1. ABSTRACT

Name of Sponsor/Company	Janssen-Cilag International NV*
Name of Finished Product	INVOKANA, VOKANAMET
Name of Active Ingredient(s)	JNJ-28431754 (canagliflozin)

* Janssen Research & Development (Janssen R&D) is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for studies of Janssen R&D may vary. The term "sponsor" is used throughout the protocol to represent these various legal entities.

Protocol No.: PCSCVM003617

Title of Study: A Real-World Database Study of Canagliflozin Utilization in Type 1 Diabetes Patients Over Time among European Countries

Sponsor's Responsible Party: Saberi Rana Ali, MD, MPH, Janssen R&D

Keywords: canagliflozin, drug utilization study, diabetic ketoacidosis, T1DM, SGLT2i

EU PAS Register Number: EUPAS47585

NCT No: N/A

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Marketing Authorization Holder(s): CCI [redacted]

Study Centers: Belgium, Italy, Spain, and the UK

Publication (Reference): Not available at this time.

Study Period: 01 January 2016 to 31 December 2022

Background and Rationale: Canagliflozin is an oral anti-hyperglycemic medicine in the class of SGLT2i. Both the single-agent canagliflozin (INVOKANA) and a fixed dose combination of canagliflozin and metformin (VOKANAMET) are indicated for use in patients with T2DM and not T1DM. A higher than anticipated risk of DKA and the occurrence of atypical normoglycemic DKA have been found in T2DM patients treated with SGLT2i. Despite the warning in the canagliflozin SmPC that canagliflozin-containing medicines should not be used for treatment of patients with T1DM, off-label utilization of canagliflozin in patients with T1DM continued to be observed in clinical practice. In August 2016 and June 2018, respectively, the MAH submitted feasibility assessments for a DUS to assess off-label use of canagliflozin in patients with T1DM. In June 2020, the MAH submitted a third feasibility assessment for a DUS based on the greatest uptake and exposure in EU markets. Following this feasible assessment, PRAC requested the MAH to conduct a descriptive analysis to evaluate annual and overall prevalence and incidence of patients with T1DM who are treated with canagliflozin from January 2016 to December 2022 and to perform a time-trend analysis to elucidate whether the off-label use has increased, stayed constantly low, or decreased over time. This CSR provides an overview of the study and presents a summary of the results for each database studied. For more information on the design, methods, and analysis, refer to the Protocol and SAP. Full results for each database are provided in the individual CSRs.

Research Question and Objectives: What is the proportion of patients with T1DM among canagliflozin users during the period from January 2016 to December 2022 in a European setting and does this proportion change over time?

Study Design: This study was an observational, retrospective cohort study using secondary data from healthcare databases that reflected routine clinical practice in Belgium, Italy, Spain, and the UK. The study primarily identified all users of canagliflozin, and among them, the patients with and without T1DM in each database, and estimated the prevalence and incidence of patients with T1DM in all canagliflozin users. As an exploratory objective, the study explored the occurrence of DKA events in patients with T1DM and in patients with T2DM after exposure to canagliflozin treatment.

Setting: The study period was from 01 January 2016 to 31 December 2022. In each database, patients (all ages and both sexes) to be eligible for this study had to have both 1) ≥1 canagliflozin exposure record during the study period (ie, being identified as canagliflozin users), and 2) ≥180 days of continuous observation before the first exposure to canagliflozin (ie, the index date).

Subject Population and Study Size: This study utilized 7 cohorts of interest. These cohorts are briefly described in this section.

- T01P/T01I - Cohorts included patients who were treated with canagliflozin during the study period and had ≥180 days of continuous observation before the exposure. Patients in the cohort of T01I represented incident users of canagliflozin, patients in the cohort of T01P represented prevalent users of canagliflozin.
- T02P/T02I - Cohorts included patients within the cohorts of all canagliflozin users who had T1DM based on the primary definition. Patients must have ≥1 diagnosis of T1DM on or prior to the canagliflozin exposure, have no T2DM diagnosis or SDM diagnosis, and have not received non-insulin antidiabetic treatment apart from SGLTi. The patients must also have been exposed to insulin for no less than 90% of the observable time from the first T1DM diagnosis until study end to be considered true T1DM patients.
- T03P/T03I - Cohorts included patients within the cohorts of all canagliflozin users who had T1DM based on the sensitivity definition. Compared with the primary definition, the sensitivity definition retained canagliflozin users who received treatment of metformin in the cohorts as patients with T1DM.
- T04I - Cohort included patients within the cohorts of all canagliflozin users who had T2DM. Patients must have ≥1 diagnosis of T2DM on or prior to the canagliflozin exposure and no diagnosis of gestational diabetes or SDM on or before exposure to canagliflozin.

Variables and Data Sources: This report summarizes the overall findings reported in 3 individual CSRs based on the results generated from a total of 6 databases:

- 2 CPRD databases [CPRD_GOLD and CPRD_Aurum] consisting of patients in the UK;
- 3 IQVIA LPD databases [LPD-Belgium, LPD-Italy, and LPD-Spain] consisting of patients in Belgium, Italy, and Spain, respectively;
- 1 SIDIAP database consisting of patients in Catalonia-Spain;

Variables of interest included canagliflozin drug utilization (ie, understanding the initial ingredient given, total number of prescriptions/dispensing, total days of supply, days of supply per prescription/dispensing, dosage at initial use, and duration of continuous exposure), exploratory outcomes (ie, count of DKA events after exposure to canagliflozin and canagliflozin utilization among patients with DKA events), and patient characteristics (ie, demographics, baseline conditions of interest, baseline drugs exposure, clinical measurements of interest, and baseline procedures of interest).

Statistical Methods: All patient-level data were de-identified by the vendors prior to receipt, and upon receipt, were stored in a secure server infrastructure hosted within Johnson & Johnson's, IQVIA's, and

SIDIAP's internal networks respectively. Data access required approved user authentication. All databases require censoring when reporting low counts of patients. Numbers >0 but <5 are censored within the report.

No specific statistical testing was performed based on the descriptive data. Attrition tables show the identification of canagliflozin users with T1DM using 2 definitions. The utilization patterns of canagliflozin were described for new users of canagliflozin with T1DM. The unadjusted prevalence and incidence of patients with T1DM in canagliflozin users were calculated overall and by year. Due to the low patient counts in all databases, the time-trend analysis of annual prevalence and incidence was not performed. As the exploratory objective, DKA events that occurred in patients with T1DM and patients with T2DM after exposure to canagliflozin treatment were identified, the clinical characteristics of the new canagliflozin users with T1DM were investigated.

Results:

This CSR presents a high-level, key summary of the study findings across 6 databases from 4 countries. Additional details can be found in each individual CSR (CPRD Analysis CSR, IQVIA Analysis CSR, and SIDIAP Analysis CSR).

Participants:

The study examined attrition among canagliflozin users in the 6 databases, with a focus on those new users with T1DM. Attrition tables based on primary and sensitivity definitions of T1DM were presented. The analysis found that only a small percentage of canagliflozin users had T1DM in all databases.

Drug Utilization*:*

The drug utilization patterns among canagliflozin new users with T1DM were investigated in the 6 databases. In all databases, using the primary definition of T1DM, <5 new users of canagliflozin were identified with T1DM, and their drug utilization varied between databases. Similar results were found using the sensitivity definition for T1DM. The study found low counts for these patients in all databases, making it challenging to determine the exact drug utilization characteristics.

Descriptive Data:

Demographic and baseline characteristics of canagliflozin new users with T1DM within 180 days prior to the first exposure were described. Across all databases, using the primary and sensitivity definitions, very few patients with T1DM had prespecified conditions relating to diabetes, were exposed to non-insulin diabetic medications, or had undergone major surgeries within 180 days prior to first exposure to canagliflozin. Given the low patient counts and data censorship, patient characteristics should be interpreted with caution.

Outcome Data:

No DKA event was identified in new users of canagliflozin with T1DM in CPRD_GOLD, IQVIA LPDs, and SIDIAP; a censored number of events were reported in CPRD_Aurum. In contrast, among new users of canagliflozin with T2DM, 35 DKA events were captured in 7,038 patients in CPRD_GOLD, 201 events were captured in 26,325 patients in CPRD_Aurum, 33 events were captured in 4,833 patients in SIDIAP, and 85 events were captured in 2,403 patients in IQVIA LPD-Spain. No DKA event was recorded among new users of canagliflozin with T2DM after exposure to canagliflozin in LPD-Belgium (n=270) or LPD-Italy (n=938).

Main Results:

The unadjusted prevalence and incidence of T1DM among canagliflozin users were calculated using both primary and sensitivity definitions. The prevalence and incidence were consistently low over the study period and across databases, with some data censorship, making it infeasible to conduct time-trend analysis.

Adverse Events/Adverse Reactions:

The study used coded data from an electronic database, and reporting criteria for adverse events were not met, preventing the reporting of individual case safety reports.

Discussion and Conclusions:

During the study period from 2016 to 2022, among all users of canagliflozin, the number of new users of canagliflozin identified to have T1DM were consistently very low across the 6 databases in Belgium, Italy, Spain, and the UK (range: 0 to 5 patients using the primary definition; 0 to 11 using the sensitivity definition) and for most databases the data were censored due to the low patient counts.

The overall unadjusted prevalence and incidence of T1DM among canagliflozin users (using either primary or sensitivity definitions) ranged from 0% to <0.1% across the 6 databases.

The annual prevalence and incidence could not be calculated for most of the individual calendar years, during the study period so the trend-test could not be conducted. However, it is reasonable to conclude that the prevalence and incidence had been consistently very low over time.

None to very few cases of DKA (ie, a censored number) were identified among patients with T1DM (using either primary or sensitivity definition) treated with canagliflozin in each database, partly due to the overall low off-label use for T1DM (both INVOKANA and VOKANAMET are indicated for use in patients with T2DM and not T1DM).

DKA is a known risk of SGLT2i, including canagliflozin, in patients with T2DM. No new users of canagliflozin with T2DM were found to have experienced DKA events after exposure to canagliflozin in LPD-Belgium and LPD-Italy. A small proportion of patients with T2DM experienced DKA events after exposure to canagliflozin in the UK and Spain (range: 0.5% to 0.7%).

Conclusions:

From the analyses of the CPRD, IQVIA, and SIDIAP databases, the use of canagliflozin in T1DM patients during the study period was very limited, and there were too few DKA events reported among these patients for a meaningful interpretation.