Canagliflozin Provides Durable Glycemic Improvements and Body Weight Reduction Over 104 Weeks Versus Glimepiride in Patients With Type 2 Diabetes on Metformin: A Randomized, Double-Blind, Phase 3 Study

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OBJECTIVE

To assess the efficacy/safety of canagliflozin, a sodium–glucose cotransporter 2 inhibitor, compared with glimepiride over 104 weeks in patients with type 2 diabetes inadequately controlled with metformin.

RESEARCH DESIGN AND METHODS

In this randomized, double-blind study, patients (N = 1,450) received canagliflozin 100 or 300 mg or glimepiride (titrated up to 6 or 8 mg/day) during a 52-week core period followed by a 52-week extension.

RESULTS

At week 104, reductions from baseline in A1C were −0.65%, −0.74%, and −0.55% (−7.1, −8.1, and −6.0 mmol/mol) with canagliflozin 100 and 300 mg and glimepiride, respectively. Durability analyses showed sustained A1C lowering with both canagliflozin doses versus glimepiride. Reductions in body weight (−4.1%, −4.2%, and 0.9%, respectively) and systolic blood pressure (−2.0, −3.1, and 1.7 mmHg, respectively) were seen with canagliflozin 100 and 300 mg compared with glimepiride at week 104. The overall adverse event (AE) incidence was 73.3%, 77.9%, and 78.4% with canagliflozin 100 and 300 mg and glimepiride; the incidence of AE-related discontinuations was low across groups (6.2%, 9.5%, and 7.3%, respectively). Incidences of genital mycotic infections, urinary tract infections, and osmotic diuresis–related AEs were higher with canagliflozin than glimepiride; these were generally mild to moderate in intensity and led to few discontinuations. Fewer patients had hypoglycemia episodes with canagliflozin 100 and 300 mg than glimepiride (6.8%, 8.2%, and 40.9%). Mild decreases in estimated glomerular filtration rate occurred initially with canagliflozin; these attenuated over 104 weeks.

CONCLUSIONS

Canagliflozin provided durable glycemic improvements compared with glimepiride and was generally well tolerated in patients with type 2 diabetes receiving background treatment with metformin over 104 weeks.

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The prevalence of type 2 diabetes and obesity have been increasing, and many patients with type 2 diabetes are overweight or obese (1,2). Metabolic changes associated with obesity can lead to insulin resistance and the impaired insulin secretion that are characteristic of type 2 diabetes (3). As a result, lifestyle changes to promote weight reduction are an important component of type 2 diabetes management, with weight loss associated with improvements in glycemic control and other cardiovascular risk factors (2,4). Because of the progressive nature of type 2 diabetes, many patients require additional antihyperglycemic therapies when adequate glycemic control is not achieved with metformin, the standard first-line pharmacologic treatment (2,5,6). However, some antihyperglycemic agents (AHAs) commonly added on to metformin, such as sulfonylureas, may be associated with weight gain, an increased risk of hypoglycemia, and reduced efficacy over time (2,7). Despite these concerns, sulfonylureas are still regularly used, in part because of their relatively low cost (less than $1 per day). Thus, agents that can provide durable glucose lowering, together with beneficial effects on body weight and other cardiovascular risk factors and a low risk of hypoglycemia, are needed for the treatment of patients with type 2 diabetes.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are a novel class of AHAs with an insulin-independent mechanism for reducing plasma glucose and are associated with weight loss and a low risk of hypoglycemia (8–10). Longer-term data are needed to more completely assess the treatment effects of these agents. Canagliflozin is an SGLT2 inhibitor that was developed for the treatment of adult patients with type 2 diabetes (11–18). Across phase 3 studies (11,12,14–16,18), canagliflozin improved glycemic control and reduced body weight and systolic blood pressure (BP) in patients with type 2 diabetes receiving a variety of background diabetes treatments. In a randomized, active-controlled study in patients with type 2 diabetes receiving background treatment with metformin, canagliflozin 100 and 300 mg demonstrated noninferiority, and canagliflozin 300 mg further demonstrated superiority to glimepiride in the primary end point of A1C lowering over 52 weeks; both canagliflozin doses provided significant weight loss and lower incidence of hypoglycemia than glimepiride, and were generally well tolerated (12). While 52 weeks was sufficient to compare the efficacy and safety of canagliflozin 100 and 300 mg once daily with glimepiride, a 52-week extension was prespecified to provide a more complete evaluation of efficacy, glycemic durability, and potential long-term safety effects over 104 weeks. This article reports the findings from this study over 104 weeks of treatment, including the 52-week core period and the prespecified 52-week extension.

RESEARCH DESIGN AND METHODS

Patients and Study Design

This phase 3, randomized, double-blind, active-controlled study (ClinicalTrials.gov identifier NCT00968812) was conducted at 157 centers in 19 countries from 28 August 2009 to 30 January 2013. The study consisted of a 2-week, single-blind, placebo run-in period and a 52-week, double-blind core period (findings previously reported) (12), followed by a 52-week, double-blind extension period. Details of the study design, and patient inclusion and exclusion criteria have previously been reported (12). Briefly, eligible patients were men and women ≥18 and ≤80 years of age with type 2 diabetes and A1C ≥7.0% (53 mmol/mol) and ≤9.5% (80 mmol/mol) whose conditions were stable while receiving metformin therapy (≥2,000 mg/day, or ≥1,500 mg/day if unable to tolerate a higher dose) for ≥10 weeks. Key exclusion criteria included repeated fasting plasma glucose (FPG) or self-monitored blood glucose (SMBG) measurements of ≥15.0 mmol/L (270 mg/dL) during the pretreatment phase; a history of type 1 diabetes; a history of more than one severe hypoglycemia episode within 6 months before screening; estimated glomerular filtration rate (eGFR) <55 mL/min/1.73 m^2 (or <60 mL/min/1.73 m^2 if based upon the restriction of metformin use in local label); or taking thiazolidinediones within 16 weeks before screening.

During the core period, patients were randomly assigned to receive canagliflozin 100 or 300 mg or glimepiride (1:1:1); details regarding randomization and masking were previously reported (12). Study drug was provided in five levels to allow for masked titration of glimepiride (from 1 to 6 or 8 mg, based on the maximum approved dose in the country of the investigational site). Glimepiride was up-titrated if patients met protocol-specified criteria (≥50% of fasting SMBG measurements >6.0 mmol/L [108 mg/dL] with no hypoglycemia events in the preceding 2 weeks) after ≥2 weeks at the current dose; up-titration could occur at any time during the study. Patients receiving canagliflozin were mock up-titrated. During the double-blind treatment period, glycemic rescue therapy with pioglitazone (where approved) was initiated for patients who were at the maximum level of study drug titration and met 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, and >11.1 mmol/L [200 mg/dL] after week 12 to week 26; and A1C >8.0% [64 mmol/mol] after week 26 through week 104; after week 52, rescue therapy could be initiated for patients with A1C >7.0% [53 mmol/mol] and ≤8.0% [64 mmol/mol] if the investigator believed additional treatment was appropriate to achieve the patient's individualized glycemic goal); the pioglitazone dose was titrated according to local prescribing information.

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. Institutional review boards or independent ethics committees at participating institutions approved the study protocol and amendments. Prior to participation, all patients provided written informed consent.

Study End Points and Assessments

The primary end point was the change in A1C from baseline to week 52 (reported previously) (12). Secondary end points assessed at week 104 included change in A1C, FPG, and systolic and diastolic BP; percentage change in body weight and fasting plasma lipids (including triglycerides, HDL cholesterol [HDL-C], LDL cholesterol [LDL-C], LDL-C/HDL-C ratio, and non–HDL-C); and the proportion of patients achieving A1C <7.0% (53 mmol/mol). The durability of A1C lowering was assessed based on the

coefficient of durability (COD), which was defined as the rate of rise in A1C from week 26 through week 104. The proportion of patients who achieved A1C <7.0% (53 mmol/mol) by week 26 and then maintained that level at week 104 was also evaluated.

Safety was assessed based on adverse event (AE) reports, vital sign measurements, safety laboratory tests, SMBG, physical examinations, and 12-lead electrocardiograms. Additional data were collected for selected AEs of interest, including genital mycotic infections and urinary tract infections (UTIs); specific analyses were performed for AEs related to osmotic diuresis and volume depletion. Documented hypoglycemia episodes included biochemically documented episodes (concurrent fingerstick glucose or plasma glucose ≤3.9 mmol/L [70 mg/dL] with or without symptoms) and severe episodes (i.e., requiring the assistance of another individual or resulting in seizure or the loss of consciousness).

Statistical Analyses

The determination of sample size was based on the primary end point, as previously reported (12). Efficacy and safety analyses were performed using the modified intent-to-treat (mITT) analysis set, consisting of all randomized patients who received ≥1 dose of study drug. For efficacy analyses, missing data were imputed using the last observation carried forward (LOCF) approach; the last observation prior to the initiation of rescue therapy was used for patients who received glycemic rescue therapy.

Continuous efficacy end points were assessed using an ANCOVA model with treatment and stratification factors (i.e., whether the patient underwent the metformin dose adjustment or AHA washout period, and country) as fixed effects, and the corresponding baseline value as a covariate. Least squares (LS) mean differences between groups (each canagliflozin dose vs. glimepiride) and two-sided 95% CIs were estimated. Categorical efficacy end points (i.e., the proportion of patients achieving A1C <7.0% [53 mmol/mol] and the proportion of patients with documented hypoglycemia episodes) were analyzed using a logistic regression model with terms for treatment, stratification factors, and baseline A1C. Change in A1C was also analyzed using the mixed-model repeated measures (MMRM) method, a restricted maximum likelihood repeated-measures approach, using the mITT analysis set. The analysis was based on observed data and included the effects of treatment, stratification factors, visit, and treatment-by-visit interaction, and the covariates of baseline A1C and baseline-by-visit interaction; an unstructured covariance was used to model the within-patient errors.

The COD was analyzed in patients in the mITT population with a week 26 and one or more post–week 26 A1C measurements using a mixed-effect model similar to that used for the MMRM analysis, but including covariates of A1C at week 26 and week 26-by-visit interaction. The proportion of patients who achieved A1C <7.0% (53 mmol/mol) through week 26 and maintained that level at week 104 was analyzed using a normal approximation to binomial distribution with continuity correction.

There was no prespecified hypothesis testing conducted at week 104; therefore, no P values are reported, but 95% CIs are provided.

RESULTS

Patients

Of the 1,450 patients who received ≥1 dose of double-blind study drug (mITT population), 1,161 (80.1%) patients completed the 52-week core period and 1,151 (79.4%) patients entered the 52-week extension period (Supplementary Fig. 1). The proportions of patients who received glycemic rescue therapy during the entire 104-week treatment period were 19.9%, 13.0%, and 20.9%, respectively, in the canagliflozin 100 and 300 mg and glimepiride groups; among patients who did not receive glycemic rescue during the core period, 17.6%, 11.0%, and 15.0%, respectively, received glycemic rescue during the extension (weeks 52–104). Rates of discontinuation over 104 weeks with canagliflozin 100 and 300 mg and glimepiride were 29.0%, 33.4%, and 34.9%, respectively, with the most common reasons for discontinuation being AE (7.5%), other (7.0%), and withdrawal of consent (4.5%). Over 104 weeks, 91.3% of glimepiride-treated patients up-titrated study drug, with a mean maximum dose of ∼5.8 mg and a mean final dose of ∼5.6 mg. During the extension period, 12.6% of glimepiride-treated patients up-titrated study drug. Baseline demographic and disease characteristics were similar across groups (Supplementary Table 1). The mean age in the mITT population was 56.2 years, and 52.1% of patients were male; 67.4% of patients were white, and 19.7% were Asian. At baseline, mean A1C was 7.8% (62 mmol/mol), body weight was 86.6 kg, BMI was 31.0 kg/m^2, and eGFR was 90.2 mL/min/1.73 m^2.

Efficacy

Over 104 weeks, canagliflozin 100 and 300 mg and glimepiride reduced A1C from mean baseline values of 7.78%, 7.79%, and 7.83% (62 mmol/mol for all), respectively, with changes from baseline to week 104 of −0.65%, −0.74%, and −0.55% (−7.1, −8.1, and −6.0 mmol/mol), respectively (Fig. 1A). Sensitivity analysis for A1C using the MMRM approach showed A1C reductions of −0.58%, −0.68%, and −0.38% (−6.3, −7.4, and −4.2 mmol/mol), respectively, with canagliflozin 100 and 300 mg and glimepiride (Fig. 1B). The proportions of patients who achieved A1C <7.0% (53 mmol/mol) at week 104, from a baseline A1C of 7.8% (62 mmol/mol) in each treatment group, were 42.5%, 50.2%, and 43.9%, respectively, with canagliflozin 100 and 300 mg and glimepiride.

Maximal A1C lowering occurred at week 52 with both canagliflozin groups, with small increases thereafter; with glimepiride, the greatest reduction in A1C was observed at week 18 followed by increases through week 104 (Fig. 1A). The COD was 0.16% (1.7 mmol/mol), 0.16% (1.7 mmol/mol), and 0.37% (4.0 mmol/mol), respectively, with canagliflozin 100 and 300 mg and glimepiride; 95% CIs excluded 0 for the comparisons of both canagliflozin 100 mg (−0.29 to −0.13) and canagliflozin 300 mg (−0.30 to −0.13) versus glimepiride. Additionally, the proportions of patients who achieved A1C <7.0% (53 mmol/mol) by week 26 and maintained it at week 104 were 31.1%, 35.7%, and 29.2%, respectively, with canagliflozin 100 and 300 mg and glimepiride, with the 95% CI excluding 0 for the comparison of canagliflozin 300 mg versus glimepiride (0.2 to 12.7).
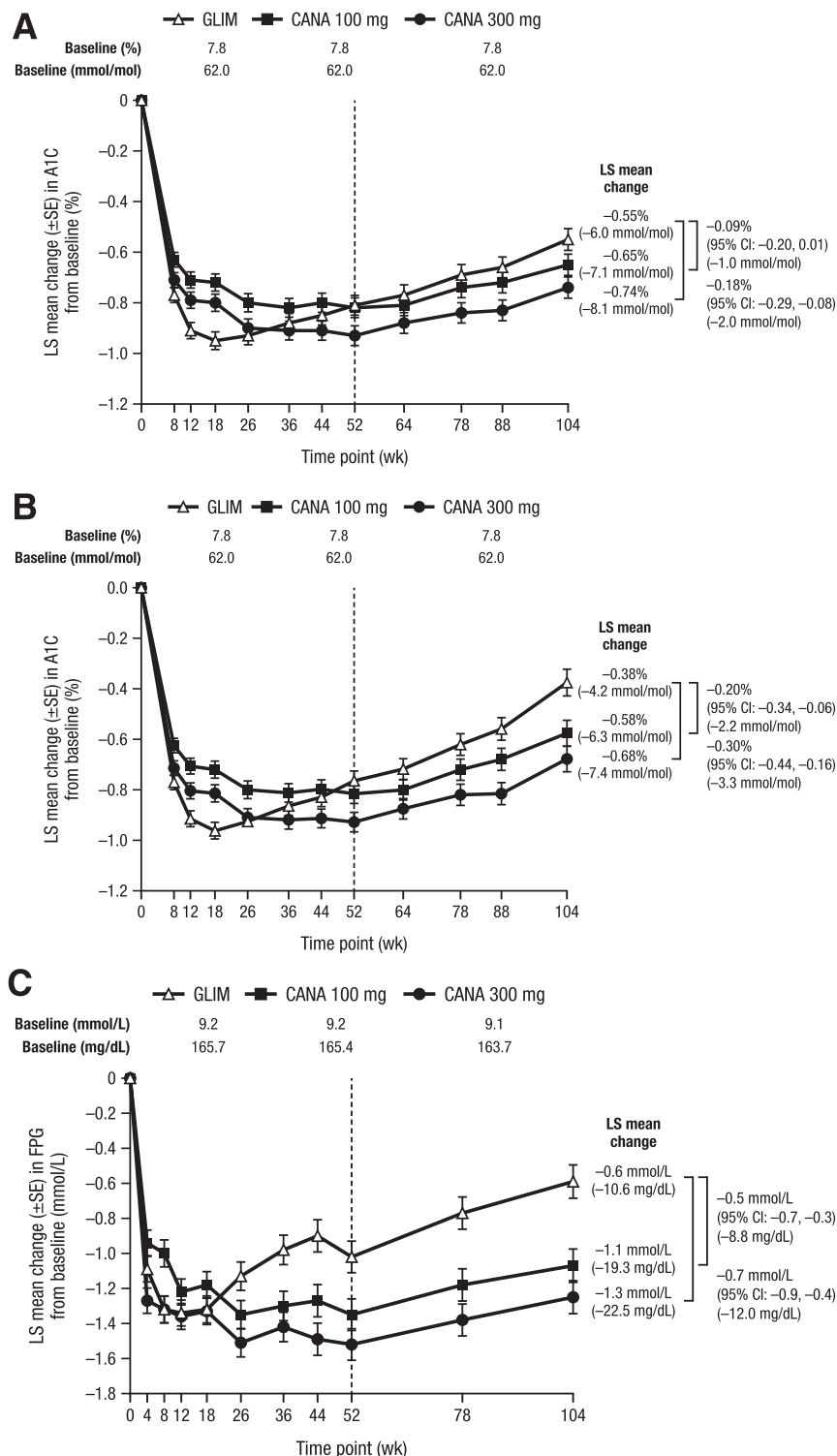
Figure 1—Change in efficacy parameters. Change in A1C (LOCF) (*A*), change in A1C (MMRM) (*B*), change in FPG (LOCF) (*C*), percentage change in body weight (LOCF) (*D*), and change in systolic BP (LOCF) (*E*) through week 104. CANA, canagliflozin; GLIM, glimepiride.

Greater reductions from baseline in FPG were observed with canagliflozin 100 and 300 mg compared with glimepiride at week 104 (−1.1 mmol/L [−19.3 mg/dL], −1.3 mmol/L [−22.5 mg/dL], and −0.6 mmol/L [−10.6 mg/dL], respectively) (Fig. 1*C*). Similar to findings with A1C, maximal reductions in FPG were observed at week 52 for canagliflozin 100 and 300 mg with increases thereafter; glimepiride provided a maximal reduction at week 12, with subsequent continual increases through week 104. Greater differences between each canagliflozin dose and glimepiride in the change in FPG were seen from week 52 to week 104.

Canagliflozin 100 and 300 mg were associated with reductions in body weight over 104 weeks (−4.1% [−3.6 kg] and −4.2% [−3.6 kg], respectively),
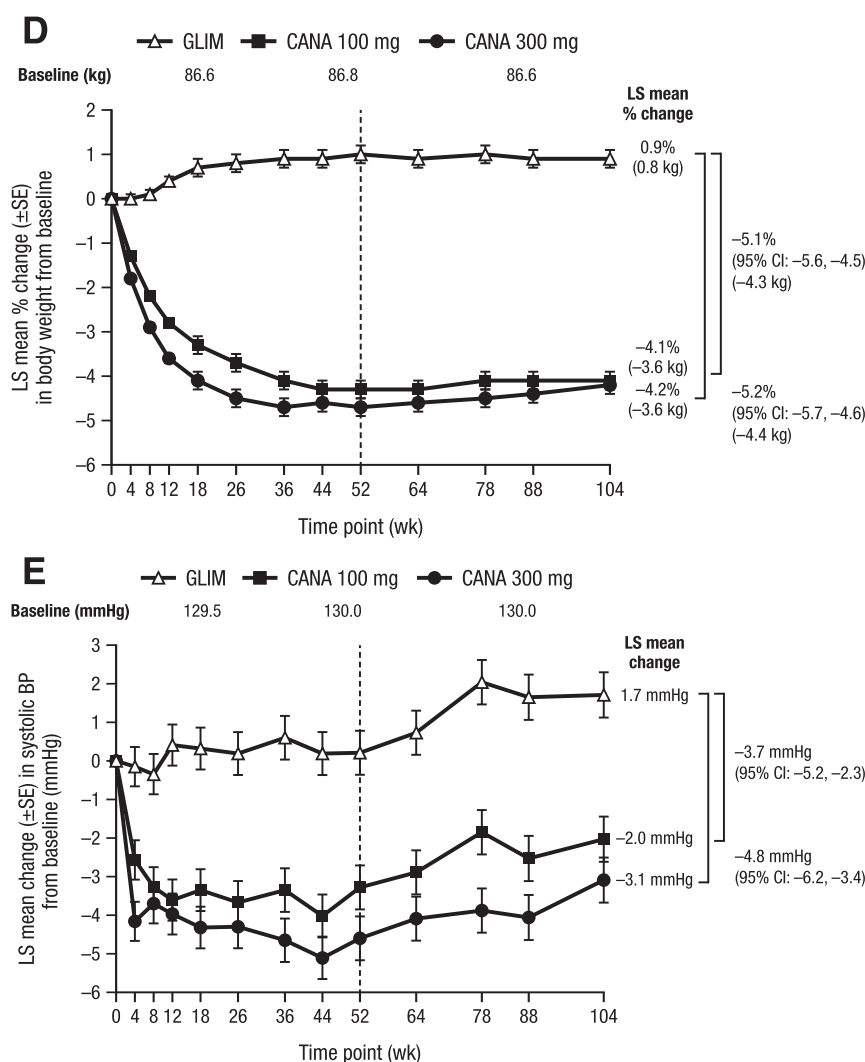
D

Legend: GLIM △ CANA 100 mg ■ CANA 300 mg ●

Baseline (kg) 86.6 86.8 86.6

LS mean % change

0.9% (0.8 kg)

−5.1% (95% CI: −5.6, −4.5) (−4.3 kg)

−4.1% (−3.6 kg)

−4.2% (−3.6 kg)

−5.2% (95% CI: −5.7, −4.6) (−4.4 kg)

Y-axis: LS mean % change (±SE) in body weight from baseline

X-axis: Time point (wk) — 0 4 8 12 18 26 36 44 52 64 78 88 104

E

Legend: GLIM △ CANA 100 mg ■ CANA 300 mg ●

Baseline (mmHg) 129.5 130.0 130.0

LS mean change

1.7 mmHg

−3.7 mmHg (95% CI: −5.2, −2.3)

−2.0 mmHg

−3.1 mmHg

−4.8 mmHg (95% CI: −6.2, −3.4)

Y-axis: LS mean change (±SE) in systolic BP from baseline (mmHg)

X-axis: Time point (wk) — 0 4 8 12 18 26 36 44 52 64 78 88 104

Figure 1—*Continued.*

whereas body weight increased with glimepiride (0.9% [0.8 kg]) (Fig. 1D). Progressive decreases in body weight were seen with canagliflozin 100 and 300 mg from baseline through week 36, with maximal reductions observed by week 52 (−4.3% [−3.7 kg] and −4.7% [−4.0 kg], respectively) followed by generally stable reductions through week 104 in both canagliflozin groups. In contrast, body weight increased with glimepiride treatment through week 26 (0.8% [0.6 kg]) and remained generally stable thereafter.

Changes from baseline in BP and fasting plasma lipids at week 104 are reported in Supplementary Table 2. Canagliflozin 100 and 300 mg were associated with reductions in systolic BP, whereas an increase was seen with glimepiride at week 104 (−2.0, −3.1, and

1.7 mmHg, respectively). With both canagliflozin doses, systolic BP decreased through week 44, with increases seen thereafter; systolic BP was generally stable through week 52 with glimepiride, followed by an increase through week 78 (Fig. 1E). Reductions in diastolic BP with canagliflozin 100 and 300 mg and glimepiride were −1.3, −2.2, and −0.02 mmHg, respectively. No notable changes in pulse rate were observed with canagliflozin 100 and 300 mg and glimepiride (−0.1, −0.2, and 0.7 bpm, respectively).

At 104 weeks, LDL-C and HDL-C were increased with canagliflozin treatment compared with glimepiride treatment (Supplementary Table 2). Across treatment groups, LDL-C increased through week 26 and remained generally stable thereafter (Fig. 2A); at week 104,

changes from baseline in LDL-C were 11.2%, 14.3%, and 6.3%, respectively, with canagliflozin 100 and 300 mg and glimepiride. HDL-C increased through week 78 with both canagliflozin doses and stabilized thereafter, whereas HDL-C remained generally stable over the entire 104-week treatment period with glimepiride (Fig. 2B). Increases from baseline in LDL-C/HDL-C ratio were observed across groups. Increases in non–HDL-C were seen in all treatment groups that were smaller than the increases observed in LDL-C. Canagliflozin treatment was associated with smaller increases from baseline in triglycerides compared with glimepiride treatment. The proportions of patients who started or modified therapy with lipid-modifying agents during the 104-week period were 13.0%, 11.5%, and 13.3%, respectively,
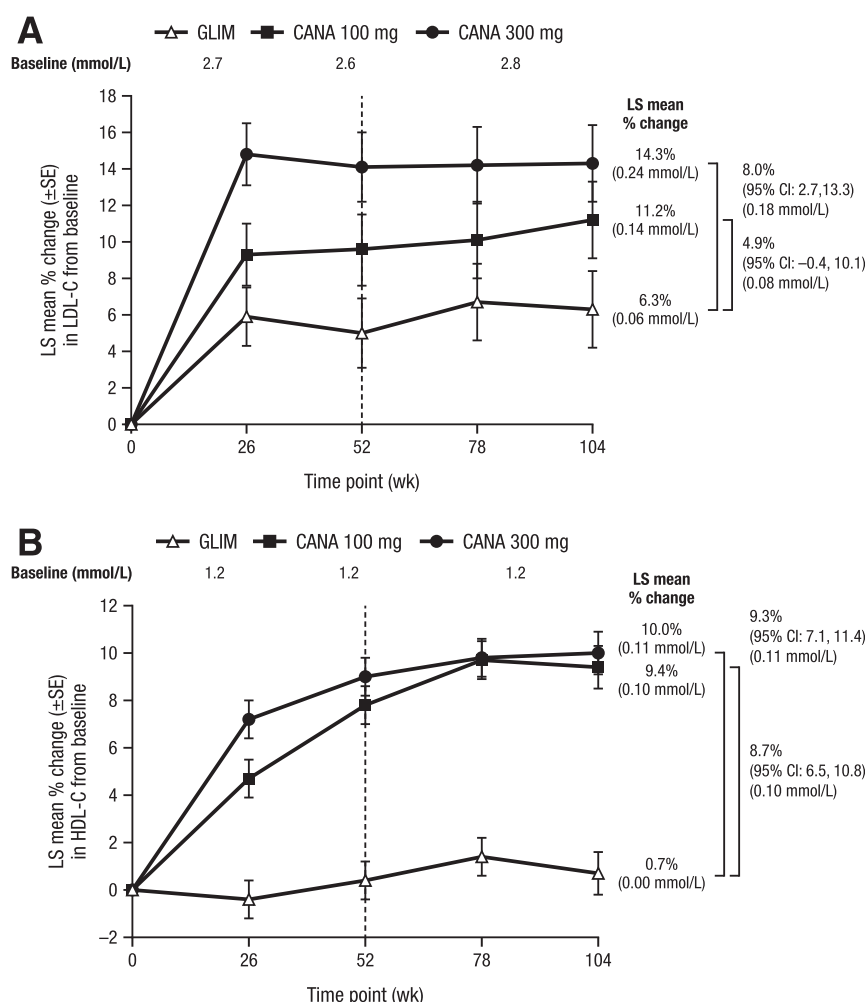
A

GLIM   CANA 100 mg   CANA 300 mg

Baseline (mmol/L)   2.7   2.6   2.8

LS mean % change (±SE) in LDL-C from baseline

LS mean % change

14.3% (0.24 mmol/L)   8.0% (95% CI: 2.7, 13.3) (0.18 mmol/L)

11.2% (0.14 mmol/L)   4.9% (95% CI: −0.4, 10.1) (0.08 mmol/L)

6.3% (0.06 mmol/L)

Time point (wk)

B

GLIM   CANA 100 mg   CANA 300 mg

Baseline (mmol/L)   1.2   1.2   1.2

LS mean % change (±SE) in HDL-C from baseline

LS mean % change

10.0% (0.11 mmol/L)   9.3% (95% CI: 7.1, 11.4) (0.11 mmol/L)

9.4% (0.10 mmol/L)   8.7% (95% CI: 6.5, 10.8) (0.10 mmol/L)

0.7% (0.00 mmol/L)

Time point (wk)

Figure 2—Percentage change in LDL-C (*A*) and HDL-C (*B*) through week 104 (LOCF). CANA, canagliflozin; GLIM, glimepiride.

in the canagliflozin 100 and 300 mg and glimepiride groups.

Safety
The overall incidence of AEs over the entire 104-week treatment period was higher with canagliflozin 300 mg and glimepiride (77.9% and 78.4%, respectively) than with canagliflozin 100 mg (73.3%) (Table 1). The incidences of AEs leading to discontinuation were 6.2%, 9.5%, and 7.3%, respectively, with canagliflozin 100 and 300 mg and glimepiride. There were no individual AEs leading to discontinuation of therapy in more than two patients treated with canagliflozin 100 mg. The only AEs leading to discontinuation in more than two patients with canagliflozin 300 mg were glomerular filtration rate decreased (seven patients [1.6%]), renal failure (three patients [0.6%]), and pruritus general (three patients [0.6%]); with glimepiride, the AEs leading to

discontinuation in more than two patients were hypoglycemia (three patients [0.6%]) and glomerular filtration rate decreased (three patients [0.6%]). The incidences of serious AEs were 9.7%, 9.7%, and 14.3%, respectively, with canagliflozin 100 and 300 mg and glimepiride. The incidence of AEs that occurred during the extension period (weeks 52–104) is reported in Supplementary Table 3.

Over 104 weeks, the incidence of genital mycotic infections in males and females was higher with canagliflozin than with glimepiride, with a dose relationship observed in females but not in males (Table 1); these were generally mild or moderate in intensity and few led to discontinuation (three males [one with canagliflozin 100 mg, two with canagliflozin 300 mg]; three females [one with canagliflozin 100 mg, two with canagliflozin 300 mg]). The incidence of UTIs was higher in both

canagliflozin groups compared with the glimepiride group, with no dose relationship; UTIs with canagliflozin treatment were mostly mild or moderate in intensity, with few events that were serious or led to discontinuation. Upper UTIs were reported in one and two patients treated with canagliflozin 100 and 300 mg, respectively, and in no patients treated with glimepiride. One event of upper UTI in the canagliflozin 300 mg group (acute pyelonephritis) was reported as a serious AE and resulted in discontinuation of therapy. All genital mycotic infections and UTIs reported during the extension period were recurrences in patients who had previously reported these AEs during the core period. Both canagliflozin doses were associated with a higher incidence of osmotic diuresis–related AEs (e.g., pollakiuria [increased urine frequency], polyuria [increased urine volume]) compared with glimepiride, with no severe

Table 1—Summary of overall safety and selected AEs

	Patients, *n* (%)		
	GLIM (*n* = 482)	CANA 100 mg (*n* = 483)	CANA 300 mg (*n* = 485)
Any AE	378 (78.4)	354 (73.3)	378 (77.9)
AEs leading to discontinuation	35 (7.3)	30 (6.2)	46 (9.5)
AEs related to study drug*	134 (27.8)	138 (28.6)	159 (32.8)
Serious AEs	69 (14.3)	47 (9.7)	47 (9.7)
Deaths	2 (0.4)†	3 (0.6)‡	3 (0.6)§
Genital mycotic infection			
Male‖,¶	5 (1.9)	24 (9.5)	22 (9.1)
Female#,**	6 (2.7)	32 (13.9)	38 (15.6)
UTIs	33 (6.8)	51 (10.6)	42 (8.7)
Osmotic diuresis–related AEs††	10 (2.1)	28 (5.8)	32 (6.6)
Volume depletion AEs‡‡	11 (2.3)	8 (1.7)	12 (2.5)

All AEs are reported for regardless of rescue medication. CANA, canagliflozin; GLIM, glimepiride. *Possibly, probably, or very likely related to study drug, as assessed by investigators. †One patient died due to squamous cell carcinoma of the cervix, and one patient died due to unwitnessed cardiac arrest. ‡One patient died due to acute chemical poisoning, one patient died due to intracranial hemorrhage, and one patient died due to pulmonary embolism and acute renal failure. §One patient died due to anemia, one patient died due to a road traffic accident, and one patient died due to trauma from a fall from the roof. ‖GLIM, *n* = 263; CANA 100 mg, *n* = 252; CANA 300 mg, *n* = 241. ¶Including balanitis, balanitis candida, balanoposthitis, genital candidiasis, genital infection fungal, and posthitis. #GLIM, *n* = 219; CANA 100 mg, *n* = 231; CANA 300 mg, *n* = 244. **Including genital infection fungal, vaginal infection, vulvitis, vulvovaginal candidiasis, vulvovaginal mycotic infection, and vulvovaginitis. ††Including dry mouth, micturition urgency, nocturia, pollakiuria, polydipsia, polyuria, thirst, and urine output increased. ‡‡Including BP decreased, dehydration, postural dizziness, hypotension, orthostatic hypotension, presyncope, and syncope.

or serious events and few leading to discontinuation of therapy. The incidence of AEs related to volume depletion (e.g., postural dizziness, orthostatic hypotension) was similar across groups, with a low incidence (≤1%) for each specific term. There were three serious AEs related to volume depletion reported (two AEs with canagliflozin 300 mg in the same patient; one AE with glimepiride).

The proportion of patients with documented hypoglycemia episodes was lower with canagliflozin 100 and 300 mg than with glimepiride (6.8%, 8.2%, and 40.9%, respectively). Severe hypoglycemia was reported in three patients (0.6%), one patient (0.2%), and 16 patients (3.3%), respectively, in the canagliflozin 100 and 300 mg and glimepiride groups, with all four events with canagliflozin occurring during the 52-week core period. Two patients in the canagliflozin 100 mg group had severe episodes of hypoglycemia that were confirmed by glucose measurement (fingerstick glucose ≤3.9 mmol/L [70 mg/dL]); both patients reported additional hypoglycemia episodes during the 104-week study. The other two reports of severe hypoglycemia (one each with canagliflozin 100 and 300 mg) were not

confirmed. None of the hypoglycemia episodes with canagliflozin led to study discontinuation.

Overall, only small differences in mean percentage changes from baseline in safety laboratory parameters were observed with canagliflozin compared with glimepiride at week 104 (Supplementary Table 4). Whereas glimepiride was associated with increases from baseline in alanine aminotransferase and aspartate aminotransferase, minimal changes and decreases from baseline were observed with canagliflozin 100 and 300 mg, respectively. Few patients had changes in alanine aminotransferase (six patients [1.3%], seven patients [1.5%], and three patients [0.6%]) or aspartate aminotransferase (five patients [1.1%], three patients [0.6%], and two patients [0.4%]) that were more than three times the upper limit of normal with canagliflozin 100 and 300 mg and glimepiride, respectively, over 104 weeks. Increases in bilirubin were observed with canagliflozin 100 and 300 mg compared with glimepiride (6.4%, 13.1%, and 1.5%, respectively). Decreases in eGFR were observed in all groups, with a greater reduction seen with glimepiride than

with canagliflozin (Fig. 3); commensurate changes in serum creatinine were observed across groups. The pattern of change in eGFR was different between the canagliflozin groups and the glimepiride group, with decreases in eGFR that occurred early after initiation of therapy and subsequently attenuated and remained stable over 104 weeks seen with treatment with both canagliflozin doses, versus a progressive decline in eGFR throughout the 104-week treatment period observed with treatment with glimepiride. Mean changes from baseline in the urine albumin-to-creatinine ratio at week 104 were −0.02, −0.27, and 1.55 g/mol, respectively, with canagliflozin 100 and 300 mg and glimepiride (median changes of 0.11, 0.02, and 0.03 g/mol, respectively). Both canagliflozin doses were associated with increases in blood urea nitrogen and magnesium compared with glimepiride; serum urate levels were decreased from baseline with canagliflozin, whereas an increase was seen with glimepiride. Small increases from baseline in hemoglobin were seen with canagliflozin 100 and 300 mg versus small decreases with glimepiride.

CONCLUSIONS

This 104-week study represents the longest active-controlled follow-up of individuals receiving canagliflozin treatment to date, extending findings from the previously reported 52-week core period of this study (12) to allow for longer-term evaluation of efficacy and safety. Treatment with canagliflozin 100 and 300 mg provided durable glycemic improvements in patients with type 2 diabetes on background metformin therapy over 104 weeks; reductions in body weight and systolic BP were seen with canagliflozin compared with glimepiride treatment. Canagliflozin was generally well tolerated over 104 weeks, with higher incidences of genital mycotic infections, UTIs, and AEs related to osmotic diuresis that were generally mild to moderate in intensity and infrequently led to discontinuation. A lower proportion of patients experienced documented hypoglycemia episodes in the canagliflozin groups than in the glimepiride group.

At 52 weeks, canagliflozin 100 and 300 mg demonstrated noninferiority to glimepiride, and canagliflozin 300 mg demonstrated superiority to glimepiride
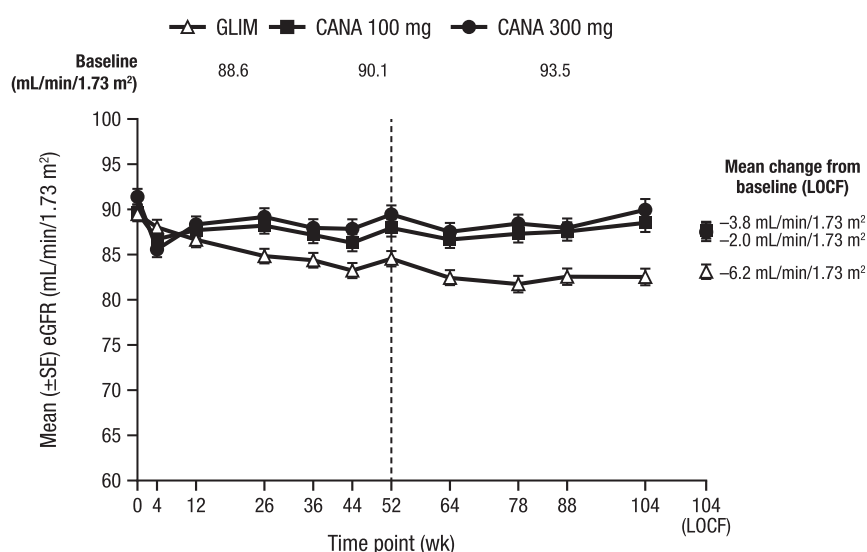
Figure 3—Mean eGFR over time. CANA, canagliflozin; GLIM, glimepiride.

in A1C lowering (12); over 104 weeks, these effects were maintained. A lower COD (rate of change per year in A1C from week 26 to week 104) was observed with both canagliflozin doses compared with glimepiride, suggesting a sustained effect of canagliflozin on A1C lowering. An increase in A1C was observed after week 52 with both canagliflozin doses and after week 18 with glimepiride, with a greater increase observed with glimepiride, and the difference between each canagliflozin dose and glimepiride increasing from week 52 through week 104. This pattern suggests that while progression of disease occurred across treatment groups, canagliflozin may provide a greater delay in progression than glimepiride (19). Canagliflozin also provided reductions in FPG versus glimepiride over 104 weeks. Together, these findings suggest that canagliflozin may be an option for longer-term treatment of patients with type 2 diabetes. The dosage of glimepiride could be up-titrated throughout the double-blind treatment period, and the reduction in A1C with glimepiride at week 104 was generally consistent with that observed in other studies (20–22), suggesting appropriate up-titration of glimepiride in this study.

Consistent with findings at week 52 (12), treatment with canagliflozin 100 and 300 mg provided durable body weight reduction over 104 weeks, whereas an increase in body weight was observed with glimepiride. Previous

assessments of body composition in a subset of patients at week 52 showed that approximately two-thirds of the weight loss observed with canagliflozin is due to loss of fat mass rather than lean mass (12), consistent with findings from studies of other AHAs that are also associated with weight loss (23,24). Both canagliflozin doses reduced systolic and diastolic BP over 104 weeks compared with glimepiride, with no notable changes in pulse rate. The reductions in BP may be related to a mild osmotic diuresis associated with increased urinary glucose excretion, with the weight loss associated with canagliflozin also contributing to BP lowering (25). Treatment with canagliflozin was also associated with increases in HDL-C and LDL-C, which is consistent with findings at week 52 and those from other studies (11,12,14–16,18); LDL-C increased through week 26 and remained generally stable thereafter. The mechanism for the increase in LDL-C observed with canagliflozin is unknown; however, increases in LDL-C have also been observed with other SGLT2 inhibitors (26), suggesting that metabolic changes associated with increased urinary glucose excretion may be related to this change. Considering that increases in LDL-C may be associated with elevated risk of cardiovascular disease, it is recommended that LDL-C levels are monitored during treatment with canagliflozin (27). The ongoing CANagliflozin cardioVascular Assessment Study (CANVAS)

will better assess the overall impact of canagliflozin on cardiovascular risk (28).

Overall, canagliflozin was generally well tolerated over 104 weeks. As previously observed (11,12,14–16,18), canagliflozin was associated with higher incidences of genital mycotic infections, UTIs, and AEs related to osmotic diuresis (e.g., pollakiuria, polyuria). These events were generally mild to moderate in intensity, and few led to study discontinuation. These AEs are likely related to the mechanism of action of canagliflozin, and have also been reported with other SGLT2 inhibitors (29–32). All genital mycotic infections and UTIs reported during the extension period were recurrences in patients who had previously reported these AEs during the core period. Canagliflozin was associated with a lower incidence of documented hypoglycemia compared with glimepiride over 104 weeks, which is consistent with the lowering of the renal threshold for glucose with canagliflozin to a level above the usual threshold for hypoglycemia (13,33), and with a low risk of hypoglycemia observed with canagliflozin treatment in other phase 3 studies (11,12,15–17). In this study, documented hypoglycemia was defined as glucose values ≤3.9 mmol (70 mg/dL) with or without symptoms. Studies with other agents have used more restrictive criteria for hypoglycemia (34,35). Of note, studies of canagliflozin may show higher rates of hypoglycemia

compared with studies that used a more restrictive definition. In general, only small differences were observed between canagliflozin and glimepiride in changes in safety laboratory parameters. Initial decreases in eGFR were observed with both canagliflozin doses that attenuated over the treatment period, compared with a gradual decline over time with glimepiride. Overall, safety findings with canagliflozin over 104 weeks were consistent with those observed at 52 weeks (12,35), with no additional safety signals noted with longer-term treatment.

A limitation of this study was the A1C range specified in patient eligibility criteria (7.0–9.5% [53–80 mmol/mol]), which may limit the generalizability of these findings to patients with more severe hyperglycemia. This study also enrolled a relatively low proportion of black/African American and Hispanic patients; however, pooled analyses of data from phase 3 studies of canagliflozin showed no significant differences in the effects of canagliflozin on A1C and body weight based on race or ethnicity (36), suggesting that findings from this study may be generalizable to other racial/ethnic groups. Although this study did not include a placebo control group (12), another phase 3 study of canagliflozin as add-on to metformin therapy showed significant improvement in glycemic control with canagliflozin compared with placebo over 26 weeks of treatment; in that study, canagliflozin 100 and 300 mg also demonstrated non-inferiority, and canagliflozin 300 mg further demonstrated statistical superiority to sitagliptin 100 mg in A1C lowering over 52 weeks (17). In addition, canagliflozin has also demonstrated superiority and favorable safety and tolerability in head-to-head studies with sitagliptin as add-on to therapy with metformin plus sulfonylurea over 52 weeks (14). These comparative studies demonstrate the value of canagliflozin for managing type 2 diabetes versus another currently available treatment option. Further studies providing longer-term, direct comparisons of canagliflozin with other AHAs that are commonly added on to metformin therapy would be useful.

In summary, treatment with canagliflozin 100 and 300 mg provided durable decreases in A1C and sustained body weight reduction with a low risk of hypoglycemia compared with glimepiride, and was generally well tolerated over 104 weeks in patients with type 2 diabetes on background metformin therapy. These results support the use of canagliflozin for longer-term treatment of patients with type 2 diabetes.

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