Canagliflozin Compared With Sitagliptin for Patients With Type 2 Diabetes Who Do Not Have Adequate Glycemic Control With Metformin Plus Sulfonylurea

A 52-week randomized trial

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OBJECTIVE—To evaluate the efficacy and safety of canagliflozin, a sodium glucose cotransporter 2 inhibitor, compared with sitagliptin in subjects with type 2 diabetes inadequately controlled with metformin plus sulfonylurea.

RESEARCH DESIGN AND METHODS—In this 52-week, randomized, double-blind, active-controlled, phase 3 study, subjects using stable metformin plus sulfonylurea ($N = 755$) received canagliflozin 300 mg or sitagliptin 100 mg daily. Primary end point was change from baseline in A1C at 52 weeks. Secondary end points included change in fasting plasma glucose (FPG) and systolic blood pressure (BP), and percent change in body weight, triglycerides, and HDL cholesterol. Safety was assessed based on adverse event (AE) reports.

RESULTS—At 52 weeks, canagliflozin 300 mg demonstrated noninferiority and, in a subsequent assessment, showed superiority to sitagliptin 100 mg in reducing A1C (-1.03% [-11.3 mmol/mol] and -0.66% [-7.2 mmol/mol], respectively; least squares mean difference between groups, -0.37% [95% CI, -0.50 to -0.25] or -4.0 mmol/mol [-5.5 to -2.7]). Greater reductions in FPG, body weight, and systolic BP were observed with canagliflozin versus sitagliptin ($P < 0.001$). Overall AE rates were similar with canagliflozin (76.7%) and sitagliptin (77.5%); incidence of serious AEs and AE-related discontinuations was low for both groups. Higher incidences of genital mycotic infections and osmotic diuresis–related AEs were observed with canagliflozin, which led to one discontinuation. Hypoglycemia rates were similar in both groups.

CONCLUSIONS—Findings suggest that canagliflozin may be a new therapeutic tool providing better improvement in glycemic control and body weight reduction than sitagliptin, but with increased genital infections in subjects with type 2 diabetes using metformin plus sulfonylurea.

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P atients with type 2 diabetes often require combinations of antihyperglycemic agents (AHAs) to maintain glycemic control because of the progressive nature of the disease (1,2). Metformin is the recommended first-line pharmacologic therapy for type 2 diabetes (1,2). For patients who do not achieve or sustain sufficient glycemic control with metformin, a second AHA is often added (2). With further decline in glycemic control (3,4), the addition of a third oral agent is increasingly common. Currently available classes of AHAs, such as dipeptidyl peptidase-4 inhibitors, peroxisome proliferator–activated receptor (PPAR)γ agonists, and sulfonylureas, have distinct risk/benefit profiles (2,5). A recent position statement by the American Diabetes Association and the European Association for the Study of Diabetes recommends individualization of treatment for patients and suggests the use of pharmacologic agents with complementary mechanisms of action in triple therapy combinations if A1C targets are not attained with dual combination therapy (2).

Canagliflozin is an inhibitor of the sodium glucose cotransporter 2 (SGLT2) in development for the treatment of patients with type 2 diabetes (6–10). SGLT2 is responsible for the majority of glucose reabsorption in the kidney (11). Almost all glucose is reabsorbed from the tubules until renal tubular resorptive capacity is exceeded and urinary glucose excretion (UGE) ensues; the glucose concentration at which this occurs is referred to as the renal threshold for glucose. Canagliflozin lowers the renal threshold for glucose, markedly increasing UGE and thereby reducing blood glucose concentrations in patients with hyperglycemia. The increase in UGE results in a mild osmotic diuresis and also provides a net caloric loss (with most patients with type 2 diabetes losing an average of 80–120 g/day) (12). This mechanism of action, distinct from the mechanisms of glucose-lowering of current AHA classes and independent of insulin, should provide additive glycemic control across stages of type 2 diabetes and range of classes, including add-on to the combination of metformin and a sulfonylurea agent. This 52-week Canagliflozin Treatment and Trial Analysis–dipeptidyl peptidase-4 inhibitor (CANTATA-D2; second comparator trial) study evaluated the

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efficacy and safety of canagliflozin 300 mg compared with sitagliptin 100 mg as add-on therapy in subjects with type 2 diabetes inadequately controlled with metformin plus a sulfonylurea agent.

RESEARCH DESIGN AND METHODS

Subjects and study design

This randomized, double-blind, active-controlled, phase 3 study was conducted at 140 centers in 17 countries. The study consisted of a 2-week single-blind placebo run-in period, a 52-week double-blind treatment phase, and a 4-week follow-up period.

Eligible subjects were men and women 18 years of age or older with type 2 diabetes using stable metformin and sulfonylurea therapy. Subjects at screening already using the combination of metformin and sulfonylurea with both agents at maximally or near-maximally effective doses (metformin $\geq$2,000 mg/day [or $\geq$1,500 mg/day if unable to tolerate a higher dose]; sulfonylurea at half-maximal labeled dose or more), who had A1C $\geq$7.0% (53 mmol/mol) and $\leq$10.5% (91 mmol/mol), and who met all other enrollment criteria directly entered the 2-week single-blind placebo run-in period before randomization. All other subjects underwent an AHA adjustment period of up to 12 weeks (including an 8-week dose-stable period) to use maximally or near-maximally effective doses of metformin and a sulfonylurea agent. These subjects then entered the 2-week single-blind placebo run-in period if they had A1C of $\geq$7.0% (53 mmol/mol) and $\leq$10.5% (91 mmol/mol) and met all enrollment criteria before being randomized.

Exclusion criteria included the following: repeated fasting plasma glucose (FPG) or fasting self-monitored blood glucose measurements $\geq$16.7 mmol/L (300 mg/dL), or both, during the pretreatment phase; history of type 1 diabetes, cardiovascular disease, or uncontrolled hypertension; treatment with either a PPARγ agonist, ongoing insulin therapy, another SGLT2 inhibitor, or any other AHA (other than metformin and a sulfonylurea) within 12 weeks before screening; or estimated glomerular filtration rate (eGFR) <55 mL/min/1.73 m^2 (or <60 mL/min/1.73 m^2 if based on restriction of metformin use in the metformin local label); or serum creatinine $\geq$124 μmol/L (men) and $\geq$115 μmol/L (women).

At week $-$2, all subjects received single-blind placebo capsules matching the double-blind study drug for once-daily administration. After the placebo run-in period, subjects were randomly assigned to receive oral doses of canagliflozin 300 mg or sitagliptin 100 mg once daily (1:1) using an Interactive Voice Response System/Interactive Web Response System. The computer-generated randomization schedule was prepared by the sponsor before the study, and randomization was balanced using permuted blocks with the following two stratification criteria: whether the prerandomization A1C was $\geq$9.0% (75 mmol/mol) and whether a subject underwent the frequently sampled mixed-meal tolerance test (FS-MMTT).

After randomization, A1C and FPG values and all glucose levels from the FS-MMTT were masked to the study centers, unless FPG/A1C values met specific study criteria for discontinuation; similarly, urine glucose results were not reported for urine dipsticks. Subjects, investigators, and local sponsor personnel remained blinded to treatment assignment and urine samples for glucosuria until all subjects completed the study (week 52 visit) and the final database was locked.

Subjects meeting prespecified glycemic criteria (FPG >15.0 mmol/L [270 mg/dL] after day 1 to week 6, >13.3 mmol/L [240 mg/dL] after week 6 to week 12, >11.1 mmol/L [200 mg/dL] after week 12 to week 26, and A1C >8.0% [64 mmol/mol] after week 26) were discontinued (no rescue therapy was implemented). Subjects with serum creatinine $\geq$133 μmol/L (men) or $\geq$124 μmol/L (women), eGFR <50 mL/min/1.73 m^2, or with eGFR values that constituted contraindications to metformin use in the country of the investigational site (<60 mL/min/1.73 m^2 in some countries) also were discontinued from the study.

The study was conducted in accordance with ethical principles that comply with the Declaration of Helsinki and is consistent with Good Clinical Practices and applicable regulatory requirements. Approval was obtained from Institutional Review Boards and independent Ethics Committees for participating centers. All participants provided written informed consent.

Study end points and assessments

The prespecified primary efficacy end point was change in A1C from baseline through week 52. Prespecified secondary efficacy end points included change from baseline in FPG and systolic blood pressure (BP), and percent change from baseline in body weight, triglycerides, and HDL cholesterol (HDL-C). Additional efficacy measures included proportion of subjects reaching A1C <7.0% (53 mmol/mol) and <6.5% (48 mmol/mol), change in diastolic BP, and percent change in other fasting plasma lipids.

Indices of β-cell function (βCF) were evaluated. Homeostasis model assessment of β-cell function (HOMA2-%B), proinsulin/insulin ratio, and proinsulin/C-peptide ratio (post hoc analysis) were assessed in the overall study population. The ratio of C-peptide area under the curve (AUC$_C$) to glucose AUC (AUC$_G$) was assessed in a subset of subjects who underwent a FS-MMTT ($\sim$700 kcal and 100 g carbohydrates) on day 1 and at week 52. Postprandial glucose measurements were also performed in these subjects. For FS-MMTT end points, blood samples were collected 15 min before and immediately before the meal (time 0), and 30, 60, 90, 120, and 180 min after the meal.

Safety evaluations included adverse events (AEs), clinical laboratory tests, vital sign measurements, physical examinations, self-monitored blood glucose, 12-lead electrocardiograms, and documentation of hypoglycemic episodes. AEs prespecified for additional data collection and analysis included genital mycotic infections and urinary tract infections (UTIs). The incidence of hypoglycemia was assessed by the number of subjects with documented events (i.e., concurrent finger stick glucose $\leq$3.9 mmol/L [70 mg/dL]) and severe events (i.e., requiring the assistance of another or resulting in seizure or loss of consciousness).

Statistical analyses

The primary hypothesis for this study was that canagliflozin 300 mg was noninferior to sitagliptin 100 mg in reducing A1C from baseline to week 52. The primary analysis was based on the modified intent-to-treat population (all randomized subjects who received one or more doses of study drug) with a last observation carried forward approach to impute missing data at the end point. Assuming no difference between canagliflozin and sitagliptin in A1C-lowering efficacy and a common SD of 1.0% with respect to change in A1C, it was estimated that 234 subjects per treatment group would

provide ~90% power to demonstrate the noninferiority of canagliflozin compared with sitagliptin. In addition, per-protocol analysis (subjects completing the 52-week study and without protocol deviations that could impact efficacy assessment) was conducted to further support the noninferiority assessment. To provide 90% power for the per-protocol analysis, assuming a discontinuation rate of 35% over 52 weeks, the sample size was increased to 360 subjects per treatment group.

Safety analyses and the primary efficacy analysis were conducted using the modified intent-to-treat population. The last observation carried forward approach was used for the primary analysis of efficacy data. All statistical tests were interpreted at a two-sided significance level of 5%, and all CIs were interpreted at a two-sided confidence level of 95%. Primary and continuous secondary end points were assessed using an ANCOVA model, including treatment and stratification factors as fixed effects and the corresponding baseline value as a covariate. The least squares (LS) mean differences and two-sided 95% CIs were estimated for the comparisons of canagliflozin versus sitagliptin. Noninferiority of canagliflozin to sitagliptin was assessed based on a prespecified margin of 0.3% for the upper limit of the two-sided 95% CI for the comparison in the primary last observation carried forward analysis. If noninferiority was demonstrated, then superiority was assessed, as determined by an upper bound of the 95% CI around the between-group difference (canagliflozin minus sitagliptin) of <0.0%. A prespecified hierarchical testing sequence was implemented to strongly control overall type I error attributable to multiplicity; *P* values are reported for prespecified comparisons only.

For subgroup analysis, descriptive statistics and 95% CIs for the change from baseline in A1C were provided for subgroups of subjects with baseline A1C of <8.0% (64 mmol/mol), ≥8.0% (64 mmol/mol) to <9.0% (75 mmol/mol), and ≥9.0% (75 mmol/mol). For indices of βCF, descriptive statistics and 95% CIs for the changes from baseline were provided; comparisons of canagliflozin with sitagliptin for changes from baseline at week 52 were assessed using an ANCOVA model with treatment and stratification factors as fixed effects and the corresponding baseline value as a covariate.

RESULTS

Subject disposition and baseline characteristics

This study was conducted from 30 June 2010 through 9 March 2012. Of 1,672 subjects screened, 916 (54.8%) were excluded from the study (Fig. 1). Of 756 randomized subjects, 755 received one or more doses of study drug and were included in the modified intent-to-treat analysis set; 464 (61%) completed the 52-week treatment period. A higher rate of discontinuation was observed with sitagliptin 100 mg (44.4%) than with canagliflozin 300 mg (32.6%); the largest contribution was the discontinuation of subjects who met glycemic withdrawal criteria (22.5% [sitagliptin] and 10.6% [canagliflozin]), because glycemic rescue therapy was not provided in this study, with the majority (88%) of these subjects discontinued after week 26. After meeting glycemic withdrawal criteria, the most common reasons for withdrawal were meeting creatinine or eGFR withdrawal criteria or AEs (Fig. 1). Subject demographic and baseline characteristics

were similar with canagliflozin and sitagliptin (Table 1). Baseline mean A1C was 8.1% (65 mmol/mol [A1C values in mmol/mol were directly converted from values in percent]) and mean known duration of type 2 diabetes was 9.6 years. Details of background sulfonylurea therapies are shown in Supplementary Fig. 1.

Efficacy

At 52 weeks, canagliflozin 300 mg demonstrated noninferiority to sitagliptin 100 mg in A1C lowering (LS mean change of −1.03% [−11.3 mmol/mol] and −0.66% [−7.2 mmol/mol], respectively), with a difference in LS means of −0.37% (95% CI, −0.50 to −0.25) or −4.0 mmol/mol (−5.5 to −2.7); upper limit of the 95% CI was less than the prespecified margin of 0.3% and thus met the primary hypothesis of the study. Further, canagliflozin demonstrated superiority in reducing A1C compared with sitagliptin (upper limit of the 95% CI <0.0%) (Fig. 2*A, B*). A smaller between-group difference was observed for the per-protocol analysis (−0.21% [95% CI, −0.34 to −0.08] or −2.3 mmol/mol [−3.7 to
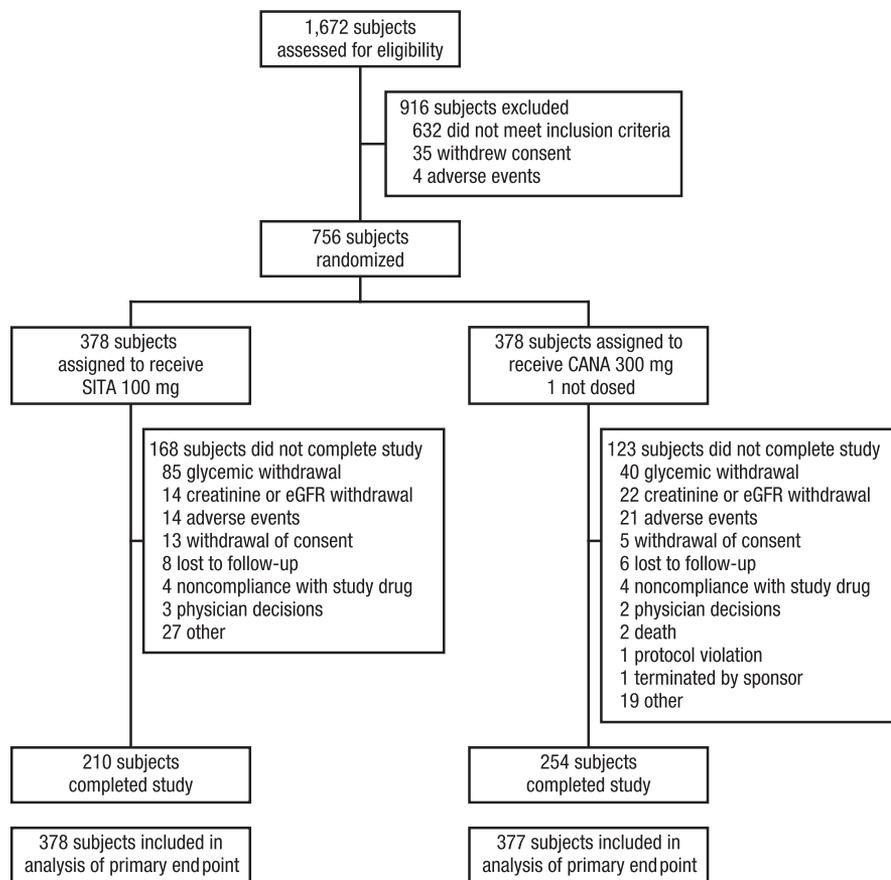

Figure 1—*Study flow diagram. SITA, sitagliptin; CANA, canagliflozin.*

Table 1—*Baseline demographics and disease characteristics*

	SITA 100 mg (n = 378)	CANA 300 mg (n = 377)	Total (N = 755)
Age, years	56.7 ± 9.3	56.6 ± 9.6	56.7 ± 9.5
Sex, n (%)			
Male	215 (56.9)	207 (54.9)	422 (55.9)
Female	163 (43.1)	170 (45.1)	333 (44.1)
Race, n (%)*			
White	240 (63.5)	245 (65.0)	485 (64.2)
Black or African American	45 (11.9)	43 (11.4)	88 (11.7)
Asian	65 (17.2)	67 (17.8)	132 (17.5)
Other†	28 (7.4)	22 (5.8)	50 (6.6)
Ethnicity, n (%)*			
Hispanic or Latino	80 (21.2)	79 (21.0)	159 (21.1)
Not Hispanic or Latino	296 (78.3)	298 (79.0)	594 (78.7)
Other‡	2 (0.5)	0	2 (0.3)
Body weight, kg	89.1 ± 23.2	87.4 ± 23.2	88.3 ± 23.2
BMI, kg/m^2	31.7 ± 6.9	31.5 ± 6.9	31.6 ± 6.9
A1C, % (mmol/mol)	8.1 ± 0.9 (65 ± 9.8)	8.1 ± 0.9 (65 ± 9.8)	8.1 ± 0.9 (65 ± 9.8)
FPG, mmol/L (mg/dL)	9.2 ± 2.5 (165.8 ± 44.9)	9.4 ± 2.6 (169.4 ± 47.4)	9.3 ± 2.6 (167.6 ± 46.1)
Duration of type 2 diabetes, years	9.7 ± 6.3	9.4 ± 6.1	9.6 ± 6.2

Data are mean ± SD unless otherwise indicated. SITA, sitagliptin; CANA, canagliflozin. *Percentages may not total 100% because of rounding. †Includes American Indian or Alaska Native, Native Hawaiian or other Pacific islander, multiple, other, unknown, or not reported. ‡Includes unknown or not reported.

−0.9]) (Supplementary Fig. 1), but canagliflozin met both noninferiority to sitagliptin (upper limit of the 95% CI <0.3%) and superiority to sitagliptin (upper limit of the 95% CI <0.0%) in this analysis.

A greater proportion of subjects treated with canagliflozin compared with sitagliptin achieved A1C <7.0% (53 mmol/mol; 47.6 vs. 35.3%, respectively) and A1C <6.5% (48 mmol/mol; 22.5 vs. 18.9%, respectively) at week 52.

Subgroup analyses showed stepwise greater A1C reductions from baseline for canagliflozin relative to sitagliptin with increasing categories of baseline A1C as follows: <8.0% (64 mmol/mol); ≥8.0% (64 mmol/mol) to <9.0% (75 mmol/mol); and ≥9.0% (75 mmol/mol) (Supplementary Fig. 2).

Significantly greater reductions from baseline in FPG were observed at week 52 with canagliflozin 300 mg compared with sitagliptin 100 mg (P < 0.001; Fig. 2C). Among subjects who underwent the FS-MMTT, canagliflozin provided greater reductions from baseline in 2-h postprandial glucose compared with sitagliptin (difference in LS means: −1.0 mmol/L [95% CI, −1.9 to −0.1]) (Fig. 2D).

Canagliflozin 300 mg provided significant reductions in body weight at week 52 relative to sitagliptin 100 mg (P < 0.001; Fig. 2E). Canagliflozin significantly decreased systolic BP compared with sitagliptin (−5.1 and 0.9 mmHg,

respectively; difference in LS means, −5.9 mmHg [95% CI, −7.6 to −4.2]; P < 0.001) (Supplementary Table 2). Diastolic BP also was reduced with canagliflozin compared with sitagliptin (−3.0 and −0.3 mmHg, respectively; difference in LS means, −2.7 mmHg [95% CI, −3.8 to −1.7]). No meaningful change in heart rate was observed with canagliflozin or sitagliptin (mean change of −0.1 and 0.7 bpm, respectively). An increase in HDL-C was seen with canagliflozin and a minimal change was seen with sitagliptin (LS mean percent change of 7.6 and 0.6%, respectively; difference in LS means, 7.0% [95% CI, 4.6 to 9.3]); increases in LDL-C were seen in both groups, with a larger increase seen with canagliflozin relative to sitagliptin (11.7 and 5.2%, respectively; difference in LS means, 6.4% [95% CI, 1.7 to 11.2]). Smaller increases in non–HDL-C were observed in both groups, with no notable difference in the change from baseline in the LDL-C/HDL-C ratio between groups. Modest increases in triglycerides, similar in both groups, also were observed (Supplementary Table 2).

At week 52, a greater increase from baseline in HOMA2-%B was observed with canagliflozin 300 mg compared with sitagliptin 100 mg (Supplementary Table 3). Modest increases in the proinsulin/insulin ratio were observed in both groups, with a numerically greater increase seen with canagliflozin compared with sitagliptin. Post hoc analysis showed a

decrease in the proinsulin/C-peptide ratio with canagliflozin, whereas an increase was seen with sitagliptin. Both groups showed similar increases from baseline in the AUC_C/AUC_G ratio.

Safety
The overall incidences of AEs, serious AEs, and study discontinuations attributable to AEs were similar for canagliflozin 300 mg and sitagliptin 100 mg (Table 2). Canagliflozin was associated with higher rates of genital mycotic infections in females (e.g., vulvovaginitis) and males (e.g., balanitis) compared with sitagliptin, which led to one study discontinuation (male subject) and no serious AEs, and responded to usual treatment with antifungal agents. Among female subjects with genital mycotic infections, 8 of 26 and 2 of 7 subjects in the canagliflozin and sitagliptin groups, respectively, had recurrences; 2 of 19 male subjects with genital mycotic infections had recurrences in the canagliflozin group and no recurrences were reported in the sitagliptin group. Incidences of UTIs were similar for canagliflozin and sitagliptin, with no serious AEs of UTI reported with canagliflozin. Low incidences (<2%) of AEs related to osmotic diuresis (i.e., thirst, pollakiuria) were seen with canagliflozin treatment. The proportion of subjects having at least one documented hypoglycemic episode was similar with canagliflozin (43.2%) and sitagliptin (40.7%). Incidence of severe hypoglycemic episodes was similar
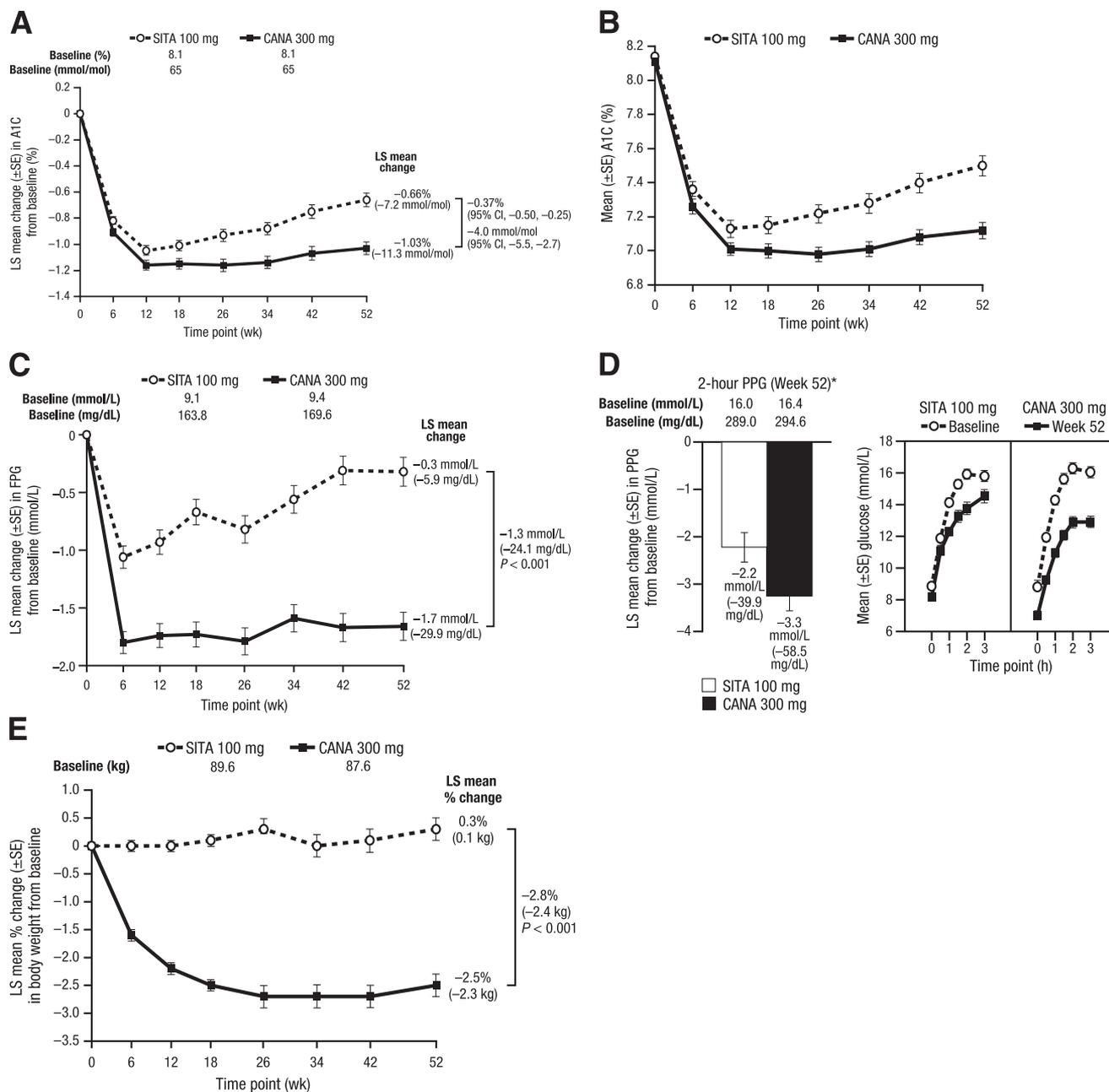
Figure 2—*Changes in efficacy parameters (last observation carried forward [LOCF]). Change in A1C* (A), *mean A1C over time* (B), *change in FPG* (C), *change in postprandial glucose (PPG)* (D), *and percent change in body weight* (E). *SITA, sitagliptin; CANA, canagliflozin. *Statistical comparison for CANA 300 mg versus SITA 100 mg not performed (not prespecified).*

with canagliflozin (4.0%) and sitagliptin (3.4%).

Overall, there were only minor differences observed in laboratory parameters with canagliflozin 300 mg compared with sitagliptin 100 mg (Supplementary Table 4). Small to moderate decreases in alanine aminotransferase, γ-glutamyl transferase, and serum urate and small to moderate increases in hemoglobin, bilirubin, and blood urea nitrogen were observed with canagliflozin compared with sitagliptin.

Similar small reductions in eGFR were observed in both groups.

CONCLUSIONS—For patients with type 2 diabetes to achieve and maintain glycemic control, combination therapies with AHAs are often needed (1,2). However, currently available AHAs have decreased efficacy over time and some have side effects, including weight gain or increased risk of hypoglycemia (2,3,13). Inhibition of SGLT2 and increasing UGE

is a novel insulin-independent approach to lowering plasma glucose in patients with type 2 diabetes that is associated with caloric loss and low risk of hypoglycemia (14). SGLT2 inhibitors therefore may present a new therapeutic option that provides a mechanism of action that is complementary to those of other AHAs.

In this phase 3 study of subjects with type 2 diabetes inadequately controlled with metformin plus sulfonylurea, the addition of canagliflozin 300 mg provided

Table 2—Summary of overall safety and selected AEs

Subjects, n (%)	SITA 100 mg (n = 378)	CANA 300 mg (n = 377)
Any AE	293 (77.5)	289 (76.7)
AEs leading to discontinuation	11 (2.9)	20 (5.3)
AEs related to study drug*	105 (27.8)	128 (34.0)
Serious AEs	21 (5.6)	24 (6.4)
Deaths	0	2 (0.5)†
AEs of special interest		
Genital mycotic infection		
Male‡§	1 (0.5)	19 (9.2)
Female‖¶	7 (4.3)	26 (15.3)
UTI	21 (5.6)	15 (4.0)
Osmotic diuresis–related AEs		
Pollakiuria**	5 (1.3)	6 (1.6)
Polyuria††	0	3 (0.8)
Volume-related AEs		
Postural dizziness	2 (0.5)	0
Orthostatic hypotension	1 (0.3)	0

SITA, sitagliptin; CANA, canagliflozin. *Possibly, probably, or very likely related to study drug, as assessed by investigators. †One death was attributable to respiratory arrest and cardiac arrest, and the other death was attributable to cardiac arrest. Both deaths were considered by the investigator to be doubtfully related to the study drug. ‡SITA 100 mg, n = 215; CANA 300 mg, n = 207. §Including balanitis, balanitis candida, balanoposthitis, genital candidiasis, and genital infection fungal. ‖SITA 100 mg, n = 163; CANA 300 mg, n = 170. ¶Including vaginal infection, vulvovaginal candidiasis, vulvovaginal mycotic infection, and vulvovaginitis. **Increased urine frequency. ††Increased urine volume.

a significantly greater reduction in A1C compared with sitagliptin 100 mg at 52 weeks. Significantly greater reductions in FPG also were observed with canagliflozin compared with sitagliptin. Both medications lowered postmeal glucose levels, with numerically greater reductions seen with canagliflozin, as shown by similar decreases in incremental glucose after the meal with both agents; however, canagliflozin provided substantially greater premeal reductions in glucose. The effects of canagliflozin in lowering A1C and FPG were sustained over 52 weeks of treatment, whereas increases from the achieved nadirs in A1C and FPG were observed with sitagliptin. The results with sitagliptin in the current study, both with regard to the pattern of change over time and the extent of A1C-lowering efficacy, are consistent with the 52-week results seen in a previous sitagliptin study (in particular, comparing the primary per-protocol analysis reported in the previous study with the per-protocol analysis results from the current study) (Supplementary Fig. 1) considering baseline differences in glycemic control (15,16).

In addition to improvements in glycemic parameters, canagliflozin provided statistically significant and clinically relevant reductions in body weight over 52 weeks, whereas a slight increase was observed with sitagliptin. The effect of canagliflozin on body weight is likely attributable to the marked increase in UGE, because each gram of glucose lost equates to the loss of 4 kcal; previous studies of canagliflozin have demonstrated that this agent leads to 80–120 g/day of UGE in subjects with type 2 diabetes, or a deficit of ~400 kcal/day; note that studies of canagliflozin have shown that the augmentation of UGE with this agent is sustained (9,10). This caloric deficit sustained over 52 weeks might predict an even greater weight loss than observed, suggesting that compensatory mechanisms (e.g., increased food intake) likely limit weight loss. An important observation was that although the weight loss plateaued with canagliflozin, no meaningful weight regain occurred. Body composition analyses conducted in other phase 3 studies of subjects with type 2 diabetes have shown that the weight loss observed with canagliflozin is predominantly (approximately two-thirds) from the loss of fat mass (17). Canagliflozin also lowered systolic BP at week 52, with no meaningful change seen with sitagliptin. The BP-lowering effect with canagliflozin is likely related to the mild osmotic diuretic response and some natriuretic effect, but weight loss also may contribute.

Canagliflozin and sitagliptin were associated with improvements in HOMA2-%B, an index of fasting insulin secretion, with a numerically greater increase seen with canagliflozin. Postmeal improvement in βCF based on the AUC_C/AUC_G ratio (assessed during the FS-MMTT) also was seen with both agents. Modest increases in the proinsulin/insulin ratio were observed with canagliflozin and sitagliptin. The proinsulin/C-peptide ratio has been reported to be a more accurate reflection of the degree of disproportional hyperproinsulinemia (18); this was assessed in the current study and showed a reduction with canagliflozin, suggesting improved insulin processing efficiency with no discernible change seen with sitagliptin. Because β-cells are not known to express the SGLT2 transporter, an indirect mechanism of these improvements in βCF seems likely. Now classic studies of the nonselective SGLT inhibitor, phlorizin, by Rossetti and DeFronzo et al. (19) in a diabetic rodent model demonstrated marked βCF improvements considered to be related to reversal of glucotoxicity. The results of these studies with phlorizin are supported by experimental studies in mice harboring a gene knockout of SGLT2 (20), preclinical studies of SGLT inhibitors in diabetic rodent models (21–23), and previous clinical studies of canagliflozin demonstrating improvements in βCF (10). In addition to reversal of glucotoxicity, by reducing plasma glucose concentrations through a noninsulin-dependent mechanism, the β cells may be "unloaded," also contributing to improved function (24). Furthermore, improvements in β-cell function could be related to the weight loss seen with canagliflozin, with potential improvements in insulin sensitivity reducing β-cell demand, thus improving insulin secretion (25,26).

The overall rate of study discontinuation (38.5%) was high but consistent with expectations given the absence of glycemic rescue therapy in this study; nearly 80% of subjects in both groups could have completed the study had rescue therapy rather than withdrawal been specified for poorer glycemic control. The higher discontinuation rate observed with sitagliptin was primarily attributable to the discontinuation of subjects who met glycemic withdrawal criteria. Rates of discontinuation observed with sitagliptin are consistent with those previously reported in the 52-week study comparing sitagliptin with glipizide (15), discussed here, that also did not provide rescue therapy. In that study, the rate of discontinuations attributable to reasons other than meeting glucose discontinuation criteria was similar to that observed in the current study.

Overall incidences of AEs were similar for canagliflozin and sitagliptin. Canagliflozin was associated with an increased incidence of genital mycotic infections; however, these were generally assessed by the investigators as mild to moderate in intensity, responded to usual antifungal therapy, and led to few discontinuations. There was a higher rate of AEs related to osmotic diuresis (i.e., polyuria) compared with sitagliptin, with an overall low incidence and infrequently leading to discontinuation. Incidences of UTIs were similar between groups. Despite greater reductions in A1C and FPG with canagliflozin compared with sitagliptin, the incidence of documented and severe hypoglycemia was similar in both groups and consistent with other studies conducted on the background of AHAs associated with hypoglycemia (e.g., sulfonylureas, insulin) (27–31). In studies of subjects not using background AHAs associated with hypoglycemia, the low risk of hypoglycemia observed with canagliflozin is consistent with its mechanism of action, because the renal threshold for glucose is typically reduced to 4.4–5.0 mmol/L (~80–90 mg/dL) in patients with type 2 diabetes, above the hypoglycemia threshold (9,10). A different profile of lipid changes was observed with canagliflozin relative to sitagliptin; there were increases in HDL-C and LDL-C seen with canagliflozin, and no change in HDL-C and a small increase in LDL-C seen with sitagliptin, resulting in no difference in the change from baseline in the LDL-C/HDL-C ratio between treatment groups.

The recent American Diabetes Association and European Association for the Study of Diabetes position statement recommends that selection of AHA therapy should be individualized to meet the needs of each patient based on the risk/benefit profiles of the various AHA classes (2). Findings from this study demonstrated that in patients using metformin and a sulfonylurea, relative to sitagliptin, canagliflozin provided a greater and more sustained reduction in A1C, weight loss, a reduction in systolic BP, and a similar incidence of hypoglycemia. However, these benefits of canagliflozin relative to sitagliptin were associated with a higher incidence of female and male genital infections and AEs related to osmotic diuresis. Thus, in selecting treatments, physicians will have to weigh the benefits with the side effects, taking into account the needs and tolerances of the patient based on age and comorbidities.

The overall profile of canagliflozin in the current study of patients with type 2 diabetes inadequately controlled with metformin plus sulfonylurea suggests that this agent may be a beneficial option when a third agent is needed. Although the current study specifically evaluated the potential use of canagliflozin as an add-on therapy to metformin plus a sulfonylurea, other studies have assessed the efficacy and safety of canagliflozin in subjects inadequately controlled with diet or exercise (monotherapy) or metformin (10,32,33). Canagliflozin also may represent an alternative to the addition of injectable AHAs that have shown efficacy as add-on therapies to metformin plus sulfonylurea, such as glucagon-like peptide 1 receptor agonists (e.g., liraglutide, exenatide) without gastrointestinal symptoms or insulin without weight gain or frequent hypoglycemia (beyond that expected from improved glycemic control) (29,34).

A limitation of this study was its 1-year duration, because longer-term studies will be needed to evaluate the durability of the effects of canagliflozin. This study enrolled subjects using background therapy with metformin plus a sulfonylurea and included subjects with a reasonably wide range of baseline A1C values; therefore, the findings may not be generalizable to patients using other AHA regimens or those with milder or more severe hyperglycemia at baseline. Additionally, studies including other AHAs as active comparators will be useful for evaluating the relative efficacy/safety profile of canagliflozin compared with other AHAs commonly used as third agents in combination therapy with metformin plus sulfonylurea.

In conclusion, canagliflozin significantly improved glycemic control and reduced body weight and systolic BP compared with sitagliptin over 52 weeks, with an increase in genital infections and osmotic diuresis–related AEs, but it was generally well-tolerated in subjects with type 2 diabetes inadequately controlled with metformin plus sulfonylurea. These results support the potential value of canagliflozin in triple combination therapy with metformin plus a sulfonylurea for the treatment of patients with type 2 diabetes.

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