The Effect of Canagliflozin, a Sodium Glucose Cotransporter 2 Inhibitor, on Glycemic End Points Assessed by Continuous Glucose Monitoring and Patient-Reported Outcomes Among People With Type 1 Diabetes

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Diabetes Care 2017;40:171–180 | DOI: 10.2337/dc16-1353

OBJECTIVE

To assess the effects of canagliflozin, a sodium glucose cotransporter 2 inhibitor, on glycemic parameters and measures of glucose variability assessed by a 9-point self-monitoring blood glucose (SMBG) and continuous glucose monitoring (CGM) profiles, and patient-reported outcomes as an add-on to insulin among participants with type 1 diabetes.

RESEARCH DESIGN AND METHODS

In this randomized, double-blind study, 351 participants received canagliflozin 100 or 300 mg or placebo for 18 weeks. Change from baseline in daily mean glucose and SD was measured using a 9-point SMBG profile. In a subset of 89 participants who underwent CGM, the change from baseline in mean glucose, measures of glycemic variability (SD, coefficient of variation, and mean amplitude of glycemic excursions), and time spent in glycemic ranges were assessed. Change in treatment satisfaction was evaluated using the Diabetes Treatment Satisfaction Questionnaire (*n* = 328).

RESULTS

At week 18, reductions in daily mean glucose and SD measured using the 9-point SMBG profile were seen with canagliflozin 100 and 300 mg versus placebo. Reductions in mean glucose (−1.2, −0.7, and 0.6 mmol/L) and measures of glycemic variability assessed by CGM, such as changes in glucose SD (−0.3, −0.7, and 0.1 mmol/L), were also seen with canagliflozin 100 and 300 mg versus placebo, respectively. Canagliflozin 100 and 300 mg were associated with increases in time spent within target (glucose >3.9 to ≤10.0 mmol/L) compared with placebo (11.6%, 10.1%, and −3.5%, respectively) and commensurate reductions in time spent above the target level (glucose >10.0 mmol/L; −12.7%,−7.6%, and 5.7%, respectively). Participants showed greater improvement in treatment satisfaction with canagliflozin versus placebo; reductions in insulin dose, SD of glucose, and body weight contributed to the relationship between canagliflozin and satisfaction change.

CONCLUSIONS

Canagliflozin improved indices of glycemic variability and was associated with improvement in treatment satisfaction versus placebo over 18 weeks among participants with type 1 diabetes. Although these data from this study demonstrate the potential benefits of canagliflozin in people with type 1 diabetes, canagliflozin is not approved for the treatment of type 1 diabetes and should not currently be used in people with type 1 diabetes.

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Received 23 June 2016 and accepted 2 November 2016.

Clinical trial reg. no. NCT02139943, clinicaltrials.gov.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc16-1353/-/DC1.

Intensive insulin treatment has been shown to prevent and delay the development of microvascular and macrovascular complications among people with type 1 diabetes (1,2). Even with intensive treatment, people with type 1 diabetes can experience acute and profound glucose fluctuations, which may be related to variability in insulin activity and changes in day-to-day activities, such as meal size and type, illness, and level of exercise (3–5). Therefore, one of the major challenges in the treatment of type 1 diabetes is to achieve patient-specific glycemic control while avoiding hyperglycemia and hypoglycemia episodes (6). Glycemic fluctuations can be dangerous, especially because some people may perform unhealthy behaviors, such as keeping blood glucose levels high, to avoid future hypoglycemic episodes (7–9).

Continuous glucose monitoring (CGM) can be an important tool for the awareness of glycemic variability among people with type 1 diabetes (10). Knowledge of blood glucose fluctuations may help to improve diabetes management; however, awareness of excessive variability can also be frustrating and worrisome (11). Improvements in glycemic variability, as measured by SD of blood glucose, have been shown to reduce the risk of hypoglycemia in people with type 1 diabetes and may also reduce the risk of developing other complications (i.e., peripheral neuropathy and hypoglycemia), although further studies are needed to determine the longer-term implications of reduced glycemic variability (12–15). Because there is no standardized metric for assessing glucose variability, the evaluation of multiple measures can provide an overall assessment of variability (16,17). Among people with type 1 diabetes, improved glycemic control and lower glycemic variability have been associated with improved disease-specific quality of life and treatment satisfaction related to better and easier disease management (11,18). In turn, greater diabetes treatment satisfaction has been associated with better adherence to and compliance with treatment (19,20), better outcomes (21), and reduced costs (22). Thus, treatments that reduce hyperglycemia and glycemic variability without increasing the risk of hypoglycemia may be beneficial among people with type 1 diabetes.

Canagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor approved for the treatment of type 2 diabetes (23), is under study for type 1 diabetes. Canagliflozin lowers blood glucose through an insulin-independent mechanism by lowering the renal threshold for glucose and increasing urinary glucose excretion (24–26). Findings from a retrospective analysis of people with type 1 diabetes who were prescribed canagliflozin 100 mg and used CGM showed that canagliflozin improved measures of glycemic control, including HbA_{1c}, CGM SD, time in hyperglycemia, and total daily insulin dose, in addition to lowering body weight (27). In a phase 2 study of canagliflozin as an add-on to insulin among participants with type 1 diabetes, canagliflozin 100 and 300 mg provided reductions in HbA_{1c}, body weight, and insulin dose, with no increase in documented hypoglycemia over 18 weeks (28). Canagliflozin was generally well tolerated with a safety profile consistent with that seen in people with type 2 diabetes, with the exception of an increased incidence of ketone-related adverse events (AEs), including diabetic ketoacidosis (DKA) with both canagliflozin doses and severe hypoglycemia with canagliflozin 300 mg (28,29). This article describes the effects of canagliflozin on parameters of glycemic control and indices of glucose variability from a substudy of participants with type 1 diabetes who used CGM, as well as data from self-monitoring blood glucose (SMBG) profiles that were assessed in all participants. To determine whether canagliflozin impacts treatment satisfaction in participants with type 1 diabetes, patient-reported outcomes were measured using the Diabetes Treatment Satisfaction Questionnaire (DTSQ) (30–33).

RESEARCH DESIGN AND METHODS

Study Design and Patients

This randomized, double-blind, treat-to-target, placebo-controlled, multicenter, phase 2 study consisted of a 2-week prerandomization period followed by an 18-week double-blind treatment phase and 2 weeks of post-treatment follow-up for all participants. Participants were randomized to receive canagliflozin 100 or 300 mg or placebo once daily before the first meal of the day. Randomization was stratified based on use of multiple daily insulin (MDI) injections or continuous subcutaneous insulin infusion (CSII). Eligible participants were 25–65 years of age with BMI values of 21–35 kg/m^2, fasting C-peptide concentration of $<$0.2 pmol/L ($<$0.6 ng/mL), and had type 1 diabetes for $\geq$1 years with an HbA_{1c} of 7.0–9.0% (53–75 mmol/mol) at screening. Participants were receiving a stable insulin regimen (total daily dose $\geq$0.6 international units [IU]/kg at screening) with MDI or CSII for $\geq$8 weeks prior to screening. The key exclusion criteria included a history of type 2 diabetes; a severe hypoglycemic event (i.e., requiring assistance from another person or resulting in seizure or loss of consciousness) or DKA within 6 months prior to randomization; myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident $\leq$12 weeks before screening; history of New York Heart Association Class III–IV cardiac disease; uncontrolled hypertension; estimated glomerular filtration rate (eGFR) $<$70 mL/min/1.73 m^2; or use of any antihyperglycemic agent other than insulin within 12 weeks before screening. Details of the study design have been reported (28).

This study was conducted in accordance with ethical principles that comply with the Declaration of Helsinki, and was consistent with Good Clinical Practice and applicable regulatory requirements. Approval was obtained from institutional review boards and independent ethics committees for each participating center. Participants provided informed written consent prior to the study.

Insulin Therapy

To mitigate the potential increased risk of hypoglycemia with canagliflozin, participants with HbA_{1c} $\leq$8.0% ($\leq$64 mmol/mol) at screening were recommended to reduce their basal insulin dose by 20%; participants with HbA_{1c} $>$8.0% ($>$64 mmol/mol) at screening were recommended to reduce their basal insulin dose by 10%. After randomization, participants were instructed to titrate basal and bolus insulin doses to achieve prespecified premeal-time and bedtime glucose levels. All changes in insulin dose were made at the discretion of the investigator upon review of a participant's recent fingerstick glucose values and clinical assessment of hypoglycemia risk (28).

9-Point SMBG

All participants (*N* = 351) were to record 9-point SMBG measurements at baseline (week prior to randomization) and at the end of the study (week 17–18). Only participants with 2 days of valid 9-point SMBG reading (i.e., five or more SMBG values at the following six time points: prior to morning meal, 120 min after morning meal, 120 min after midday meal, 120 min after the evening meal, 4:00 A.M., and fasting in the morning; and one or more SMBG value among the following three time points: prior to midday meal, prior to evening meal, and before bedtime) were included in the SMBG analysis. During the remainder of the study period, participants were required to measure SMBG as per the standard of care. SMBG measurements were not blinded to participants or investigators.

CGM Substudy

CGM assessments were performed in a subgroup (*n* = 89) at selected study centers. Only participants not using CGM at the time of screening were eligible to participate in the optional substudy. Substudy participants signed a separate informed consent form and wore a sponsor-provided CGM device (G4 Platinum; Dexcom) continuously for 7 days during run-in and were required to have ≥3 days of successful CGM readings (i.e., daily reading without a continuous interruption of >120 min in any postmealtime interval or a continuous interruption of >180 min during the nocturnal/sleeping time interval). After randomization, participants repeated the CGM assessment for 7 days from week 17 to 18. Study centers, participants, and the sponsor were masked to CGM readings. During the two separate 1-week CGM procedures, participants were required to also obtain 9-point SMBG measurements following the same instructions as the remainder of the study population.

End Points and Assessments

The primary efficacy end point was the proportion of participants at week 18 with an HbA_{1c} reduction of ≥0.4% (≥4.4 mmol/mol) and no increase in body weight relative to baseline (28). Change from baseline in insulin dose, after the initial down-titration, was assessed at week 18. Overall safety and tolerability were assessed based on AE reports, safety laboratory tests, vital signs measurements, and physical examinations. The incidence of documented hypoglycemia, including biochemically documented episodes (i.e., concurrent fingerstick or plasma glucose of ≤3.9 mmol/L [≤70 mg/dL]) and severe episodes, was also assessed.

In the overall population, the change from baseline in mean daily glucose and daily glucose SD based on the 9-point SMBG profile were assessed at week 18. In the CGM substudy, the change from baseline in mean daily glucose, parameters of glucose variability (i.e., SD, coefficient of variation, and mean amplitude of glycemic excursions [MAGE]), and time spent in the protocol-specified target glucose range (>3.9 and ≤10.0 mmol/L [>70 and ≤180 mg/dL]), above target (>10 and >13.9 mmol/L [>180 and >250 mg/dL]), or below target (≤3.9 and ≤2.8 mmol/L [≤70 and ≤50 mg/dL]) were assessed at week 18. Glucose SD was calculated using all valid measurements during the two 7-day CGM assessments. Coefficient of variation was calculated as the ratio of SD to mean glucose values. MAGE (i.e., the average of all glucose excursions >1 SD) was calculated using the algorithm developed by Baghurst (34) and Henry et al. (35).

Diabetes treatment satisfaction was assessed in the total population at baseline and at week 18 using two versions of the DTSQ: the DTSQ status version (DTSQs), administered at baseline, and the DTSQ change version (DTSQc), administered after treatment (30–33). The DTSQ is composed of eight items, six of which are used to compute the treatment satisfaction scale score (satisfied, convenient, flexible, understanding, recommend, and continue). These components measure participants' perceptions of satisfaction, convenience, and flexibility of their current treatment as well as participants' satisfaction with their understanding of diabetes, likelihood to recommend their current treatment to someone else, and satisfaction with continuing their current treatment. The remaining two DTSQ items, regarding the perception of time spent in hyperglycemia and hypoglycemia, are assessed independently. DTSQs and DTSQc are available in >100 languages and were administered in the appropriate language based on the location of the study center. DTSQs treatment satisfaction scale scores range from 0 to 36, with higher scores representing better satisfaction. DTSQc scores range from −18 to +18, with positive scores reflecting improvement in satisfaction relative to baseline.

Statistical Analyses

Efficacy and safety analyses were conducted using the modified intent-to-treat (mITT) analysis set (i.e., all randomized patients who received one or more doses of the double-blind study drug). Safety analyses included all reported AEs with onset during the treatment phase (i.e., treatment-emergent AEs). The hypoglycemia event rate was calculated as the number of hypoglycemia episodes per patient-year of exposure. Further details regarding statistical analyses have been reported (28).

Change from baseline at week 18 for daily mean glucose and daily SD of glucose were summarized for all mITT participants with sufficient 9-point SMBG data at baseline and week 18. Change from baseline at week 18 for daily mean glucose; glucose variability end points (SD, coefficient of variation, MAGE); and time spent within, below, and above target were summarized for the CGM analysis set (i.e., all mITT participants with sufficient CGM data at baseline and week 18). Least squares (LS) mean differences and 95% CIs for MAGE time spent within, below, and above target levels were calculated based on an ANCOVA model with treatment and stratification factor as fixed effects and baseline value as a covariate.

Changes from baseline in DTSQc treatment satisfaction scale score at week 18 were compared across treatment groups for all mITT participants with DTSQ data at baseline and week 18 using an ANCOVA model with treatment and stratification factor as fixed effects and the corresponding baseline score as a covariate. LS mean differences and 95% CIs for DTSQc treatment satisfaction scale scores were estimated. Improvement from baseline in DTSQc scores and all components was defined as any score >0. The proportion of participants with improvement in DTSQc scores and components was compared using logistic regression models adjusted for baseline score and stratification factor. Pearson correlation coefficients measured the strength of the relationship between the change in

mediators and DTSQc at week 18. A list of candidate mediators of the effect of canagliflozin on DTSQc was derived based on factors that were observable by and potentially meaningful to participants. Product–method mediation analysis, a regression-based technique that allows the exploration of various causal pathways, was used to produce upper bounds for the proportion of the canagliflozin treatment effect on DTSQc scores that was mediated by insulin reduction, improvement in glycemic variability (measured by change in daily glucose SD via 9-point SMBG), and the percentage change in body weight (36,37).

RESULTS

Participants

In the overall population (N = 351), baseline demographic and disease characteristics were generally similar across treatment groups (Table 1) (28). Sixty-seven percent (n = 236) of participants had sufficient SMBG data at baseline and week 18 to be included in the SMBG analysis.

The CGM substudy included 89 participants, 75 of whom had successful CGM readings prior to randomization. Baseline demographic and disease characteristics in the CGM substudy were generally similar to the overall population, though fewer participants reported a history of severe hypoglycemia and fewer participants were using CSII (Table 1).

DTSQ data were available for the majority of participants (93%; n = 328). Baseline demographic and disease characteristics among the participants with patient-reported outcomes data were generally similar compared with the overall population (Table 1).

Efficacy and Safety (Overall Population)

Complete efficacy and safety results for the overall population have been reported, and key results are briefly summarized below (28). More participants met the primary end point of HbA_{1c} reduction of ≥0.4% (≥4.4 mmol/mol) and no increase in body weight with canagliflozin 100 and 300 mg versus placebo at week 18 (36.9%, 41.4%, and 14.5%, respectively; $P < 0.001$) (28). HbA_{1c} was reduced at week 18 with canagliflozin 100 and 300 mg compared with placebo (LS mean changes of −0.27%, −0.24%, and 0.01% [−3.0, −2.6, and 0.1 mmol/mol], respectively; differences of −0.29% [−3.2 mmol/mol] and −0.25% [−2.7 mmol/mol]) (28). Participants treated with canagliflozin 100 and 300 mg had larger reductions in the total daily insulin dose over 18 weeks versus those treated with placebo (−2.5, −6.0, and 1.6 IU/day, respectively) that were driven by reductions in basal insulin (−1.0, −2.0, and 3.3 IU/day, respectively) (28).

The overall incidence of AEs at week 18 with canagliflozin 100 and 300 mg and placebo was 55.6%, 67.5%, and 54.7%, respectively; the incidence of serious AEs was 7.7%, 6.8%, and 0%, respectively, and the rates of study discontinuation were low across groups (28). Increased incidence of ketone-related AEs, including serious AEs of DKA requiring hospitalization, was seen with canagliflozin 100 and 300 mg versus placebo (5.1%, 9.4%, and 0%, respectively) (28). The incidence of documented hypoglycemia at week 18 was 98.3%, 99.1%, and 96.6% with canagliflozin 100 and 300 mg and placebo, respectively; the incidence of severe hypoglycemic events was 2.6%, 6.8%, and 1.7%, respectively (28).

Glycemic End Points Assessed by 9-Point SMBG Profile (Overall Population)

The changes in daily mean glucose assessed by 9-point SMBG at week 18 with canagliflozin 100 and 300 mg and placebo were −1.2, −1.1, and 0.2 mmol/L (−22.4, −19.4, and 3.0 mg/dL), respectively. The 24-h mean glucose profiles for canagliflozin 100 and 300 mg at week 18 generally showed a downward shift of the entire glucose curve relative to baseline, with the exception of 120 min after the evening meal, where baseline and week 18 measurements with canagliflozin 300 mg were similar (Fig. 1). Changes from baseline in daily glucose SD at week 18 with canagliflozin 100 and 300 mg and placebo were −0.9, −1.0, and −0.1 mmol/L (−16.4, −18.1, and −1.9 mg/dL), respectively.

Glycemic End Points Assessed Using CGM (CGM Substudy)

As in the overall study, HbA_{1c} reductions were also seen in the CGM substudy (LS mean changes of −0.25%, −0.27%, and 0.11% [−2.7, −3.0, and 1.2 mmol/mol] with canagliflozin 100 and 300 mg and placebo, respectively; differences of −0.36% [−3.9 mmol/mol] and −0.38% [−4.2 mmol/mol]). Canagliflozin 100 and 300 mg provided reductions in mean glucose at week 18 compared with an increase with placebo (Table 2). Dose-dependent reductions in glucose SD at week 18 were also seen with canagliflozin 100 and 300 mg compared with placebo. Changes in the coefficient of variation were similar across groups since canagliflozin provided reductions in both mean glucose and measures of glucose variation. Reductions in MAGE were seen with canagliflozin 100 and 300 mg compared with placebo at week 18.

Representative CGM profiles for participants treated with canagliflozin 100 mg and placebo at baseline and week 18 are shown in Supplementary Fig. 1. At baseline across treatment groups, participants spent ∼54–55% of the time within target (>3.9 to ≤10.0 mmol/L [>70 to ≤180 mg/dL]), ∼36–42% of the time above target (>10.0 mmol/L [>180 mg/dL]), and ∼4–9% of the time below target (≤3.9 mmol/L [≤70 mg/dL]) (Fig. 2). Over 18 weeks, participants treated with canagliflozin 100 and 300 mg had an increase in time spent within target compared with a reduction with placebo, with commensurate reductions in time spent above target with canagliflozin 100 and 300 mg compared with an increase with placebo. Reductions in the percentage of time spent >13.9 mmol/L glucose (>250 mg/dL) were also seen with canagliflozin 100 and 300 mg compared with placebo (−6.0%, −5.2%, and 2.5%, respectively). Change in time spent below target at week 18 was not meaningfully different with canagliflozin 100 and 300 mg versus placebo. Change in time spent ≤2.8 mmol/L glucose (≤50 mg/dL) with canagliflozin 100 and 300 mg and placebo was 0.6%, −1.1%, and −1.1%, respectively.

Diabetes Treatment Satisfaction

Baseline DTSQs treatment satisfaction scale scores were similar for canagliflozin 100 and 300 mg and placebo (29.0, 28.4, and 28.6, respectively). At week 18, mean changes in DTSQc treatment satisfaction scale scores were larger with canagliflozin 100 and 300 mg compared with placebo (Fig. 3*A*), with a greater percentage of participants experiencing any improvement in treatment satisfaction with canagliflozin compared with placebo (Fig. 3*B*).

Table 1—Baseline demographic and disease characteristics

Overall population (Ref. 28)	PBO (*n* = 117)	CANA 100 mg (*n* = 117)	CANA 300 mg (*n* = 117)	Total (*N* = 351)
Sex, *n* (%)				
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, *n* (%)†				
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
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, *n* (%)	72 (61.5)	74 (63.2)	73 (62.4)	219 (62.4)
MDI use, *n* (%)	45 (38.5)	43 (36.8)	44 (37.6)	132 (37.6)
Prior severe hypoglycemia, *n* (%)	18 (15.4)	15 (12.8)	19 (16.2)	52 (14.8)
Prior DKA, *n* (%)	14 (12.0)	13 (11.1)	15 (12.8)	42 (12.0)
Patients with valid 9-point SMBG, *n* (%)	77 (66.4)	81 (69.2)	78 (67.8)	236 (67.2)
CGM substudy	**PBO (*n* = 31)**	**CANA 100 mg (*n* = 28)**	**CANA 300 mg (*n* = 30)**	**Total (*N* = 89)**
Sex, *n* (%)				
Male	16 (51.6)	18 (64.3)	14 (46.7)	48 (53.9)
Female	15 (48.4)	10 (35.7)	16 (53.3)	41 (46.1)
Age, years*	43.3 ± 13.2	43.2 ± 13.2	41.6 ± 11.7	42.7 ± 12.6
Race, *n* (%)				
White	27 (87.1)	27 (96.4)	27 (90.0)	81 (91.0)
Black/African American	1 (3.2)	0	2 (6.7)	3 (3.4)
Asian	1 (3.2)	0	0	1 (1.1)
Other‡	2 (6.5)	1 (3.6)	1 (3.3)	4 (4.5)
HbA_{1c}*				
%	7.9 ± 0.6	7.8 ± 0.5	8.0 ± 0.5	7.9 ± 0.5
mmol/mol	63 ± 6.6	62 ± 5.5	64 ± 5.5	63 ± 5.5
Body weight, kg*	79.7 ± 15.7	82.6 ± 13.0	83.4 ± 17.9	81.9 ± 15.7
BMI, kg/m^2*	27.8 ± 3.9	27.5 ± 3.9	28.1 ± 4.4	27.8 ± 4.0
eGFR, mL/min/1.73 m^2*	94.0 ± 15.7	95.0 ± 14.1	92.3 ± 15.3	93.7 ± 14.9
Duration of type 1 diabetes, years*	21.6 ± 10.1	23.9 ± 12.8	19.6 ± 10.5	21.6 ± 11.1
CSII use, *n* (%)	17 (54.8)	17 (60.7)	16 (53.3)	50 (56.2)
MDI use, *n* (%)	14 (45.2)	11 (39.3)	14 (46.7)	39 (43.8)
Prior severe hypoglycemia, *n* (%)	2 (6.5)	1 (3.6)	3 (10.0)	6 (6.7)
Prior DKA, *n* (%)	4 (12.9)	3 (10.7)	3 (10.0)	10 (11.2)
Participants in the DTSQ analysis	**PBO (*n* = 108)**	**CANA 100 mg (*n* = 111)**	**CANA 300 mg (*n* = 109)**	**Total (*N* = 328)**
Sex, *n* (%)				
Male	58 (53.7)	65 (58.6)	59 (54.1)	182 (55.5)
Female	50 (46.3)	46 (41.4)	50 (45.9)	146 (44.5)
Age, years*	41.8 ± 11.9	42.2 ± 11.8	42.6 ± 10.9	42.2 ± 11.5
Race, *n* (%)†				
White	98 (90.7)	106 (95.5)	96 (88.1)	300 (91.5)
Black/African American	6 (5.6)	4 (3.6)	5 (4.6)	15 (4.6)
Asian	2 (1.9)	0	4 (3.7)	6 (1.8)
Other‡	2 (1.9)	1 (0.9)	4 (3.7)	7 (2.1)
HbA_{1c}*				
%	7.9 ± 0.6	7.8 ± 0.5	8.0 ± 0.5	7.9 ± 0.5
mmol/mol	63 ± 6.6	62 ± 5.5	64 ± 5.5	63 ± 5.5

Continued on p. 176

Table 1—Continued

Participants in the DTSQ analysis	PBO (*n* = 108)	CANA 100 mg (*n* = 111)	CANA 300 mg (*n* = 109)	Total (*N* = 328)
Body weight, kg*	83.4 ± 14.8	84.1 ± 14.1	82.6 ± 14.5	83.4 ± 14.4
BMI, kg/m^2*	28.0 ± 3.6	28.0 ± 4.0	28.1 ± 3.8	28.1 ± 3.8
eGFR, mL/min/1.73 m^2*	95.9 ± 14.8	97.9 ± 14.5	95.6 ± 16.5	96.5 ± 15.3
Duration of type 1 diabetes, years*	23.3 ± 10.7	22.0 ± 11.5	21.6 ± 10.7	22.3 ± 11.0
CSII use, *n* (%)	68 (63.0)	69 (62.2)	70 (64.2)	207 (63.1)
MDI use, *n* (%)	40 (37.0)	42 (37.8)	39 (35.8)	121 (36.9)
Prior severe hypoglycemia, *n* (%)	18 (16.7)	15 (13.5)	18 (16.5)	51 (15.5)
Prior DKA, *n* (%)	13 (12.0)	13 (11.7)	15 (13.8)	41 (12.5)
DTSQs§	28.6 ± 5.2	29.0 ± 5.5	28.4 ± 5.3	28.7 ± 5.3

CANA, canagliflozin; PBO, placebo. *Data are mean ± SD; †Percentages may not total 100.0 due to rounding; ‡Includes multiple, other, and not reported; §Includes participants with all components of the DTSQs treatment satisfaction scale score at baseline or week 18 (*N* = 324; PBO, *n* = 105; CANA 100 mg, *n* = 110; CANA 300 mg, *n* = 109). Overall DTSQ analysis set includes all participants with any individual DTSQ component at both baseline and week 18 (*N* = 328).

Improvement in the six individual DTSQc treatment satisfaction scale score items was seen for all treatment groups; five of the six items revealed treatment differences (Supplementary Fig. 2*A*). Satisfaction with understanding of diabetes improved within each group, but with no observed treatment differences. A greater proportion of participants treated with canagliflozin 100 and 300 mg reported a reduction in perceived time experiencing hyperglycemia versus placebo (Supplementary Fig. 2*B*). Although these analyses were not prespecified for hypothesis testing, odds ratios (ORs) and 95% CIs indicate that, relative to placebo, the proportion of participants with less perceived time experiencing hyperglycemia were significant with canagliflozin 100 and 300 mg (OR 3.8 [95% CI 2.2, 6.8] and 5.9 [3.3, 10.8], respectively); the proportion with less perceived time experiencing hypoglycemia was significant with canagliflozin 300 mg versus placebo (OR 2.2 [95% CI 1.2, 3.9]).

The estimated correlations between DTSQc and changes in the mediators were −0.312 for the percentage change in weight ($P < 0.001$), −0.229 for the change in the SD of blood glucose ($P < 0.001$), and −0.159 for the change in total insulin dose ($P = 0.006$). Product-method mediation analyses using pooled canagliflozin 100 and 300 mg groups suggest that reduction in total insulin dose, reduction in daily glucose SD assessed using the 9-point SMBG profile, and change in body weight accounted for up to 4%, 9%, and 21%, respectively, of the relationship between canagliflozin treatment and satisfaction change (Fig. 3*C*).

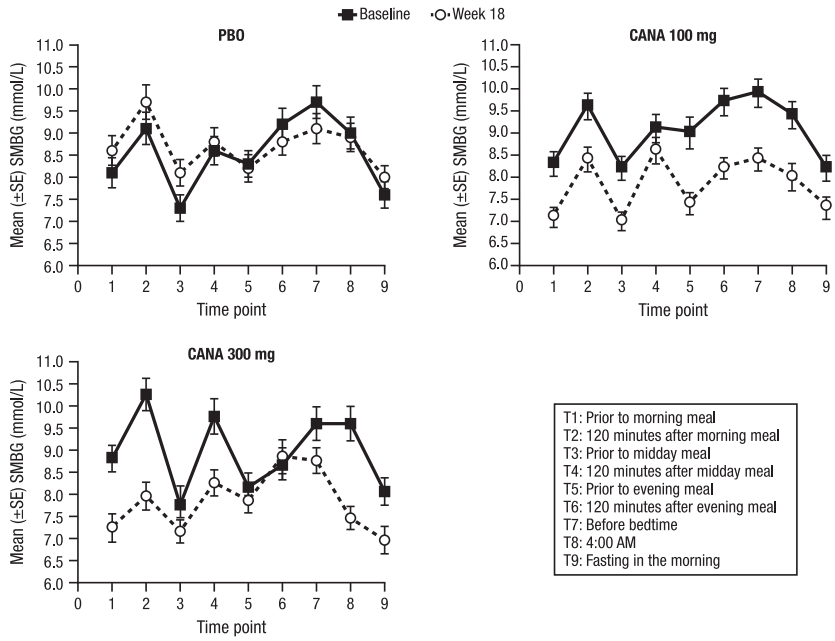

Figure 1—Mean glucose values over time at baseline and week 18 assessed by a 9-point SMBG profile. CANA, canagliflozin; PBO, placebo.

CONCLUSIONS

Canagliflozin 100 and 300 mg provided reductions in mean glucose and improvements in measures of glycemic variability, as measured by SMBG or CGM, in participants with type 1 diabetes over 18 weeks. The percentage of time spent within the glycemic target range was greater with canagliflozin 100 and 300 mg compared with placebo. The percentage of time spent above the target was lower with both canagliflozin doses compared with placebo. No meaningful changes were seen in the time spent below target across groups. The improvements in glycemic control and measures of glycemic variability seen with canagliflozin in the CGM substudy were generally consistent with those reported for other SGLT2 inhibitors as an add-on to insulin in people with type 1 diabetes (35,38–41).

Participants in the canagliflozin 100 and 300 mg groups had a significantly greater improvement in treatment satisfaction compared with placebo as measured by the DTSQc. The proportion of patients with improvement was greater with each dose of canagliflozin versus placebo; ~95% of all canagliflozin-treated participants experienced at least some improvement in treatment

Table 2—Summary of the changes from baseline in measures of glycemic variability at week 18 (CGM Substudy)

Parameter	PBO (*n* = 24)	CANA 100 mg (*n* = 25)	CANA 300 mg (*n* = 26)
Mean glucose, mmol/L (mg/dL)			
Baseline	9.0 ± 1.7 (162.1 ± 31.1)	9.8 ± 1.5 (175.7 ± 27.3)	9.2 ± 1.4 (164.9 ± 24.4)
Change	0.6 ± 2.0 (10.2 ± 35.2)	−1.2 ± 1.2 (−20.9 ± 22.2)	−0.7 ± 1.2 (−12.3 ± 21.7)
Glucose SD, mmol/L (mg/dL)			
Baseline	3.8 ± 0.7 (68.1 ± 12.8)	3.5 ± 0.9 (63.5 ± 16.3)	3.9 ± 0.7 (69.3 ± 12.7)
Change	0.1 ± 0.8 (1.6 ± 14.0)	−0.3 ± 0.9 (−5.2 ± 16.8)	−0.7 ± 0.8 (−12.2 ± 13.9)
Coefficient of variation, %			
Baseline	42.8 ± 9.0	36.3 ± 8.1	42.3 ± 7.3
Change	−2.4 ± 5.6	1.4 ± 9.3	−4.8 ± 8.3
MAGE, mmol/L (mg/dL)			
Baseline	9.2 ± 1.8 (163.8 ± 31.5)	8.4 ± 2.0 (149.9 ± 36.1)	9.4 ± 1.6 (166.6 ± 28.8)
Change	0.3 ± 2.0 (5.1 ± 33.8)	−0.6 ± 2.0 (−11.4 ± 36.5)	−1.8 ± 2.1 (−32.7 ± 37.0)

Data are reported as mean ± SD. CANA canagliflozin; PBO, placebo.

satisfaction. Treatment differences were seen in five of six individual items of the DTSQc; as expected, an understanding of diabetes did not show treatment differences in this analysis. Of note, a similar positive impact on treatment satisfaction, assessed using the DTSQ, was previously reported among participants with type 1 diabetes treated with NPH insulin plus unmodified human insulin who switched to a combination of insulin glargine and insulin lispro, a rapid-acting insulin analog (42). Participants treated with canagliflozin also reported a reduction in the perceived percentage of time spent in hyperglycemia and hypoglycemia. This is consistent with the clinical findings, and also suggests that the magnitude of improvement in glycemic control with canagliflozin treatment may be large enough to be both noticeable and meaningful to people with type 1 diabetes.

In addition to improving glycemic parameters, such has HbA_{1c}, mean daily glucose, and measures of glycemic variability, both canagliflozin doses reduced insulin dose and body weight in participants with type 1 diabetes (28). Findings from the product-method mediation analyses suggest that insulin reduction, reduced glycemic variability, and weight loss contributed to the increased treatment satisfaction observed with canagliflozin, accounting for ~35% of the relationship between canagliflozin treatment and satisfaction change. Other, unmeasured factors also mediate the relationship between canagliflozin and treatment satisfaction. For example, while not evaluated due to the short duration of this study, weight change patterns over time, in addition to overall weight change, can also impact treatment satisfaction and willingness to perform healthy behaviors (43). Patients are less likely to continue with a treatment regimen they perceive to be ineffective, associated with negative side effects, and/or infringing upon their lifestyle (44). Several studies have demonstrated a significant link between treatment satisfaction and adherence (19), and higher satisfaction has been associated with better outcomes among people with diabetes (20,21). These findings suggest that canagliflozin and, by extension, other therapies that can offer insulin reduction, reduced glycemic variability, and weight loss while avoiding hyperglycemia and hypoglycemia can lead to increased treatment satisfaction among people with type 1 diabetes. In turn, this may contribute to improved treatment adherence and performance of self-care behaviors and therefore to better long-term outcomes (45).

The limitations of this analysis include the small sample size of study participants in the CGM subset and the shorter duration of monitoring in the current study (7 days) compared with recommendations in the literature (14 days) (46). Furthermore, CGM was not used for real-time insulin dose adjustments, and mealtimes were not recorded by substudy participants. An additional limitation is the lack of a control group that provides glycemic control without improvement in measures of glycemic variability. Therefore, improvements in patient satisfaction due to the reduction in measures of glycemic variability versus the benefits of better glycemic control were not assessed. Additionally, the potential impact of knowledge of CGM data on patient satisfaction was not evaluated. Data from longer-term studies will help to characterize the effects

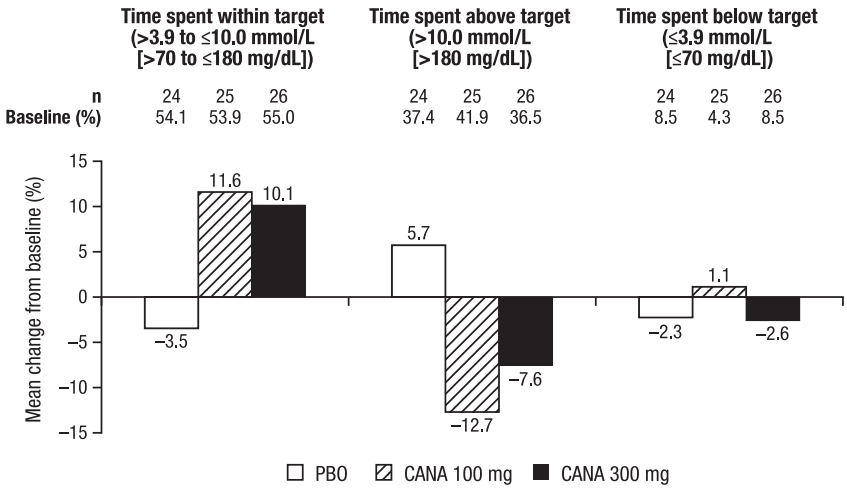

Figure 2—Change from baseline in the percentage of time spent within, above, and below target at week 18 as measured by CGM. CANA, canagliflozin; PBO, placebo.

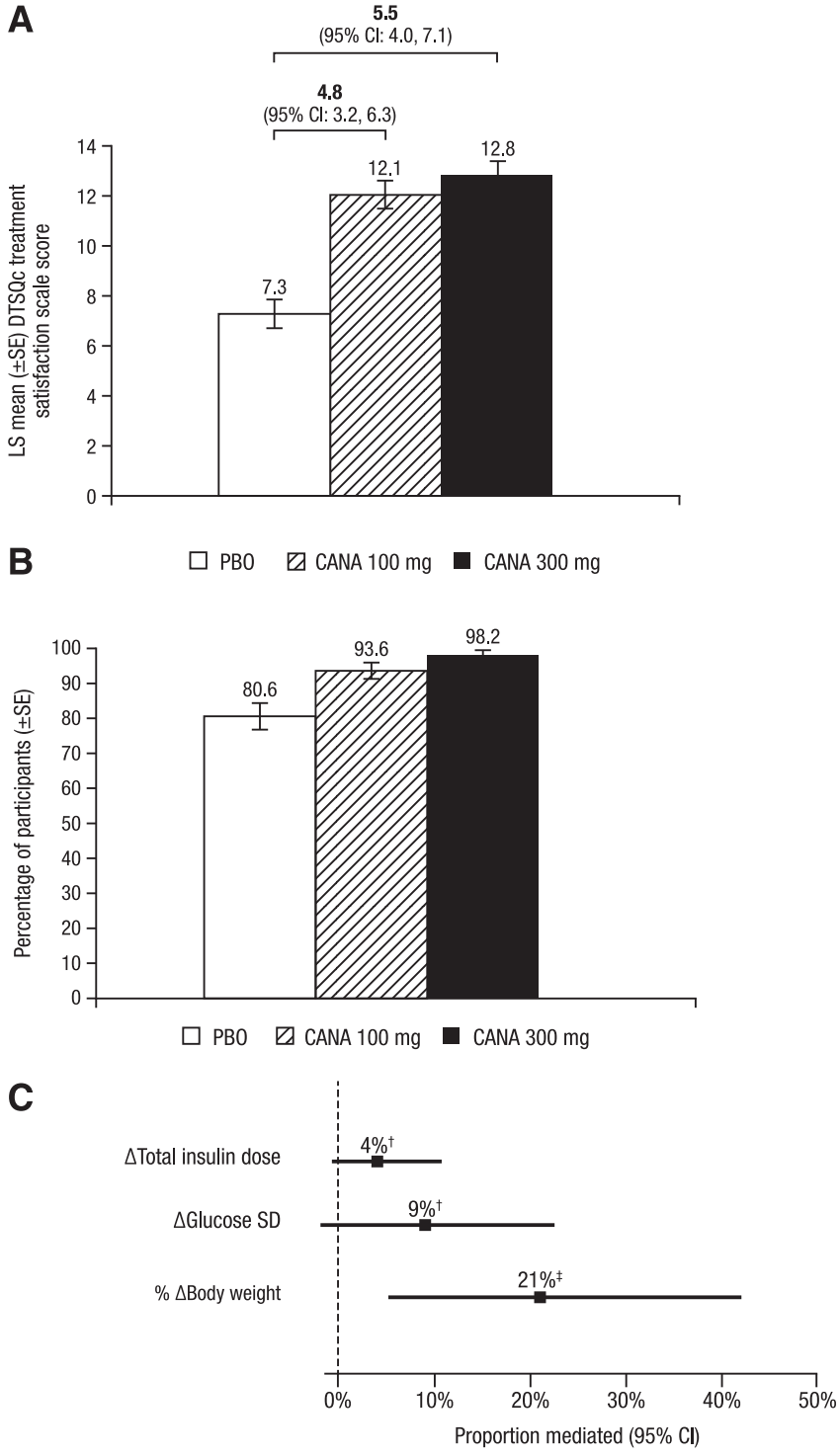

Figure 3—*A*: Mean DTSQc treatment satisfaction scale score (adjusted for baseline score and stratification factor). *B*: Proportion of participants with any improvement in DTSQc treatment satisfaction scale score. *C*: Mediators of the relationship between canagliflozin treatment and change in overall treatment satisfaction measured by the DTSQc at week 18. CANA, canagliflozin; PBO, placebo. Mediation analysis was performed on the pooled CANA 100 and 300 mg groups. †P = 0.09; ‡P = 0.01.

of canagliflozin on glycemic variability in participants with type 1 diabetes and to explain how canagliflozin-associated glycemic benefits impact satisfaction. Canagliflozin is not approved for the treatment of type 1 diabetes and should not currently be used in type 1 diabetes. While the data from this study demonstrate the potential benefits of canagliflozin in patients with type 1 diabetes, further clinical development must proceed with caution due to the SGLT2 inhibitor–associated complication of DKA in this population and the potential increased risk of severe hypoglycemia with canagliflozin 300 mg (29). Potential mitigation strategies, such as the use of lower doses of canagliflozin, may balance the benefits of canagliflozin treatment with the risk of DKA. Additionally, treatment adjustments in the run-in phase prior to baseline DTSQs collection and randomization may have influenced baseline DTSQs values; however, treatment comparisons are not systematically impacted. The absolute estimates, however, may not accurately reflect the prestudy treatment experience.

In summary, glycemic fluctuations are a major concern for people with type 1 diabetes. In this study, canagliflozin improved glycemic control and measures of glycemic variability, with no increase in documented nonsevere hypoglycemia compared with placebo over 18 weeks in adults with type 1 diabetes that was inadequately controlled with insulin. These improvements, along with the reduction in insulin dose and weight loss, were associated with noticeable and robust improvements in treatment satisfaction, which may lead to better treatment adherence and performance of self-care behaviors in people with type 1 diabetes.

Acknowledgments. The authors thank all investigators, study teams, and patients for participating in this study. License for use of the Diabetes Treatment Satisfaction Questionnaire (DTSQ), owned by Professor Clare Bradley (Royal Holloway, University of London, Surrey, U.K.), was provided by HPR Ltd. The questionnaire can be found at: www.healthpsychologyresearch.com.

Funding. This study was supported by Janssen Research & Development, LLC. Medical writing support was provided by Kimberly Dittmar, PhD, of MedErgy and was funded by Janssen Global Services, LLC. Canagliflozin has been developed by Janssen Research & Development, LLC, in collaboration with Mitsubishi Tanabe Pharma Corporation.

Duality of Interest. H.W.R. has served as a consultant and speaker for AstraZeneca, Boehringer Ingelheim, Biodel, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi, and Regeneron; and has received research support from AstraZeneca, Biodel, Bristol-Myers Squibb, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi, and Regeneron. A.L.P. has been an investigator, speaker, and/or consultant for Abbott Diabetes Care, Amgen, AstraZeneca, BD, Biodel, Bristol-Meyers Squibb, Boehringer

Ingelheim, CVS/Caremark, Janssen, Lexicon, Eli Lilly, Medtronic, Merck, Novo Nordisk, OptumRx, Sanofi, Takeda, and Thermalin. A.S. is a full-time employee of Axio Research and has received payment from Janssen for statistical support of the analyses reported in this manuscript. A.C. and M.A. are full-time employees of Janssen Research & Development, LLC. S.B.T. is a full-time employee of Janssen Global Services, LLC. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. H.W.R. and A.L.P. contributed to the conduct of the study; the acquisition, analysis, and interpretation of the data; and drafted, reviewed, and approved the manuscript. A.S. and A.C. contributed to the analysis and interpretation of the data and drafted, reviewed, and approved the manuscript. S.B.T. and M.A. contributed to the design and conduct of the study; the acquisition, analysis, and interpretation of the data; and drafted, reviewed, and approved the manuscript. H.W.R., S.B.T., and M.A. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in abstract form at the 76th Scientific Sessions of the American Diabetes Association, New Orleans, LA, 10–14 June 2016.

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