating empagliflozin to new users of other oral non-incretin/non-SGLT2i-containing hypoglycaemic agents between 1 August 2014 and the latest data-cut available in Marketscan (30 September 2020) and Optum (31 March 2021).

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Medicinal product name, other

Empagliflozin

Medical condition to be studied

Diabetes mellitus

Pancreatitis acute

Population studied

Short description of the study population

The study population included type 2 diabetes mellitus (T2DM) patients aged 18 years or older, received treatment with empagliflozin or other oral non-incretin/non-SGLT2i-containing glucose lowering drugs (metformin, SU, or TZD) between 1 August 2014 to 31 March 2021 identified from the Truven Marketscan (CCAE and MDCR) database and Optum Clinformatics® Data Mart.
Inclusion criteria:

- Patients >= 18 years old
- A diagnosis of T2DM as demonstrated by at least one qualifying diagnosis code (International Classification of Diseases (ICD)-9-CM diagnosis code of 250.x0 or 250.x2; ICD-10-CM diagnosis code of E11.x) from any encounter type recorded in the claims in the 6 months prior to the drug initiation.
-Have at least 6 months of continuous registration in the database prior to initiation of empagliflozin or a comparator drug

Exclusion criteria:

- Patients with missing or ambiguous age or sex information.
- Use of a SGLT2i, DPP-4i or GLP-1 RA in the 6 months prior to study drug initiation.
- Chronic use of insulin in the outpatient setting in the 6 months prior to the study drug initiation. This criterion will help to remove severe cases of diabetes and reduce the risk of residual confounding as diabetes is a risk factor for developing acute pancreatitis [R10-6620, R10-2088].
- Patients with type 1 diabetes mellitus (T1DM) defined as at least 1 inpatient or

outpatient ICD-9-CM diagnosis code of 250.x1 or 250.x3 or ICD-10-CM diagnosis code of E10.x in the 6 months prior to the study drug initiation.
- Patients with secondary diabetes or gestational diabetes in the 6 months prior to the study drug initiation.
- Claims for acute or chronic pancreatitis, pancreatic cancer, or other disease of the pancreas any time prior to the study drug initiation.

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

Patients with type 2 diabetes

Estimated number of subjects

70.000

Study design details

Outcomes

The objective of the study is to compare the incidence rate of acute pancreatitis in T2DM patients initiating empagliflozin to new users of other oral non-incretin/non-SGLT2i-containing hypoglycaemic agents between 1 August 2014

and the latest data-cut available in Marketscan (30 September 2020) and Optum (31 March 2021).

Data analysis plan

The incidence rates (per 1000 PY) and corresponding 95% confidence intervals (CI) of acute pancreatitis during the follow-up time will be calculated in each exposure group of interest in the unmatched and propensity score (PS)-matched cohorts. Cox proportional hazards regression models based on time-to first acute pancreatitis event will be used to estimate hazard ratios (HR) and 95% CIs for each treatment line comparison of interest in the unmatched and PS-matched cohorts.

Documents

Study results

1245-0201_Synopsis.pdf (275 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), other

Truven Marketscan (CCAE and MDCR) Database, Optum Clinformatics® Data Mart (CDM)

Data sources (types)

Administrative healthcare records (e.g., claims)

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