Efficacy and Safety of Canagliflozin, a Sodium Glucose Cotransporter 2 Inhibitor, as Add-On to Insulin in Patients With Type 1 Diabetes

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OBJECTIVE

This study assessed the efficacy and safety of canagliflozin, a sodium glucose cotransporter 2 inhibitor, as add-on to insulin in adults with type 1 diabetes.

RESEARCH DESIGN AND METHODS

This 18-week, double-blind, Phase 2 study randomized 351 patients (HbA_{1c} 7.0–9.0% [53–75 mmol/mol]) on multiple daily insulin injections or continuous subcutaneous insulin infusion to canagliflozin 100 or 300 mg or placebo. The primary end point was the proportion of patients achieving at week 18 both HbA_{1c} reduction from baseline of ≥0.4% (≥4.4 mmol/mol) and no increase in body weight. Other end points included changes in HbA_{1c}, body weight, and insulin dose, as well as hypoglycemia incidence. Safety was assessed by adverse event (AE) reports.

RESULTS

More patients had both HbA_{1c} reduction ≥0.4% and no increase in body weight with canagliflozin 100 and 300 mg versus placebo at week 18 (36.9%, 41.4%, 14.5%, respectively; $P < 0.001$). Both canagliflozin doses provided reductions in HbA_{1c}, body weight, and insulin dose versus placebo over 18 weeks. The incidence of hypoglycemia was similar across groups; severe hypoglycemia rates were low (1.7–6.8%). Overall incidence of AEs was 55.6%, 67.5%, and 54.7% with canagliflozin 100 and 300 mg and placebo; discontinuation rates were low (0.9–1.3%). Increased incidence of ketone-related AEs (5.1%, 9.4%, 0%), including the specific AE of diabetic ketoacidosis (DKA) (4.3%, 6.0%, 0%), was seen with canagliflozin 100 and 300 mg versus placebo.

CONCLUSIONS

Canagliflozin provided reductions in HbA_{1c}, body weight, and insulin dose with no increase in hypoglycemia, but increased rates of ketone-related AEs, including DKA, in adults with type 1 diabetes inadequately controlled with insulin.

Type 1 diabetes is an autoimmune disease characterized by progressive destruction of pancreatic β-cells, resulting in loss of endogenous insulin production and hyperglycemia (1). Consequently, treatment of type 1 diabetes requires lifelong insulin therapy to maintain normal blood glucose levels. Type 1 diabetes is associated with increased morbidity and mortality related to microvascular and macrovascular

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complications such as renal insufficiency, peripheral neuropathy, retinopathy, coronary artery disease, and stroke (1,2). These complications reduce the estimated life expectancy for patients with type 1 diabetes by ~11 years in men and 13 years in women (3). Patients with type 1 diabetes are also at increased risk of diabetic ketoacidosis (DKA), a serious condition caused by absolute or relative deficiency of circulating insulin levels, commonly due to precipitating factors such as intercurrent illness or interruption of insulin therapy (4).

Intensive insulin treatment has been shown to reduce the onset and/or progression of microvascular and macrovascular complications in patients with type 1 diabetes (5,6); however, even with the development of rapid- and long-acting insulin analogs and improvements in insulin-delivery devices, ~75% of adults with type 1 diabetes fail to achieve the target of HbA_{1c} <7.0% (<53 mmol/mol) recommended by the American Diabetes Association (7). Limitations of insulin therapy include increased risk of hypoglycemia, excessive glucose fluctuations, and weight gain, which may deter patients from adequately titrating their daily insulin dosage to meet target HbA_{1c} goals (1,2). The only approved adjunctive treatment for type 1 diabetes is pramlintide, an injectable amylin analog that inhibits glucagon secretion and delays gastric emptying; however, pramlintide is associated with an increased risk of severe hypoglycemia (8,9). Thus, new therapies are needed that help patients with type 1 diabetes improve glycemic control without increasing body weight or the risk of hypoglycemia.

Canagliflozin is a sodium glucose cotransporter 2 (SGLT2) inhibitor approved for the treatment of adults with type 2 diabetes (10) but not type 1 diabetes. Canagliflozin reduces blood glucose levels through an insulin-independent mechanism by lowering the renal threshold for glucose and increasing urinary glucose excretion, which results in a mild osmotic diuresis and net caloric loss (11–13). In Phase 3 studies, canagliflozin improved glycemic control, reduced body weight and blood pressure, and was generally well tolerated across a broad range of patients with type 2 diabetes (10,14). The incidence of hypoglycemia was low with canagliflozin in patients not on background antihyperglycemic agent therapy associated with an increased risk of hypoglycemia; in patients on background therapies associated with an increased risk of hypoglycemia (i.e., insulin or sulfonylurea), the incidence of hypoglycemia with canagliflozin was higher (15).

In a randomized, double-blind, Phase 3 trial in patients with type 2 diabetes and a history or high risk of cardiovascular disease, canagliflozin 100 and 300 mg provided reductions in HbA_{1c}, body weight, and blood pressure versus placebo over 52 weeks when used in conjunction with insulin therapy (≥20 IU/day) (16). Rates of documented hypoglycemia (i.e., episodes with fingerstick or plasma glucose ≤3.9 mmol/L [≤70 mg/dL], irrespective of symptoms, and severe episodes [i.e., episodes requiring assistance from another person or those resulting in seizure or loss of consciousness]) were 59%, 57%, and 48% with canagliflozin 100 and 300 mg and placebo, respectively; the incidence of severe hypoglycemia was low and similar across treatment groups (4–6%).

Because their mechanism of action is independent of insulin secretion, SGLT2 inhibitors may represent a complementary treatment option to insulin for patients with type 1 diabetes. Several small pilot studies with SGLT2 inhibitors, ranging from 2 to 8 weeks, have been performed in patients with type 1 diabetes (17–19). These studies have generally shown that treatment with SGLT2 inhibitors provides improved glucose control and reductions in the insulin dose without increasing hypoglycemic events. This Phase 2 study evaluated the efficacy and safety of canagliflozin compared with placebo over 18 weeks in patients with type 1 diabetes inadequately controlled with insulin therapy.

RESEARCH DESIGN AND METHODS

Study Design and Patients

This double-blind, parallel-group, multicenter, Phase 2 study consisted of a 2-week period before randomization, followed by an 18-week double-blind treatment phase and 2 weeks of safety follow-up for all patients. Eligible patients were aged 25–65 years with a BMI of 21–35 kg/m^2, a fasting C-peptide level of <0.2 pmol/L (<0.6 ng/mL) at screening, and type 1 diabetes for 1 year or more that was inadequately controlled with multiple daily insulin (MDI) injections or continuous subcutaneous insulin infusion (CSII; HbA_{1c} of 7.0–9.0% [53–75 mmol/mol] at screening). The lower age limit was chosen because patients <25 years may be less compliant with following treatment instructions and adhering to protocol procedures (20). The lower BMI limit was chosen to avoid weight loss in patients with an already low body weight.

Patients were required to be on a stable insulin regimen and a stable method of insulin administration (MDI or CSII) for ≥8 weeks before screening. Patients were excluded if they had a history of type 2 diabetes; had a severe hypoglycemic event (defined as an event that required assistance from another person or resulted in seizure or loss of consciousness) or DKA (self-reported by patients) within 6 months before randomization; myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident ≤12 weeks before screening; history of New York Heart Association Functional Classification III–IV cardiac disease; uncontrolled hypertension; estimated glomerular filtration rate (eGFR) <70 mL/min/1.73 m^2; or were taking any antihyperglycemic agent other than insulin within 12 weeks before screening. Patients were discontinued if their eGFR was <60 mL/min/1.73 m^2 during the study.

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with Good Clinical Practice and applicable regulatory requirements. Approval was obtained from institutional review boards and independent ethics committees for each participating center. Patients provided informed written consent before participation.

Insulin Therapy

To mitigate a potential increased risk of hypoglycemia due to the addition of canagliflozin, patients with HbA_{1c} ≤8.0% (≤64 mmol/mol) at screening were recommended, at the discretion of the investigator, to reduce their basal insulin dose by 20% before randomization; similarly, patients with HbA_{1c} >8.0% (>64 mmol/mol) at screening were recommended to reduce their basal insulin dose by 10%. During the 18-week treatment period, patients were instructed to titrate their basal insulin dose to achieve a prebreakfast blood glucose level of 4.4 to <6.7 mmol/L (80 to <120 mg/dL), and to titrate their bolus insulin dose to achieve a prelunch,

predinner, and bedtime blood glucose level of 4.4 to <6.7 mmol/L (80 to <120 mg/dL). Algorithms for titrating basal and bolus insulin doses to achieve target glycemic goals were provided as a general guideline (Supplementary Table 1). Investigators were allowed to use their judgement when recommending insulin adjustments based on their knowledge of the patient's individual history and risk of hypoglycemia. Patients were required to record daily glucose measurements and concomitant doses of basal and bolus insulin at specified timepoints to assess compliance with insulin dosing and to receive titration instructions.

Randomization and Blinding

A computer-generated randomization schedule prepared by the sponsor before the study was used to randomize patients (1:1:1) to receive canagliflozin 100 or 300 mg or placebo once daily before the first meal of the day over 18 weeks. Randomization was stratified according to patients' use of MDI versus CSII. Fasting plasma glucose (FPG) and HbA_{1c} values were masked to the study sites and to the sponsor.

End Points and Assessments

Patients with type 1 diabetes often fail to achieve adequate glycemic control due to fear of weight gain associated with an intense insulin treatment regimen. Hence, the proportion of patients at week 18 with HbA_{1c} reduction ≥0.4% (≥4.4 mmol/mol) and no increase in body weight relative to baseline in the context of intensified insulin treatment was selected to be a clinically meaningful prespecified primary end point in this study. Because some natural day-to-day variability occurs in body weight, the proportion of patients at week 18 with an HbA_{1c} reduction ≥0.4% (≥4.4 mmol/mol) and a change in body weight <1 kg was also calculated to assess how sensitive the conclusions were to the specific value of weight change used in the end point. Key secondary end points included change from baseline in HbA_{1c} and FPG, proportion of patients with HbA_{1c} <7.0% (<53 mmol/mol), percentage change from baseline in body weight, change from baseline in basal and bolus insulin dosage requirements (after the initial 10–20% downtitration), and the incidence and event rate of documented hypoglycemia and documented symptomatic hypoglycemia at week 18. Patients were instructed to record information on all events of possible hypoglycemia, as well as associated fingerstick glucose measurements, if available. Documented hypoglycemia episodes included biochemically confirmed episodes (concurrent fingerstick or plasma glucose ≤3.9 mmol/L [≤70 mg/dL]) or severe episodes (i.e., episodes requiring assistance from another person or those resulting in seizure or loss of consciousness). Documented symptomatic hypoglycemia included episodes with symptoms consistent with hypoglycemia with concurrent documented plasma glucose ≤3.9 mmol/L (≤70 mg/dL) or severe episodes.

Overall safety and tolerability were assessed based on adverse event (AE) reports, safety laboratory tests, vital signs measurements, and physical examinations. Analysis of ketone-related AEs was performed using a prespecified list of preferred terms (i.e., acidosis, blood ketone body increased, blood ketone body present, DKA, diabetic ketoacidotic hyperglycemic coma, ketoacidosis, ketonemia, ketonuria, ketosis, metabolic acidosis, and urine ketone body present).

Statistical Analyses

Sample size was determined based on the assumption that 40% of patients would meet the primary end point with each canagliflozin dose compared with 20% of patients in the placebo group. A total of 100 patients per group were estimated to be required to achieve ~80% power for the comparison of each canagliflozin dose with placebo, with a two-sided family-wise type I error rate of 0.05. Approximately 110 patients were planned for inclusion in each treatment group to account for potential early discontinuations.

Efficacy and safety analyses were conducted using the modified intent-to-treat analysis set (i.e., all patients who were randomized and received ≥1 dose double-blind study drug). The primary efficacy end point was analyzed longitudinally using a generalized linear mixed model that included treatment, stratification factor (i.e., use of MDI versus CSII), visit, and treatment-by-visit interaction as fixed categorical effects and baseline HbA_{1c}, baseline body weight, and baseline-by-visit interaction as continuous fixed covariates. Change from baseline in HbA_{1c}, FPG, and body weight were analyzed with a mixed-model for repeated measures using a restricted maximum likelihood approach. This analysis was based on observed data that included treatment, stratification factor, visit, and treatment-by-visit interaction as fixed categorical effects and baseline value and baseline-by-visit interaction as continuous fixed covariates. Least squares (LS) mean differences and 95% CIs were estimated at week 18 for each canagliflozin dose versus placebo. The proportion of patients with HbA_{1c} <7.0% (<53 mmol/mol) was analyzed using a logistic regression model including the fixed categorical effects of treatment and stratification factor (use of MDI versus CSII) and the fixed continuous covariate of baseline HbA_{1c}. Change from baseline in insulin dose was assessed for total daily insulin dose, basal insulin dose, and bolus insulin dose. Similar to the analysis of HbA_{1c} and body weight, the change from baseline in insulin dose was analyzed using the mixed-model for repeated-measures approach. The incidence of documented hypoglycemia and documented symptomatic hypoglycemia was assessed at week 18. The hypoglycemic event rate was calculated as the number of hypoglycemia episodes per patient-year exposure. Statistical testing of comparisons of canagliflozin versus placebo was not performed (not prespecified) for end points other than the primary end point; therefore, *P* values are only reported for the primary end point, and 95% CIs are provided for descriptive purposes for end points that were not prespecified for hypothesis testing. Safety analyses included all reported AEs with onset during the treatment phase (i.e., treatment-emergent AEs).

RESULTS

Patients

A total of 351 patients were randomized and received one or more doses of the study drug, comprising the modified intent-to-treat analysis set; of these, 328 (93.4%) completed 18 weeks of treatment (Supplementary Fig. 1). Rates of discontinuation were 5.1%, 6.0%, and 8.5% with canagliflozin 100 and 300 mg and placebo, respectively. Lost to follow-up (2.0%) and withdrawal of consent (2.0%) were the most common

Table 1—Baseline demographic and disease characteristics

	Placebo (n = 117)	Canagliflozin 100 mg (n = 117)	Canagliflozin 300 mg (n = 117)	Total (N = 351)
Sex				
Male	63 (53.8)	69 (59.0)	65 (55.6)	197 (56.1)
Female	54 (46.2)	48 (41.0)	52 (44.4)	154 (43.9)
Age, years	42.0 ± 11.9	42.0 ± 11.6	42.8 ± 11.0	42.3 ± 11.5
Race*				
White	106 (90.6)	111 (94.9)	102 (87.2)	319 (90.9)
Black/African American	7 (6.0)	5 (4.3)	5 (4.3)	17 (4.8)
Asian	2 (1.7)	0	5 (4.3)	7 (2.0)
Other†	2 (1.7)	1 (0.9)	5 (4.3)	8 (2.3)
HbA_{1c}, %	7.9 ± 0.6	7.9 ± 0.5	8.0 ± 0.5	7.9 ± 0.5
HbA_{1c}, mmol/mol	63 ± 6.6	63 ± 5.5	64 ± 5.5	63 ± 5.5
Body weight, kg	83.0 ± 15.4	84.1 ± 14.2	82.9 ± 15.0	83.4 ± 14.8
BMI, kg/m^2	28.0 ± 3.6	28.0 ± 3.9	28.1 ± 3.9	28.1 ± 3.8
eGFR, mL/min/1.73 m^2	96.0 ± 14.8	97.4 ± 14.9	95.8 ± 16.5	96.4 ± 15.4
Duration of type 1 diabetes, years	23.3 ± 11.0	22.0 ± 11.5	21.9 ± 10.6	22.4 ± 11.0
CSII use	72 (61.5)	74 (63.2)	73 (62.4)	219 (62.4)
MDI use	45 (38.5)	43 (36.8)	44 (37.6)	132 (37.6)
Prior severe hypoglycemia	18 (15.4)	15 (12.8)	19 (16.2)	52 (14.8)
Prior DKA	14 (12.0)	13 (11.1)	15 (12.8)	42 (12.0)

Data are mean ± SD or n (%). *Percentages may not total 100.0 due to rounding. †Includes multiple, other, and not reported.

reasons for discontinuation. Baseline demographic and disease characteristics were generally similar across treatment groups (Table 1). Patients had a mean baseline HbA_{1c} of 7.9% (63 mmol/mol) and BMI of 28.1 kg/m^2. A greater proportion of patients were using CSII versus MDI (62.4% vs. 37.6%). The mean duration of type 1 diabetes was 22 years; 14.8% and 12.0% of patients had a history of severe hypoglycemia or DKA, respectively.

Efficacy

HbA_{1c}, FPG, and Body Weight

At week 18, a greater proportion of patients had HbA_{1c} reduction ≥0.4% (≥4.4 mmol/mol) and no increase in body weight with canagliflozin 100 and 300 mg compared with placebo (36.9%, 41.4%, and 14.5%, respectively; $P < 0.001$ for both comparisons). With respect to the individual components of the composite end point, 45.0%, 43.2%, and 22.7% of patients had a reduction in HbA_{1c} ≥0.4% (≥4.4 mmol/mol) at week 18 with canagliflozin 100 and 300 mg and placebo, respectively; 83.8%, 96.4%, and 49.1% of patients, respectively, had no increase in body weight (Fig. 1*A*). Results of the sensitivity analysis of the proportion of patients with HbA_{1c} reduction ≥0.4% (≥4.4 mmol/mol) and change in body weight <1 kg were consistent with the primary end point, with more patients achieving this composite end point with canagliflozin versus placebo (Supplementary Table 2).

Consistent with the data for the composite end point, canagliflozin 100 and 300 mg provided greater reductions in HbA_{1c} compared with placebo at week 18. Placebo-subtracted LS mean reductions in HbA_{1c} from baseline were −0.29% (−3.2 mmol/mol) with canagliflozin 100 mg and −0.25% (−2.7 mmol/mol) with canagliflozin 300 mg (Fig. 1*B*). The proportion of patients achieving HbA_{1c} <7.0% (<53 mmol/mol) at week 18 was 10.1%, 11.2%, and 5.7% with canagliflozin 100 and 300 mg and placebo, respectively. Dose-dependent reductions in body weight were seen with canagliflozin 100 and 300 mg compared with placebo at week 18 (placebo-subtracted LS mean percentage changes of −3.4% and −5.3%, respectively; Fig.1*C*). Canagliflozin 100 and 300 mg also provided reductions in FPG compared with placebo at week 18 (placebo-subtracted LS mean changes of −0.5 mmol/L [−8.5 mg/dL] and −0.6 mmol/L [−11.5 mg/dL], respectively; Fig. 1*D*).

Insulin Dose

Canagliflozin 100 and 300 mg were associated with reductions from baseline in the daily insulin dose at week 18 (Fig. 1*E*). Placebo-subtracted absolute LS mean reductions (mean percentage change) in the total insulin dose were –4.1 IU/day (–8.9%) and –7.6 IU/day (–12.9%) with canagliflozin 100 and 300 mg, respectively. In the placebo group, small increases from baseline in basal insulin dose were observed at week 18 that restored the basal insulin doses to nearly the same level they were before pretreatment downtitration. In contrast, basal insulin doses were further decreased at week 18 with canagliflozin 100 and 300 mg; placebo-subtracted absolute LS mean reductions (mean percentage change) in basal insulin dose were −4.3 IU/day (−19.0%) and −5.3 IU/day (−22.4%), respectively. Placebo-subtracted absolute LS mean reductions (mean percentage change) in the bolus insulin dose at week 18 were –0.3 IU/day (+6.1%) and –3.2 IU/day (−12.1%) with canagliflozin 100 and 300 mg, respectively.

Hypoglycemia

Almost all patients experienced at least one documented hypoglycemic episode during the study (98.3%, 99.1%, and 96.6% with canagliflozin 100 and 300 mg and placebo, respectively; Table 2). The event rate per patient-year of exposure was 70.7, 79.2, and 80.6 with canagliflozin 100 and 300 mg and placebo, respectively. The incidence of severe hypoglycemic episodes was 2.6%, 6.8%, and 1.7% with canagliflozin 100 and 300 mg and placebo, respectively. Because the risk of hypoglycemia is known to be associated with insulin titration and insulin titration was expected to be more intense early in the study, a separate analysis was performed excluding hypoglycemic episodes between weeks 1 and 4. In this analysis, the incidence of documented hypoglycemia was 94.9%, 93.2%, and 88.9% with canagliflozin 100 and 300 mg and placebo, respectively, and the event rate per patient-year of exposure was 62.5, 67.5, and 75.8, respectively.

Safety and Tolerability

The overall incidence of AEs was 55.6%, 67.5%, and 54.7% with canagliflozin 100 and 300 mg and placebo, respectively, over 18 weeks (Table 3). Rates of

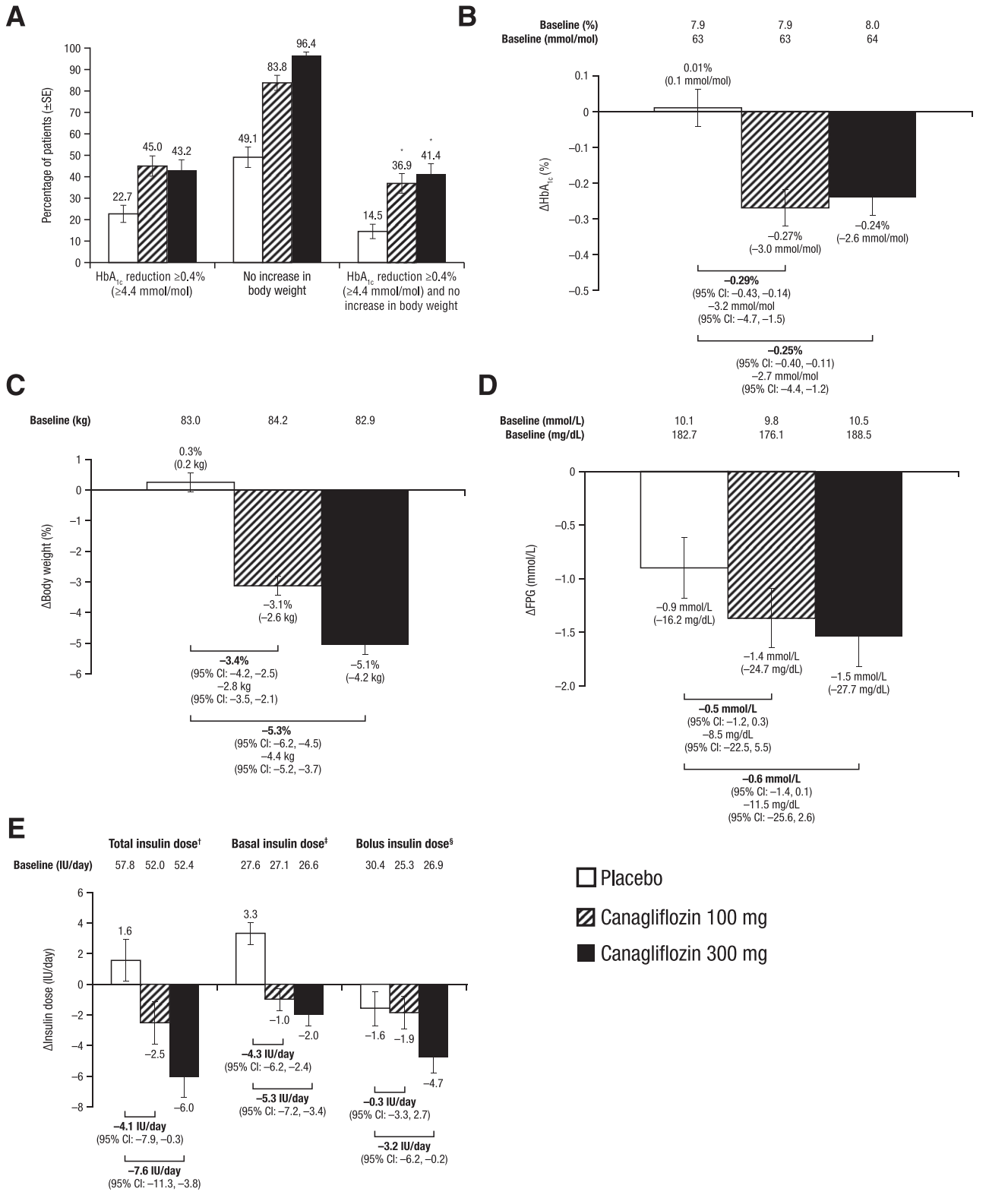

Figure 1—Proportion of patients with HbA_{1c} reduction ≥0.4% (≥4.4 mmol/mol) from baseline and no weight gain (*A*), change from baseline in HbA_{1c} (*B*), percentage change from baseline in body weight (*C*), change from baseline in FPG (*D*), and change from baseline in insulin dose at week 18 (*E*). Data are LS mean change ± SE from baseline unless otherwise indicated. Statistical testing of comparisons of canagliflozin versus placebo was not performed (not prespecified) for end points other than the primary end point. *$P < 0.001$ vs. placebo. †Total baseline insulin dose is the sum of the baseline basal and the baseline bolus insulin dose. ‡Baseline basal insulin dose is the total daily dose of basal insulin after downtitration before day 1. §Baseline bolus insulin dose is the mean of the total bolus insulin doses per day before day 1 during week −1.

Table 2—Treatment-emergent hypoglycemia episodes over 18 weeks

	Placebo	Canagliflozin	
	(*n* = 117)	100 mg (*n* = 117)	300 mg (*n* = 117)
Patients with any			
Documented hypoglycemia, *n* (%)*	113 (96.6)	115 (98.3)	116 (99.1)
Event rate per patient-year of exposure (95% CI)	80.6 (77.8, 83.4)	70.7 (68.1, 73.3)	79.2 (76.4, 82.0)
Documented symptomatic hypoglycemia, *n* (%)†	109 (93.2)	112 (95.7)	111 (94.9)
Event rate per patient-year of exposure (95% CI)	56.1 (53.8, 58.4)	50.6 (48.4, 52.8)	47.3 (45.2, 49.5)
Severe hypoglycemia, *n* (%)‡	2 (1.7)	3 (2.6)	8 (6.8)

*Concurrent fingerstick or plasma glucose ≤3.9 mmol/L (≤70 mg/dL) or a severe hypoglycemic episode. †Symptoms consistent with hypoglycemia with concurrent biochemically documented plasma glucose ≤3.9 mmol/L (≤70 mg/dL), or a severe hypoglycemic episode. ‡Requiring assistance from another person or those resulting in seizure or loss of consciousness.

AEs leading to discontinuation were low across treatment groups. The incidence of serious AEs was 7.7% and 6.8% with canagliflozin 100 and 300 mg, respectively; no patients treated with placebo had a serious AE. Canagliflozin was associated with a higher incidence of AEs related to the mechanism of SGLT2 inhibition that have been observed in studies of patients with type 2 diabetes, including urinary tract infections, and AEs related to osmotic diuresis and volume depletion. The incidence of female genital mycotic infections was higher with canagliflozin 300 mg (21.2%) than with canagliflozin 100 mg (4.2%) and placebo (5.6%); no male patients experienced a genital mycotic infection.

At week 18, the incidence of ketone-related AEs was 5.1% (6 of 117) with canagliflozin 100 mg and 9.4% (11 of 117) with canagliflozin 300 mg; no patients in the placebo group had a ketone-related AE (Table 3). Most of the ketone-related AEs (12 of 18) occurred after 1 month of treatment. Of the 17 patients with 18 ketone-related AEs, 12 were women, and 4 (24%) had a history of DKA compared with 24 of 217 (11%) of canagliflozin-treated patients without a ketone-related AE. A serious AE of DKA that required hospitalization occurred in 12 patients (5 [4.3%] with canagliflozin 100 mg and 7 [6.0%] with canagliflozin 300 mg). Among the 12 patients with a serious AE of DKA, blood glucose levels at the time of hospitalization ranged from 9.4 to >44.4 mmol/L (170 to >800 mg/dL), and 5 patients had blood glucose levels <13.9 mmol/L (<250 mg/dL), the classic cut point in defining DKA (4). All serious AEs of DKA were associated with precipitating factors at the time of the event (e.g., flu, pneumonia, insulin pump failure or malfunction, inappropriate insulin use); none were fatal and none led to discontinuation of study drug. One patient with a serious AE of DKA discontinued due to a subsequent nonserious AE of increased urine ketones.

Table 3—Summary of overall safety and selected AEs over 18 weeks

	Placebo	Canagliflozin	
	(*n* = 117)	100 mg (*n* = 117)	300 mg (*n* = 117)
Patients	*n* (%)	*n* (%)	*n* (%)
Any AE	64 (54.7)	65 (55.6)	79 (67.5)
AEs leading to discontinuation	0	1 (0.9)	2 (1.7)
AEs related to the study drug*	15 (12.8)	19 (16.2)	34 (29.1)
Serious AEs	0	9 (7.7)	8 (6.8)
Deaths	0	0	0
Urinary tract infections	2 (1.7)	5 (4.3)	6 (5.1)
Genital mycotic infections			
Male	0	0	0
Female†‡	3 (5.6)	2 (4.2)	11 (21.2)
Osmotic diuresis–related AEs§	3 (2.6)	9 (7.7)	11 (9.4)
Volume depletion–related AEs‖	0	4 (3.4)	1 (0.9)
Ketone-related AEs¶	0	6 (5.1)	11 (9.4)#
Serious DKA AEs**	0	5 (4.3)	7 (6.0)
Nonserious AEs††	0	1 (0.9)	5 (4.3)

*Possibly, probably, or very likely related to study drug, as assessed by investigators. †Placebo, *n* = 54; canagliflozin 100 mg, *n* = 48; canagliflozin 300 mg, *n* = 52. ‡Including vaginal infection, vulvovaginal candidiasis, and vulvovaginal mycotic infection. §Including dry mouth, nocturia, pollakiuria, polydipsia, polyuria, thirst, and urine output increased. ‖Including dehydration, dizziness postural, hypotension, and syncope. ¶Including DKA, ketoacidosis, and urine ketone body present. #One patient had an initial serious DKA event and a subsequent nonserious DKA event of increased urine ketones. **Requiring hospitalization. ††Including increased urinary ketones and mild and moderate DKA or acidosis.

CONCLUSIONS

Canagliflozin 100 and 300 mg provided reductions in HbA_{1c}, FPG, and body weight versus placebo in conjunction with insulin therapy over 18 weeks in patients with type 1 diabetes. The proportion of patients achieving the primary composite end point of HbA_{1c} reduction ≥0.4% (≥4.4 mmol/mol) and no increase in body weight was similar with canagliflozin 100 and 300 mg and greater compared with patients taking placebo. In addition to glycemic improvements and body weight reductions, decreases in the total daily insulin dose were seen with canagliflozin over 18 weeks that were mainly driven by decreases in the basal insulin dose. Greater reductions in total, basal, and bolus insulin doses were seen with canagliflozin 300 mg compared with canagliflozin 100 mg and placebo. Canagliflozin treatment was not associated with an increase in hypoglycemic episodes over 18 weeks, despite the greater reductions in HbA_{1c} seen with canagliflozin 100 and 300 mg versus placebo. The reductions in HbA_{1c}, FPG, body

weight, insulin dose, and the incidence of hypoglycemia with canagliflozin treatment are consistent with the effects reported with other SGLT2 inhibitors added on to insulin therapy in patients with type 1 diabetes (17,18).

Dose-related reductions in HbA_{1c} were seen with canagliflozin across Phase 3 studies in patients with type 2 diabetes (10), but no dose response was observed in the current study. In this study, HbA_{1c} lowering with canagliflozin 300 mg may have been blunted by reductions in the insulin dose, which tended to be greater than those seen with canagliflozin 100 mg and may explain why a dose response in HbA_{1c} lowering was not seen in patients with type 1 diabetes. Although dose-dependent reductions in insulin may minimize the glycemic effects of canagliflozin, they would be expected to further increase body weight reduction because insulin is associated with weight gain. Consistent with this, dose-related reductions in body weight were seen with canagliflozin in this study, similar to findings from the Phase 3 program in type 2 diabetes (10). The high baseline BMI in this study (28.1 kg/m^2) reflects an overweight population, which may partly be due to weight gain with intensive insulin therapy and suggests that patients with type 1 diabetes may benefit from weight loss, similar to patients with type 2 diabetes.

The safety and tolerability profile of canagliflozin was generally similar to that seen in patients with type 2 diabetes (10,14), with the exception of ketone-related AEs, including DKA. The incidence of overall AEs was higher with canagliflozin 300 mg relative to canagliflozin 100 mg and placebo; rates of AEs leading to discontinuation were low ($<$2.0%) with both canagliflozin doses. A higher rate of serious AEs was seen with canagliflozin 100 and 300 mg versus placebo that was driven by an increase in serious AEs of DKA.

The incidence of nonserious and serious ketone-related AEs was higher with both canagliflozin doses versus placebo. All patients with a serious AE of DKA had precipitating factors that likely contributed to the development of DKA (e.g., infection, pump failure, cessation of insulin therapy) (21). A few patients also reported changes in diet, including strict carbohydrate restriction, which previously was shown to cause DKA in a patient treated with the SGLT2 inhibitor ipragliflozin (22). DKA events have also been reported in pilot studies with other SGLT2 inhibitors in patients with type 1 diabetes. In a 4-week study with sotagliflozin, 2 of 16 patients in the sotagliflozin arm had a serious AE of DKA compared with no patients in the placebo arm (19). In an 8-week open-label study with empagliflozin, 2 of 40 patients experienced a DKA AE (18). These four reported DKA AEs occurred in the presence of other precipitating factors (e.g., insulin pump failure, gastroenteritis).

The U.S. Food and Drug Administration and European Medicines Agency have issued statements cautioning that treatment with SGLT2 inhibitors may be associated with an increased risk of DKA (23,24). Rare but serious cases of DKA have been reported in patients with type 1 or type 2 diabetes treated with SGLT2 inhibitors, including canagliflozin (25). These cases of DKA were not typical because patients had nearly normal blood glucose levels and showed few symptoms. Furthermore, a recent meta-analysis of clinical trial data demonstrated an increased risk of ketoacidosis with SGLT2 inhibitor treatment in patients with type 2 diabetes (26). A separate analysis based on data from 17,596 patients reported a low frequency ($<$0.1%) of serious DKA events across treatment groups in the canagliflozin type 2 diabetes clinical trial program (27). Among the 12 patients with serious DKA events in that report, all had a low β-cell reserve and 7 patients treated with canagliflozin were on insulin therapy. Most of the patients with DKA also had DKA-precipitating factors, including six with evidence of autoimmune diabetes (i.e., latent autoimmune diabetes of adulthood, type 1 diabetes, or positive for GAD65 antibody). We speculate that patients with type 1 or type 2 diabetes who have no or low β-cell reserve, coupled with a potential SGLT2 inhibitor–associated increase in glucagon (28–30) and other metabolic factors, such as elevated free fatty acids, may not take or may be unable to produce sufficient insulin to suppress hepatic ketogenesis (28–30), which can progress to DKA in the setting of an acute illness, inadequate carbohydrate intake, and an associated increase in insulin resistance.

Canagliflozin is not indicated for use in patients with type 1 diabetes. However, mitigation strategies to reduce the risk of DKA in patients with type 1 diabetes treated with canagliflozin will be needed for use in future clinical trials. Proposed strategies include more frequent monitoring of ketones, interruption of treatment during periods of stress or illness, and use of lower canagliflozin doses. Furthermore, treating physicians must be made aware that DKA can occur with mild hyperglycemia, which may increase the risk of delayed diagnosis and treatment in patients treated with SGLT2 inhibitors.

In summary, canagliflozin 100 and 300 mg improved glycemic control and reduced body weight compared with placebo over 18 weeks in patients with type 1 diabetes in conjunction with insulin therapy. In addition, canagliflozin treatment was not associated with an increased risk of hypoglycemia. The insulin-independent mechanism of action of canagliflozin offers a unique benefit profile in patients with type 1 diabetes, which is different from that of standard insulin therapies that are associated with hypoglycemia and weight gain. An increase in DKA events was seen with canagliflozin that may be related to the presence of a condition characterized by reduced insulin dose or insulin resistance (e.g., illness). Implementation of additional mitigation strategies in future studies may allow for earlier identification of elevated ketone levels and earlier intervention that may substantially reduce DKA risk in patients with type 1 diabetes.

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