1. ABSTRACT

Name of Sponsor/Company	Janssen Research and Development
Name of Finished Product	Invokana
Name of Active Ingredient(s)	JNJ-28431754 (Canagliflozin)

Protocol No.: RRA-21430

Title of Study: Acute Pancreatitis in Patients with Type 2 Diabetes Who are New Users of Canagliflozin as Compared with New Users of Other Antihyperglycemic Agents: A Retrospective Cohort Study Using Large Claims Databases in the United States

Sponsor's Responsible Medical Officer: Norman Rosenthal, MD

Keywords: type 2 diabetes mellitus, acute pancreatitis, canagliflozin, sodium-glucose co-transporter 2 inhibitors, observational database

EU PAS Register Number: EUPAS23531

NCT No.: N/A

Clinical Registry No.: N/A

Marketing Authorization Holder(s): Janssen Cilag International NV

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Study Center(s): N/A

Publication (Reference): None

Study Period: 01 Apr 2013 to 30 Sep 2017

Background and Rationale: Diabetes mellitus (DM), a chronic condition, is associated with significant morbidity and mortality. Many comorbid conditions are prevalent in patients with type 2 diabetes mellitus (T2DM), including hypertension, obesity, hyperlipidemia, coronary artery disease (CAD), peripheral vascular disease (PVD), and renal dysfunction. In clinical trials of canagliflozin in patients with T2DM, acute pancreatitis cases have been reported infrequently. However, because acute pancreatitis is a relatively rare event and because patients with T2DM are known to be at increased risk of acute pancreatitis relative to non-T2DM patients, it is difficult to quantify the frequency of such events with precision and to determine whether there is a causal relationship with canagliflozin therapy simply based on clinical trials data. To address this knowledge gap and gain real-world evidence, we designed this observational study using large claims databases in the United States (US).

Research Question and Objectives: This study aimed:

- To estimate the incidence rate of acute pancreatitis in patients with T2DM newly exposed to canagliflozin and comparator antihyperglycemic agents (AHAs, multiple comparators), based on both the overall crude and propensity-score matched cohorts, respectively.
- To compare the hazard of acute pancreatitis in patients with T2DM newly exposed to canagliflozin versus comparator AHAs (multiple comparators), based on propensity-score matched cohorts

Study Design: This was a retrospective, non-interventional new-user cohort, Post Authorization Safety Study (PASS).

Setting: This study was based on claims data collected in routine clinical practice.

Patient Population and Study Size: The Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) version of 3 claims databases in the US (Truven MarketScan® Commercial Claims and Encounters (CCAE), Truven MarketScan® Medicare Supplemental (MDCR), and Optum Clinformatics™ Extended Datamart Socio-Economic (SES) databases) were used for this study, which contains inpatient admission records, outpatient services, prescription drugs, eligibility status, and costs of services. Adult patients with T2DM who were newly exposed to a drug of interest (ie, canagliflozin or a comparator drug) between April 1, 2013 and September 30, 2017 were eligible for the study. The date of first drug exposure was considered the index date. Patients with a record of type 1 DM or secondary DM on or prior to the index date were excluded from the analyses. In addition, patients must have at least 1 day of follow-up after the index date to be eligible for the study.

The target exposure group of interest was canagliflozin.

New users of six classes of antihyperglycemic agents were identified as the primary comparators for the study: 1) dipeptidyl peptidase-4 (DPP-4) inhibitors, 2) glucagon-like peptide-1 (GLP-1) agonists, 3) sulfonylureas, 4) thiazolidinediones (TZD), 5) insulin, and 6) other non-metformin AHAs (as further defined below and referred as 'other AHA' henceforth). In addition, a total of 27 individual AHA therapies were identified in the protocol as secondary comparators for this study, including:

- DPP-4 inhibitors: alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin
- GLP-1 agonists: albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide
- TZDs: pioglitazone, rosiglitazone, troglitazone
- Sulfonylureas: glipizide, glyburide, glimepiride, chlorpropamide, tolazamide, tolbutamide, acetohexamide
- other AHAs: acarbose, bromocriptine, miglitol, nateglinide, repaglinide
- SGLT2 inhibitors: dapagliflozin, empagliflozin

Because of no exposure or insufficient exposure (<10 patients) in all 3 databases, 6 drugs (1 DPP-4 inhibitor [vildagliptin], 1 TZD [troglitazone], and 4 sulfonylureas [chlorpropomide, tolazamide, tolbutamide, acetohexamide]) were excluded from the study. Therefore, a total of 27 (6 primary, 21 secondary) statistical pairwise comparisons using propensity-score matched cohorts as well as propensity-score stratification were conducted, although treatment effects for several comparisons could not be estimated due to limited numbers of events. Metformin is often used as the first line therapy for managing T2DM, and therefore it was not included as a comparator group. The comparator group was defined as new users of an AHA therapy with at least 365 days of prior observation during April 1, 2013 to September 30, 2017.

Two cohorts were created for each pairwise comparison: 1) canagliflozin, and 2) an alternative AHA therapy, as identified above.

The outcome of interest was the event of acute pancreatitis (AP).

Variables and Data Sources: Definitions for the outcome, AP, were developed based on review of the literature, coding practice guideline documents, and consultation with clinical experts. Medication exposure codes were similarly identified through capture in the relevant therapeutic classification hierarchy and confirmed with clinical experts.

Statistical Methods:

For descriptive analyses, for the exposure cohorts identified, both on-treatment (per protocol, PP) and intent-to-treat (ITT) time-at-risk approaches were used for analysis, respectively, with the on-treatment time-at-risk as the primary analytical approach. For the on-treatment approach, only the events that occurred post-index date, while on-treatment (plus 30 days of the last index medication supply) were ascertained as incident events. Descriptive statistics were generated, including number of persons exposed; time-at-risk; number of persons with an outcome during time-at-risk; incidence rate (per 1,000 person-years (PYs), calculated as number of persons with an incident event during time-at-risk/time-at-risk).

For comparative analysis, formal comparisons were conducted using both on-treatment and ITT approaches for new users of canagliflozin versus new users of an alternative AHA therapy (as identified above), resulting in a total of 27 pairwise comparisons for each database. A conditional Cox proportional hazards model based on time-to-first event approach, using propensity-score matched sets (with a variable-ratio matching) and propensity-score stratification (deciles), were used to estimate the treatment effect size. The propensity score was estimated through large-scale regularized regression, with demographics, all prior conditions/drugs/procedures, risk scores, and utilization density as baseline covariates. Because multiple comparisons were performed, we applied the Hochberg step-up procedure and reported multiplicity adjusted p-values in addition to nominal p-values. In addition, because of potential systematic bias associated with administrative databases and observational studies, a set of negative control outcomes, for which the true hazard ratio was believed to be 1, were used to calibrate empirically observed p-values.

RESULTS

PARTICIPANTS AND PATIENT CHARACTERISTICS: Across the 3 databases and based on on-treatment analyses, we observed 142,167 canagliflozin new users. The CCAE data source provided the largest sample size amongst the 3 databases with 80,986 canagliflozin new users. The majority of the study patients were younger than 65 years of age, with a higher proportion of males in both target and comparator cohorts. For the propensity score (PS) matched cohorts, all baseline characteristics, including demographics, comorbidities, and medications, were well balanced between new users of canagliflozin and new users of non-SGLT2i AHA comparators to a standardized difference < 0.1, with the exception for prior use of AHA (including metformin). This single imbalance was because the baseline target and comparator AHA therapies were not included in the PS prediction model to avoid collinearity.

OUTCOME DATA: The crude incidence rate of AP among new users of canagliflozin ranged from 1.5 to 2.2 events per 1000 person-years exposed during the ‘on treatment’ time-at-risk period, and 1.4 to 2.4 events per 1000 person-years in the ‘intent-to-treat’ analysis; whereas the incidence rate of AP among new users of comparator AHAs ranged from 1.1 to 6.6 events per 1000 person-years exposed during the ‘on treatment’ period, and 1.2 to 4.5 events per 1000 person-years in the ‘intent-to-treat’ analysis.

MAIN RESULTS: A summary of the hazard ratio (HR) estimates and 95% confidence interval (CI) for the risk of AP based on the comparative analyses during the on-treatment time-at-risk period (with 30-day biological window) is briefly described below. In addition, the number (n) of AP events and total number (N) of subjects included in each pairwise comparison were summarized so that the result could be interpreted in a proper context.

Comparing canagliflozin with GLP-1 agonists:

- CCAE (canagliflozin [n/N=59/51,599]; GLP-1 agonists [n/N=85/79,500]): HR=0.88 (0.57-1.35)
- MDCR (canagliflozin [n/N=8/7,474]; GLP-1 agonists [n/N=15/9,541]): HR=0.74 (0.25-2.08)
- Optum (canagliflozin [n/N=20/31,560]; GLP-1 agonists [n/N=37/42,272]): HR=0.46 (0.21-0.93)

Comparing canagliflozin with DPP-4 inhibitors:

- CCAE (canagliflozin [n/N=70/58,881]; DPP-4 inhibitors [n/N=135/122,667]): HR=1.25 (0.85-1.83)
- MDCR (canagliflozin [n/N=15/10,118]; DPP-4 inhibitors [n/N=62/33,619]): HR=1.23 (0.62-2.33)
- Optum (canagliflozin [n/N=27/37,496]; DPP-4 inhibitors [n/N=67/85,686]): HR=0.87 (0.44-1.62)

Comparing canagliflozin with sulfonylureas:

- CCAE (canagliflozin [n/N=75/53,838]; sulfonylureas [n/N=231/139,945]): HR=0.96 (0.68-1.33)
- MDCR (canagliflozin [n/N=12/9,157]; sulfonylureas [n/N=83/34,263]): HR=1.26 (0.58-2.55)
- Optum (canagliflozin [n/N=26/35,277]; sulfonylureas [n/N=120/110,365]): HR=0.84 (0.48-1.42)

Comparing canagliflozin with thiazolidinediones (TZD):

- CCAE (canagliflozin [n/N=33/27,295]; thiazolidinediones [n/N=26/30,729]): HR=1.14 (0.59-2.23)
- MDCR (canagliflozin [n/N=10/5,352]; thiazolidinediones [n/N=15/7,028]): HR=1.06 (0.37-2.95)
- Optum (canagliflozin [n/N=12/21,478]; thiazolidinediones [n/N=17/29,393]): HR=0.70 (0.24-1.92)

Comparing canagliflozin with insulin new users:

- CCAE (canagliflozin [n/N=61/49,123]; insulin new users [n/N=278/93,864]): HR=0.55 (0.37-0.81)
- MDCR (canagliflozin [n/N=11/9,044]; insulin new users [n/N=56/29,184]): HR=1.22 (0.52-2.69)
- Optum (canagliflozin [n/N=23/31,514]; insulin new users [n/N=146/75,738]): HR=0.48 (0.26-0.84)

Comparing canagliflozin with other AHA:

- CCAE (canagliflozin [n/N=6/5,493]; other AHA users [n/N=6/5,774]): HR=0.67 (0.09-4.02)
- MDCR (canagliflozin [n/N=8/2,405]; other AHA users [n/N=5/3,307]): HR=8.68 (1.32-170.46)
- Optum (canagliflozin [n/N=2/4,713]; other AHA users [n/N=8/5,756]): HR=0.25 (0.01-1.69)

Note that nominally significant associations were observed for the comparisons of canagliflozin vs. GLP-1 agonists (Optum: HR=0.46 [0.21-0.93], with 20 and 37 AP events in each treatment arm, respectively), canagliflozin vs. insulin new users (CCAE: HR=0.55 [0.37-0.81], with 61 and 278 AP events in each treatment arm; OPTUM: HR= 0.48 [0.26-0.84)], with 23 and 146 AP events in each treatment arm), all in favor of canagliflozin therapy. However, these results need to be interpreted with caution, because a large number of comparisons were performed, and similar associations were not consistently observed in other databases and using different analytical methods. In addition, p-values no longer met the α=0.05 (2-sided) criteria for statistical significance after adjusting for multiplicity using the Hochberg procedure.

The results from ITT analyses and secondary analyses comparing to 21 individual AHAs were generally consistent with the primary analyses. Results based on the 44 negative controls suggest little to no residual bias.

OTHER ANALYSES: The results from sensitivity analyses were generally consistent with the primary analyses with no statistically significant or consistent associations of AP with canagliflozin versus other AHA drug classes when analyses were restricted to prior metformin users, individuals with a prior AP event, PS matching using 0.1 caliber, or in other on-treatment designs.

ADVERSE EVENTS/ADVERSE REACTIONS: No other adverse events were evaluated in this study.

DISCUSSION AND CONCLUSION:

DISCUSSION:

We found no consistent, statistically significant, or clinically meaningful difference in the risk of AP when comparing canagliflozin with our primary or secondary comparator AHAs. This finding was consistent in both the on-treatment and intent-to-treat analyses, across 3 databases and a variety of sensitivity analyses.

This study is subject to inherent limitations of observational database research, including the potential for unmeasured confounding and misclassification error that may cause bias. Given that the results were largely consistent across three databases, systematic error attributable to artifacts associated with the administrative claims process or provider channeling behavior could persist regardless of insurance coverage. No source record validation was performed to validate exposures, outcomes, or baseline covariates; thus, misclassification bias is possible.

CONCLUSIONS:

In this large observational study, the incidence rates of acute pancreatitis in patients with T2DM treated with canagliflozin or other AHA therapies were generally low, and there were no differences in the risk of AP between canagliflozin and other AHA comparators. Overall, these results suggest that canagliflozin is not associated with an increased risk of acute pancreatitis compared with other AHAs in patients with T2DM.