Diabetic Ketoacidosis and Related Events in the Canagliflozin Type 2 Diabetes Clinical Program

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OBJECTIVE

This study assessed the incidence of serious adverse events of diabetic ketoacidosis (DKA) among patients with type 2 diabetes treated with canagliflozin.

RESEARCH DESIGN AND METHODS

All serious adverse events of DKA and related events (ketoacidosis, metabolic acidosis, and acidosis) from 17,596 patients from randomized studies of canagliflozin through 11 May 2015 were analyzed.

RESULTS

Serious adverse events of DKA and related events were reported in 12 patients (0.07%), including 4 (0.07%), 6 (0.11%), and 2 (0.03%) treated with canagliflozin 100 and 300 mg and comparator, respectively; corresponding incidence rates were 0.522, 0.763, and 0.238 per 1,000 patient-years, respectively. Most patients with DKA and related events had a blood glucose >300 mg/dL (16.7 mmol/L) at presentation of DKA, were on insulin, and had DKA-precipitating factors, including some with type 1 diabetes/latent autoimmune diabetes of adulthood.

CONCLUSIONS

DKA and related events occurred at a low frequency in the canagliflozin type 2 diabetes program, with an incidence consistent with limited existing observational data in the general population with type 2 diabetes.

On 15 May 2015, the U.S. Food and Drug Administration (FDA) issued a Drug Safety Communication based upon a search of the FDA Adverse Event Reporting System database that indicated that medicines for type 2 diabetes in the sodium–glucose cotransporter 2 (SGLT2) inhibitor class (which includes canagliflozin, empagliflozin, and dapagliflozin) may lead to ketoacidosis. The FDA also noted that patients may present atypically, with only slightly increased levels of blood glucose (1). In addition, several case reports and series have described diabetic ketoacidosis (DKA) in patients with type 1 diabetes or type 2 diabetes treated with SGLT2 inhibitors (2–4).

RESEARCH DESIGN AND METHODS

An analysis of all serious adverse events of DKA and related terms of ketoacidosis, metabolic acidosis, and acidosis was performed using a database that contained data from 17,596 patients, with nearly 24,000 patient-years of exposure, compiled from completed and ongoing randomized, controlled clinical studies of canagliflozin. The overall mean exposure in this analysis was 1.4 years. Table 1 includes details regarding the studies included in this analysis, which was conducted by Janssen Research & Development, LLC (the sponsor of canagliflozin). A history of type 1

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Table 1—Randomized, controlled studies of canagliflozin included in the analysis of DKA and related events

Study/status	Study design and population	Key inclusion criteria: Age, years	Key inclusion criteria: HbA_{1c}, % (mmol/mol)	Key inclusion criteria: eGFR, mL/min/1.73 m^2	Treatment groups	Reference
DIA3002/ completed	• Randomized, double-blind, placebo-controlled, 3-arm, parallel-group study (with a 26-week core double-blind period plus a 26-week extension double-blind period) • Men and women with type 2 diabetes on metformin and sulfonylurea therapy	18 to 80	7.0 to 10.5 (53 to 91)	≥55	Canagliflozin 100 mg Canagliflozin 300 mg Placebo (1:1:1)	(9)
DIA3004/ completed	• Randomized, double-blind, placebo-controlled, 3-arm, parallel-group study (with a 26-week core double-blind period plus a 26-week extension double-blind period) • Men and women with type 2 diabetes who have moderate renal impairment on currently available standard-of-care AHA therapies	≥25	7.0 to 10.5 (53 to 91)	≥30 to <50	Canagliflozin 100 mg Canagliflozin 300 mg Placebo (1:1:1)	(10,11)
DIA3005/ completed	• Randomized, double-blind, placebo-controlled, 3-arm, parallel-group study (with a 26-week core double-blind period plus a 26-week active-controlled extension double-blind period)* • Men and women with type 2 diabetes (monotherapy)	18 to 80	7.0 to 10.0 (53 to 86)	≥50	Canagliflozin 100 mg Canagliflozin 300 mg Placebo (1:1:1)	(12,13)
DIA3006/ completed	• Randomized, double-blind, parallel-group study (with a 26-week placebo- and active-controlled core double-blind period and a 26-week active-controlled extension double-blind period) • Men and women with type 2 diabetes on metformin therapy	18 to 80	7.0 to 10.5 (53 to 91)	≥55	Canagliflozin 100 mg Canagliflozin 300 mg Sitagliptin Placebo (2:2:2:1)	(14)
DIA3008 (CANVAS)/ ongoing	• Randomized, double-blind, placebo-controlled, parallel-group cardiovascular assessment study • Men and women with type 2 diabetes on currently available standard-of-care AHA therapies	≥30	7.0 to 10.5 (53 to 91)	≥30	Canagliflozin 100 mg Canagliflozin 300 mg Placebo (1:1:1)	(15,16)
DIA3009/ completed	• Randomized, double-blind, active-controlled, parallel-group study (with a 52-week core double-blind period plus a 52-week extension double-blind period) • Men and women with type 2 diabetes on metformin therapy	18 to 80	7.0 to 10.5 (53 to 91)	≥55	Canagliflozin 100 mg Canagliflozin 300 mg Glimepiride (1:1:1)	(17,18)
DIA3010/ completed	• Randomized, double-blind, placebo-controlled, parallel-group study (with a 26-week core double-blind period plus a 78-week extension double-blind period) • Men and women with type 2 diabetes on currently available standard-of-care AHA therapies	55 to 80	7.0 to 10.0 (53 to 86)	≥50	Canagliflozin 100 mg Canagliflozin 300 mg Placebo (1:1:1)	(19,20)
DIA3012/ completed	• Randomized, double-blind, parallel-group, 3-arm study (with a 26-week placebo-controlled core double-blind period plus a 26-week active-controlled extension double-blind period) • Men and women with type 2 diabetes on metformin and pioglitazone therapy	18 to 80	7.0 to 10.5 (53 to 91)	≥55	Canagliflozin 100 mg Canagliflozin 300 mg Placebo (1:1:1)	(21)

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Table 1—Continued

Study/status	Study design and population	Key inclusion criteria: Age, years	Key inclusion criteria: HbA_{1c}, % (mmol/mol)	Key inclusion criteria: eGFR, mL/min/1.73 m^2	Treatment groups	Reference
DIA3015/ completed	• Randomized, double-blind, 52-week, active-controlled study • Men and women with type 2 diabetes on metformin and sulfonylurea therapy	≥18	7.0 to 10.5 (53 to 91)	≥55	Canagliflozin 300 mg Sitagliptin (1:1)	(22)
DNE3001 (CREDENCE)/ ongoing	• Randomized, double-blind, placebo-controlled, 2-arm, parallel-group, event-driven, multicenter study • Men and women with type 2 diabetes and diabetic nephropathy	≥30	6.5 to 12.0 (48 to 108)	30 to 90	Canagliflozin 100 mg Placebo (1:1)	—
DIA4002/ ongoing†	• Randomized, double-blind, placebo-controlled, 3-arm, parallel-group, multicenter study • Men and women with type 2 diabetes and hypertension	18 to <75	7.0 to <10.0 (53 to <86)	≥60	Canagliflozin 100 mg Canagliflozin 300 mg Placebo (1:1:1)	—
DIA4003 (CANVAS-R)/ ongoing	• Randomized, double-blind, placebo-controlled, 2-arm, parallel-group, multicenter study • Men and women with type 2 diabetes receiving standard of care, but with inadequate glycemic control and at elevated risk of cardiovascular events	≥30	7.0 to 10.5 (53 to 91)	≥30	Canagliflozin 100 mg (with titration to canagliflozin 300 mg) Placebo (1:1)	—
DIA4004/ ongoing	• Randomized, double-blind, placebo-controlled, 2-arm, parallel-group, multicenter study • Men and women with type 2 diabetes on metformin and sitagliptin therapy	18 to 75	7.5 to 10.5 (58 to 91)	≥60	Canagliflozin 100 mg (with titration to canagliflozin 300 mg) Placebo (1:1)	—
DIA2003/ completed	• Randomized, double-blind, placebo-controlled, 3-arm, parallel-group, 18-week, multicenter study • Men and women with type 2 diabetes with inadequate glycemic control on metformin therapy	18 to 80	7.5 to 10.5 (58 to 91)	≥55	Canagliflozin 50 mg BID Canagliflozin 150 mg BID Placebo (1:1:1)	(23)
DIA3011/ completed	• Randomized, double-blind, active-controlled, parallel-group, 26-week multicenter study of initial combination therapy with canagliflozin and metformin • Men and women with drug-naïve type 2 diabetes	18 to <75	7.5 to 12.0 (58 to 108)	≥60	Metformin XR Canagliflozin 100 mg Canagliflozin 300 mg Canagliflozin 100 mg/ metformin XR Canagliflozin 300 mg/ metformin XR (1:1:1:1:1)	(24)

AHA, antihyperglycemic agent; BID, twice daily; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; eGFR, estimated glomerular filtration rate; XR, extended release. *DIA3005 also had a 26-week high glycemic substudy that was not included in the current analysis. No adverse events of DKA, ketoacidosis, metabolic acidosis, or acidosis were reported in this substudy. †Clinical conduct is completed; final clinical study report is in progress.

diabetes or DKA was an exclusion criterion in all studies. Ascertainment of potential events for inclusion in this analysis was done using investigator-reported adverse events. Four adverse event terms (i.e., diabetic ketoacidosis, ketoacidosis, metabolic acidosis, and acidosis) from the *Medical Dictionary for Regulatory Activities* (MedDRA) were searched. Cases meeting standard criteria for a regulatory definition of a serious adverse event (e.g., resulting in hospitalization or a medically important event) were included in this analysis. All unblinded cases in this analysis came from completed studies or unblinded data sets previously used to support canagliflozin global marketing dossiers or required for responses to health authorities. Through 11 May 2015, there were 12 patients with 13 unblinded serious adverse events of DKA, ketoacidosis, metabolic acidosis, and acidosis, and 3 additional serious adverse events that remain blinded and were not included in the current analysis. These 3 additional events come from the ongoing CANagliflozin cardioVascular Assessment Study (CANVAS), which is blinded and is being monitored by an independent data monitoring committee. Data from the 12 unblinded patients with serious adverse events are discussed below.

RESULTS

The incidence of serious adverse events of DKA and related events in the canagliflozin randomized clinical trial database was 0.07% (12 of 17,596). The incidence

of serious adverse events of DKA and related events by treatment group was 0.07% (4 of 5,337), 0.11% (6 of 5,350), and 0.03% (2 of 6,909) with canagliflozin 100 and 300 mg and comparator, respectively; corresponding incidence rates were 0.522, 0.763, and 0.238 per 1,000 patient-years, respectively. After being diagnosed with a DKA-related event, 6 patients on canagliflozin (3 on canagliflozin 100 mg, 3 on canagliflozin 300 mg, and none on comparator) were reported to have autoimmune diabetes (latent autoimmune diabetes of adulthood [LADA] or type 1 diabetes) or to have tested positive for GAD65 antibodies. Excluding these 6 patients, the incidences of serious adverse events of DKA and related events by treatment group in patients with type 2 diabetes were 0.02% (1 of 5,334), 0.06% (3 of 5,347), and 0.03% (2 of 6,909) with canagliflozin 100 and 300 mg and comparator, respectively, with corresponding incidence rates of 0.130, 0.381, and 0.238 per 1,000 patient-years, respectively. The race and ethnicity of the patients with severe adverse events of DKA and related events were as follows: 1 Hispanic or Latino American Indian or Alaska native patient; 1 Hispanic or Latino white patient; and 10 non-Hispanic or Latino white patients. Compared with other patients in the canagliflozin program, these 12 patients were predominantly male, white, and older and had a longer duration of diabetes, lower BMI, higher HbA_{1c}, and lower estimated glomerular filtration rate at baseline (Table 2). Specific details of the 12 patients with serious adverse events of DKA and related events are reported in Table 3. Eight of the 12 patients in this analysis were enrolled in the CANVAS trial, which included patients with significant comorbid conditions; of these 8 patients, all 7 in the canagliflozin treatment groups were on insulin. The 10 patients with blood glucose values reported at presentation had levels that were >300 mg/dL (16.7 mmol/L) and ranged from 347 to 571 mg/dL (19.3 to 31.7 mmol/L). One other patient on canagliflozin 300 mg had several blood glucose levels ranging from 148 to 320 mg/dL (8.2 to 17.8 mmol/L), but dates and times of these measurements were not provided. Of the 10 patients on canagliflozin with a DKA-related event, 8 were receiving insulin therapy (note that ~31% of patients [*n* = 5,407] in the canagliflozin type 2 diabetes program were on background insulin therapy), with 4 having questionable compliance with insulin therapy at the time of the event. One of these 4 patients also had a second event postoperatively after a cholecystectomy. The other 4 patients on insulin therapy with a DKA-related event had concomitant diagnoses of pancreatic cancer, myocardial infarction, gastroenteritis, and viral infection. Among the 2 canagliflozin patients not on insulin therapy with an event, 1 had type 1 diabetes and 1 had a subcutaneous abscess and chronic pancreatitis.

Table 2—Background demographic and disease characteristics of patients with and without serious adverse events of DKA and related events

	Patients with DKA (*n* = 12)	Patients without DKA (*n* = 17,584)
Sex, *n* (%)		
Male	9 (75.0)	7,182 (40.8)
Female	3 (25.0)	10,401 (59.2)
Age, years	69.5 (47, 78)	61.0 (20, 96)
Race, *n* (%)		
White	11 (91.7)	13,480 (76.7)
Black/African American	0	703 (4.0)
Asian	0	2,148 (12.2)
Other†	1 (8.3)	1,253 (7.1)
Ethnicity, *n* (%)		
Hispanic or Latino	2 (16.7)	3,118 (17.7)
Not Hispanic or Latino	10 (83.3)	14,385 (81.8)
Other‡	0	81 (0.5)
HbA_{1c}, %	8.9 (7, 11)	8.0 (5, 14)
HbA_{1c}, mmol/mol	74 (53, 97)	66 (31, 130)
BMI, kg/m^2	27.1 (23, 34)	31.3 (15, 73)
eGFR, mL/min/1.73 m^2	69.0 (33, 127)	79.0 (10, 227)
Duration of diabetes, years	13.5 (1, 29)	9.0 (0, 55)

Data are median (range) unless otherwise indicated. eGFR, estimated glomerular filtration rate. †Includes American Indian or Alaskan Native, Native Hawaiian or other Pacific Islander, multiple, other, unknown, and not reported. ‡Includes unknown and not reported.

CONCLUSIONS

In summary, DKA and related events occurred at a low frequency in patients participating in the randomized, controlled canagliflozin type 2 diabetes clinical trial program. Although there are limited epidemiological data on the incidence of DKA in patients with type 2 diabetes, the overall incidence rates of these events in the current analysis are consistent with the broad range reported in existing observational data. Specifically, a study in Northern Sweden reported an estimated DKA incidence rate of 0.5 per 1,000 patient-years (5), and an analysis of four large U.S. commercial claims databases (i.e., the Truven MarketScan Commercial Claims and Encounters, MarketScan Medicare Supplemental Beneficiaries, the MarketScan Multistate Medicaid Database, and the Optum Clinformatics database) found a DKA incidence rate in the range of 0.32 to 2.0 per 1,000 patient-years (data on file). However, given the potential for incomplete reporting or underreporting of DKA, the incidence of DKA in patients with type 2 diabetes, including patients treated with canagliflozin and other SGLT2 inhibitors, may be underestimated.

Although there were some differences in baseline characteristics between all patients and the subset of patients who developed DKA and related events, there was no clear baseline clinical phenotype that allowed the identification of specific individual patients at risk for developing DKA. Nevertheless, most patients had a known precipitating factor for DKA at the time of these events. Some reports note that patients who presented with DKA had atypically low blood glucose values; however, of the 10 patients treated with canagliflozin who presented with DKA and related events and had available blood glucose values at presentation, 9 patients had blood glucose values >250 mg/dL (13.9 mmol/L). We postulate that patients diagnosed as having

Table 3—Summary of patients with treatment-emergent serious adverse events of DKA and related events in the canagliflozin development program for type 2 diabetes

Patient	1	2	3	4	5	6	7	8	9	10	11	12
Age, years	73	66	73	76	50	74	73	78	47	66	57	62
BMI, kg/m^2	25.7	27.1	28.8	22.7	22.7	25.4	34.2	27.0	29.6	30.5	24.9	29
Sex	M	M	M	M	M	M	F	F	F	M	M	M
Evidence of autoimmune diabetes (type 1 diabetes, LADA, GAD65 antibody positive)	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	No	No	No
Diabetes duration (at randomization), years	21	22	20	14	10	30	11	20	1	12	13	1
Baseline HbA_{1c}, % (mmol/mol)	9.1 (76)	7.8 (62)	8.7 (72)	8.4 (68)	8.0 (64)	7.9 (63)	10.5 (91)	9.6 (81)	9.3 (78)	7.2 (55)	9.9 (85)	10.5 (91)
Baseline C-peptide value, nmol/L (ng/mL)	0.17 (0.51) Low*	1.19 (3.57)	N/A	<0.02 (<0.07) Low*	<0.02 (<0.07) Low*	0.03 (0.10) Low*	N/A	N/A	0.14 (0.43) Low*	N/A	0.34 (1.02)	N/A
Treatment group	CANA 300 mg	Placebo	CANA 100 mg	CANA 100 mg	CANA 300 mg	CANA 300 mg	CANA 300 mg	CANA 100 mg	CANA 100 mg	CANA 300 mg	SITA 100 mg	CANA 300 mg
Adverse event	Acidosis DKA (non-TEAE)	Metabolic acidosis	DKA	DKA	Metabolic acidosis	DKA	Ketoacidosis	DKA	DKA	DKA	DKA	Ketoacidosis
Onset day relative to first dose	Acidosis: 618 DKA: 1,226 (stopped treatment day 1,194)	Admitted day 731 (stopped treatment day 693)	454	21	54	288	744	536	212	720 (stopped treatment day 719)	256	18
Background AHA(s)	INS	MET, GLIP	INS	INS	INS	INS	INS, MET	INS, MET	MET, GLIM	INS (started 2 days prior to DKA onset), EXEN, GLIC, MET	INS	None
Blood glucose, mg/dL (mmol/L)†	Acidosis: 369 (20.5) DKA: 533 (29.6)	N/A	400 (22.2)	347 (19.3)	>500 (>27.8)	>500 (>27.8)	148–320 (8.2–17.8)‡	481 (26.7)	400 (22.2)	470 (26.1)	481 (26.7)§	571 (31.7)
pH	Acidosis: 7.24 DKA: N/A	N/A	7.14	N/A	6.82	N/A	N/A	7.23	7.022	N/A	7.22§	N/A
Bicarbonate, mEq/L	Acidosis: 15 DKA: 15	N/A	15	N/A	3.4	N/A	13.6§	11.7	1.8	N/A	11.4§	N/A
Anion gap, mmol/L	Acidosis: 6 DKA: 17	N/A	25	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ketones (blood or urine)	Acidosis: +blood DKA: +blood, +urine	N/A	+Blood	N/A	+Blood	N/A	N/A	+Blood	N/A	N/A	N/A	+Urine

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Table 3—Continued

Patient	1	2	3	4	5	6	7	8	9	10	11	12
Confounding factors	Acidosis: • History of LADA • Acute cholecystitis requiring laparoscopic cholecystectomy (day 618) • Acidosis developed postoperatively DKA: • Nausea, vomiting, and diarrhea prior to hospitalization on day 1,226 • Weight loss (53.5 kg at time of DKA, 21 kg lost in <2 years) and cognitive decline prior to DKA • Noncompliant with care	• History of alcohol abuse • Admitted with left lower lobe infiltrate, sepsis, respiratory failure, metastatic colorectal cancer	• Hyperglycemia the day before hospitalization for DKA thought to be due to "bad insulin" • Changed reservoir, tubing, and site of the insulin pump • Self-administered 116–117 units of insulin because blood glucose levels remained elevated • Blood glucose still remained elevated and he went to the ER, where he presented with dehydration, hypotension, tachycardia, and elevated CK-MB • Elevated troponin levels were noted the next day, and the event was adjudicated as an MI	• Nausea, vomiting, and diarrhea the day before hospitalization for DKA • Patient did not take usual insulin dose on day of hospitalization • Nonfatal STEMI occurred day after DKA • Subsequently tested positive for GAD65 and insulin antibodies‖	• Vomiting 2 days before hospitalization, which apparently led to the interruption of insulin	• On insulin since diagnosis (~30 years) • Reduced usual insulin dose due to reduced blood glucose after study start • Unintentional weight loss of ~13.6 kg over ~6 months • Medication and dietary noncompliance • Infectious gastroenteritis with continuous vomiting 3 days prior to DKA • Elevated transaminases noted during hospitalization (nonviral hepatitis) • Subsequently tested positive for GAD65 and insulin antibodies‖	• Did not take insulin injections for 4 days prior to hospitalization due to technical problems with insulin pen • Subsequently diagnosed with LADA	• Associated with RSV infection and faulty insulin injection technique (assessed during the hospitalization) • Subsequently tested positive for GAD65 and insulin antibodies‖	• 45.4 kg weight loss within <2 years • Subsequent diagnosis with type 1 diabetes (positive for GAD65)	• UTI from days 656 to 678, 692 to 718, and day 736 • Pancreatic cancer with liver metastasis diagnosed on day 786	• Acute gastroenteritis started on day 255 • Developed septic shock and acute renal failure in addition to DKA • Patient died of acute MI (cause of death from autopsy report) on day 258	• Heart failure class II and on indapamide • Abscessed boil of the anterior abdominal wall which required dissection and antibiotics • Abdominal ultrasound showed chronic pancreatitis

AHA, antihyperglycemic agent; CANA, canagliflozin; CK-MB, creatinine kinase–myoglobin; ER, emergency room; EXEN, exenatide; F, female; GLIC, gliclazide; GLIM, glimepiride; GLIP, glipizide; INS, insulin; M, male; MET, metformin; MI, myocardial infarction; N/A, not available; RSV, respiratory syncytial virus; SITA, sitagliptin; STEMI, ST-segment elevation myocardial infarction; TEAE, treatment-emergent adverse event (defined as an adverse event that occurred during the treatment period or within 30 days since the last dose of the study medication); UTI, urinary tract infection. *Per normal laboratory range of 0.27 to 1.28 nmol/L (0.81 to 3.85 ng/mL). †Blood glucose value at presentation of the adverse event. ‡Range of all values reported; specific days and times not reported. §Specific date not reported. ‖GAD65 antibody titers ≥17× the upper limit of normal (20 DK units/mL); IA-2 antibody titers were negative.

type 2 diabetes or misdiagnosed as having type 2 diabetes (e.g., LADA, type 1 diabetes) and who have a low β-cell reserve coupled with a potential SGLT2 inhibitor–associated increase in glucagon (6–8) are unable to produce sufficient insulin to suppress hepatic ketogenesis and peripheral lipolysis, which in the setting of an acute illness (and associated increase in insulin resistance) can develop DKA. Further prospective research is needed to better understand the incidence and underlying mechanism(s) of DKA associated with SGLT2 inhibitors.

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