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Efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sulphonylurea: a randomised trial

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SUMMARY

Aims: Canagliflozin is a sodium glucose co-transporter 2 inhibitor developed for the treatment of type 2 diabetes mellitus (T2DM). This randomised, double-blind, placebo-controlled, Phase 3 study evaluated the efficacy and safety of canagliflozin as an add-on to metformin plus sulphonylurea in patients with T2DM. **Methods:** Patients (N = 469) received canagliflozin 100 or 300 mg or placebo once daily during a 26-week core period and a 26-week extension. Prespecified primary end-point was change in HbA_{1c} at 26 weeks. Secondary end-points included change in HbA_{1c} at week 52 as well as proportion of patients achieving $HbA_{1c} < 7.0\%$, change in fasting plasma glucose (FPG) and systolic blood pressure, and per cent change in body weight, high-density lipoprotein cholesterol, and triglycerides (weeks 26 and 52). **Results:** HbA_{1c} was significantly reduced with canagliflozin 100 and 300 mg vs. placebo at week 26 (–0.85%, –1.06%, and –0.13%; $p < 0.001$); these reductions were maintained at week 52 (–0.74%, –0.96%, and 0.01%). Both canagliflozin doses reduced FPG and body weight vs. placebo at week 26 ($p < 0.001$) and week 52. Overall adverse event (AE) rates were similar across groups over 52 weeks, with higher rates of genital mycotic infections and osmotic diuresis-related AEs seen with canagliflozin vs. placebo; these led to few discontinuations. Increased incidence of documented, but not severe, hypoglycaemia episodes was seen with canagliflozin vs. placebo. **Conclusions:** Canagliflozin improved glycaemic control, reduced body weight, and was generally well tolerated in T2DM patients on metformin plus sulphonylurea over 52 weeks.

What's known

- Canagliflozin decreases plasma glucose by lowering the renal threshold for glucose and increasing urinary glucose excretion.
- Canagliflozin is approved in the United States as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus (T2DM).
- Canagliflozin 300 mg has demonstrated superiority to sitagliptin 100 mg in lowering HbA_{1c} in patients with T2DM on background metformin plus sulphonylurea over 52 weeks.

What's new

- Results from a 52-week, placebo-controlled, Phase 3 study evaluating canagliflozin 100 and 300 mg as an add-on therapy to metformin plus sulphonylurea are reported.
- Both canagliflozin doses provided reductions in HbA_{1c}, fasting plasma glucose, and body weight compared with placebo over 52 weeks.
- Canagliflozin was generally well tolerated, without increases in severe hypoglycaemia episodes in this patient population on background therapy associated with an increased risk of hypoglycaemia.

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Disclosures

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Introduction

Management of hyperglycaemia in patients with type 2 diabetes mellitus (T2DM) is important for reducing the risk of long-term complications. Many patients do not achieve or maintain glycaemic goals with first-line metformin therapy and require combination therapy with a second glucose-lowering agent, such as a sulphonylurea (1,2). Over time, many patients eventually require treatment with a third agent (2–4). Underlying the progressive failure of initial and dual combination therapy is progressive β-cell dysfunction. Agents with glucose-lowering effects independent of β-cell function might offer benefits in patients needing combination therapy.

Canagliflozin is a sodium glucose co-transporter 2 (SGLT2) inhibitor developed for the treatment of patients with T2DM (5–10). After glucose is filtered through the glomerulus, SGLT2 mediates the majority of renal glucose reabsorption (11). The renal threshold for glucose excretion (RT_G) is the plasma glucose concentration below which essentially all filtered glucose is reabsorbed by the renal tubules, and above which urinary glucose excretion (UGE) rises in proportion to plasma glucose. Patients with T2DM often exhibit increased RT_G, which may contribute to sustained hyperglycaemia (12,13). In preclinical diabetes models, canagliflozin lowered RT_G and increased UGE, leading to reduced blood glucose and HbA_{1c} and improved measures of β-cell function

from AstraZeneca, Eli Lilly, Novo Nordisk, and Merck Sharpe and Dohme. G.C. is a member of the French canagliflozin board. P.H. has served on advisory boards and as a consultant for Novo Nordisk, Sanofi, and Merck. G.G. has served as a consultant for Merck Sharpe and Dohme, Novo Nordisk, Bristol-Myers Squibb, Roche, Boehringer Ingelheim, Eli Lilly, Janssen, and Sanofi; and has served as a speaker for Merck Sharpe and Dohme, Roche, Boehringer Ingelheim, Novo Nordisk, Eli Lilly, Sanofi, Bristol-Myers Squibb, and Novartis. C.M. has served on advisory panels for Bristol-Myers Squibb, AstraZeneca, Eli Lilly, Johnson & Johnson, Merck Sharpe and Dohme, Novartis, Novo Nordisk, Pfizer, and Sanofi-Aventis; and has served as a speaker and received research support from Eli Lilly, Merck Sharpe and Dohme, Novartis, Novo Nordisk, and Sanofi-Aventis.

(14). In patients with T2DM, canagliflozin lowered mean RT_G to 4.4–5.0 mmol/l, above the threshold for hypoglycaemia (5,15); thus, canagliflozin is predicted to have a low intrinsic risk of hypoglycaemia. Other factors that may contribute to the low risk of hypoglycaemia with canagliflozin are a rise in hepatic glucose production as blood glucose decreases (16) and potentially an incomplete inhibition of renal glucose reabsorption (17). Canagliflozin has been shown to improve glycaemic control and reduce body weight and systolic blood pressure (BP) in patients with T2DM (5,6,8,9,15). Improvements in these efficacy parameters have also been observed with another SGLT2 inhibitor, dapagliflozin (18–21). Because of its mechanism of action, distinct from other current classes of oral antidiabetic drugs (OADs), canagliflozin has the potential to provide complementary, additive effects in patients on background metformin plus sulphonylurea. In this context, canagliflozin 300 mg has demonstrated superiority to sitagliptin 100 mg in lowering HbA_{1c} in patients with T2DM on background metformin plus sulphonylurea over 52 weeks of treatment (8).

This Phase 3, CANagliflozin Treatment And Trial Analysis – Metformin plus SUlphonylurea (CANTATA-MSU) study evaluated the efficacy and safety of two doses of canagliflozin (100 and 300 mg) compared with placebo as an add-on therapy in patients with T2DM inadequately controlled with metformin plus sulphonylurea combination therapy.

Materials and methods

Patients and study design

This randomised, double-blind, placebo-controlled, Phase 3 study was conducted at 85 study centres in 11 countries between April 2010 and April 2012 (ClinicalTrials.gov: NCT01106625). It consisted of a 26-week, core, double-blind, treatment period followed by a 26-week, double-blind, extension period.

Eligible patients were men and women aged 18–80 years with T2DM who had inadequate glycaemic control ($HbA_{1c} \geq 7.0\%$ to $\leq 10.5\%$) on metformin plus sulphonylurea, with both agents at maximally or near-maximally effective doses. During the pretreatment phase, patients who were on protocol-specified doses of metformin plus sulphonylurea [metformin, ≥2000 mg/day (or ≥ 1500 mg/day if intolerant of higher dose); sulphonylurea, at least half-maximal labelled dose; Table 1] and had $HbA_{1c} \geq 7.0\%$ to $\leq 10.5\%$ directly entered a 2-week, single-blind, placebo run-in period. Patients taking below protocol-specified doses of metformin and/or sulphonylurea underwent an OAD adjustment period consisting of an up to 4-week metformin and/or sulphonylurea dose titration period and then an 8-week dose stable period; patients then entered the placebo run-in period if they had $HbA_{1c} \geq 7.0\%$ to $\leq 10.5\%$ and met all other enrolment criteria.

Table 1 Minimum daily dose required for sulphonylurea for randomisation

Sulphonylurea	Minimum daily dose required for randomisation
Glipizide	20 mg
Glipizide extended release	10 mg
Glyburide/glibenclamide	10 mg
Glimepiride	4 mg
Gliclazide	160 mg daily
Gliclazide modified release	60 mg daily

Exclusion criteria included a history of diabetic ketoacidosis or T1DM, repeated fasting plasma glucose (FPG) ≥ 15.0 mmol/l during the pretreatment phase, history of ≥ 1 severe hypoglycaemia 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 based upon restriction of metformin use in the local label) or serum creatinine ≥ 124 μmol/l for men and ≥ 115 μmol/l for women, uncontrolled hypertension (systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg), or taking any antihyperglycaemic agent other than metformin plus sulphonylurea within 12 weeks prior to screening.

During a 2-week placebo run-in period, all patients received a single-blind placebo capsule matching the double-blind study drug once daily before the first meal of the day. Patients were then randomly assigned into the core treatment period at a 1:1:1 ratio to receive canagliflozin 100 or 300 mg or placebo once daily before the first meal of the day. Canagliflozin 100 and 300 mg were selected based on previously published findings from a dose-ranging, Phase 2 study in patients with T2DM, in which canagliflozin 100 mg was the lowest dose providing clear glycaemic efficacy and canagliflozin 300 mg provided additional HbA_{1c} lowering relative to canagliflozin 100 mg (5). A stable dose of metformin plus sulphonylurea was to be continued throughout the run-in period and double-blind treatment phase, unless adjustment was clinically required. During the core double-blind treatment period, glycaemic rescue therapy with insulin was initiated if FPG > 15.0 mmol/l after day 1 to week 6, > 13.3 mmol/l after week 6 to week 12, and > 11.1mmol/l after week 12 to week 26, and if HbA_{1c} > 8.0% after week 26.

Randomisation was performed using an Interactive Voice Response System/Interactive Web Response

System based on a computer-generated schedule prepared by the sponsor before the study. Randomisation was balanced using permuted blocks of six patients per block and stratified based on two criteria: (i) whether a patient entered the OAD adjustment period and (ii) whether a patient participated in the frequently-sampled mixed-meal tolerance test (FS-MMTT). To maintain blinding after randomisation, HbA_{1c} and FPG values were masked to study centres unless these values met prespecified glycaemic rescue criteria or after glycaemic rescue therapy was started. After completion of the core treatment period, the database was locked and the study was unblinded by the sponsor for regulatory filing; patients, investigators and local sponsor personnel remained blinded throughout the extension period.

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

Study outcomes

The prespecified primary efficacy end-point was change from baseline in HbA_{1c} at week 26; change from baseline in HbA_{1c} to week 52 was a key secondary end-point. Other prespecified secondary efficacy end-points evaluated at weeks 26 and 52 included proportion of patients achieving $HbA_{1c} < 7.0\%$, change from baseline in FPG and systolic BP and per cent change from baseline in body weight, high-density lipoprotein cholesterol (HDL-C), and triglycerides. Homeostasis Model Assessment (HOMA2-%B), a fasting measure of β-cell function, was assessed at week 26 based on FPG and C-peptide measurements. In a subset of patients who underwent an FS-MMTT on day 1 and at week 26, 2-h postprandial glucose (PPG), glucose area under the concentration-time curve (AUC_G), incremental AUC_G (ΔAUC_G), and the ratio of C-peptide AUC (AUC_C) to AUC_G were assessed. During the FS-MMTT, blood samples were collected 15 min before and immediately prior to the meal, and 30, 60, 90, 120 and 180 min after the meal.

Safety and tolerability over 52 weeks were assessed based on adverse event (AE) reports, safety laboratory tests, vital sign measurements, 12-lead electrocardiograms and physical examinations. AEs prespecified for additional data collection and analysis included genital mycotic infections and urinary tract infections (UTIs); additional data collection was also undertaken for hypoglycaemia events. Documented hypoglycaemia events included biochemically confirmed episodes (concurrent fingerstick glucose or plasma glucose ≤ 3.9 mmol/l) with or without symptoms and severe hypoglycaemia episodes (i.e. those for which patients required assistance from another person or those resulting in seizure or loss of consciousness).

Statistical analyses

Sample size determination was based on demonstrating the superiority of canagliflozin to placebo at week 26. An estimated 85 randomised patients per treatment group were required to achieve ≥ 90% power, assuming a between-group difference of 0.5% and a common standard deviation (SD) of 1.0%, and using a two-sample, two-sided *t*-test with a type I error rate of 0.05. Sample size was expanded to 150 patients per group to enhance the safety and tolerability assessment of canagliflozin in patients on metformin plus sulphonylurea. No hypothesis testing was conducted for the week 52 assessments.

Primary efficacy analyses were conducted using the modified intent-to-treat (mITT) population (all randomised patients who took ≥ 1 dose of double-blind study drug). Efficacy data were analysed according to randomised treatment with the last observation carried forward (LOCF) approach used to impute missing values. For patients who received rescue therapy, the last postbaseline value prior to initiation of rescue therapy was used for analyses. Safety analyses were conducted in all randomised patients who took ≥ 1 dose of study drug and were analysed according to the predominant treatment received. In this study, the efficacy and safety analysis sets were identical.

Primary and continuous secondary efficacy end-points were assessed using an analysis of covariance (ANCOVA) model with treatment and stratification factors as fixed effects and the corresponding baseline value as a covariate. Differences between groups (each canagliflozin dose vs. placebo) in the least squares (LS) means (or per cent means) and the associated two-sided 95% confidence intervals (CIs) were estimated. The categorical secondary efficacy end-point (proportion of patients reaching $HbA_{1c} < 7.0\%$) was analysed using a logistic model with treatment and stratification factors as fixed effects and baseline HbA_{1c} as covariate. For indices of β-cell function assessed in the FS-MMTT subset, descriptive statistics and 95% CIs for changes from baseline were provided; LS mean differences vs. placebo at week 26 were assessed using an ANCOVA model with treatment and the stratification factor of whether a patient entered the OAD adjustment

period as fixed effects, and the corresponding baseline value as a covariate.

A prespecified hierarchical testing sequence was implemented to strongly control overall type I error because of multiplicity for the week 26 data. Two-sided statistical tests were conducted at the 0.05 significance level for all end-points except systolic BP, HDL-C and triglycerides, which were grouped into two subfamilies for canagliflozin 100 and 300 mg, respectively. Each subfamily was assessed using the Hochberg procedure at a significance level of 0.025. P-values were calculated by comparing LS means and are reported for prespecified comparisons at week 26 only. For subgroup analysis at week 26, descriptive statistics and 95% CIs for the change from baseline in HbA_{1c} were provided for subgroups of patients with baseline HbA_{1c} of $< 8.0\%$, $\geq 8.0\%$ to $< 9.0\%$, and $\geq 9.0\%$. Descriptive results, including differences in LS means for each canagliflozin dose vs. placebo with 95% CIs, at week 52 are presented; no formal statistical treatment comparisons were performed and no p-values are reported.

Results

Patients

A total of 469 patients were randomised into the core treatment period and received ≥ 1 dose of study medication, comprising the mITT analysis set; of 381 patients who completed the core period, 374 entered the extension period and 310 completed 52 weeks of treatment (Figure 1). Rates of study discontinuation over 52 weeks were higher with placebo compared with canagliflozin 100 and 300 mg (42.3%, 30.6%, and 28.8%, respectively). The most common reasons for discontinuation were other, AEs, and unable to take protocol-defined rescue therapy. Baseline patient demographic and disease characteristics were similar across groups (Table 2). The mean age was 56.8 years, 51% of patients were men, and 83% of patients were white. Mean body weight was 92.8 kg and mean body mass index (BMI) was 33.1 kg/m^2, with 66% of patients classified as obese (BMI ≥ 30 kg/m^2). Baseline mean HbA_{1c} was 8.1% and patients had a mean duration of T2DM of 9.6 years. During the 52-week treatment period, similar proportions of patients across treatment groups (≤ 4% per group) initiated or dose-adjusted antihypertensive agents (i.e. angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, thiazide diuretics, calcium channel blockers, β-blockers). Few patients initiated or dose-adjusted lipid-lowering agents (including statins), with a slightly higher proportion in the canagliflozin 100 mg group (8%) than the placebo and canagliflozin 300 mg groups (6% each).

Efficacy

Glycaemic efficacy end-points

At week 26, HbA_{1c} was significantly reduced from baseline with canagliflozin 100 and 300 mg compared with placebo (–0.85%, –1.06%, and –0.13%, respectively; $p < 0.001$ for both canagliflozin doses; Figure 2A). Differences in LS mean changes for canagliflozin 100 and 300 mg relative to placebo were –0.71% and –0.92%, respectively. Subgroup analysis conducted at week 26 showed substantially greater reductions in HbA_{1c} with both canagliflozin doses compared with placebo in patients with higher, relative to those with lower, baseline HbA_{1c} (Table 3). Reductions in HbA_{1c} with canagliflozin 100 and 300 mg compared with placebo were sustained over 52 weeks of treatment (Figure 2A), with differences in LS mean changes (95% CI) vs. placebo of –0.75% (–0.95, –0.55) and –0.97% (–1.17, –0.77) for canagliflozin 100 and 300 mg, respectively, at week 52. HbA_{1c} reductions with both canagliflozin doses were observed starting at week 6, with a nadir at week 12 followed by small increases over the remainder of the 52-week treatment period that were similar to the increases seen with placebo. A greater proportion of patients treated with canagliflozin 100 or 300 mg compared with placebo achieved $HbA_{1c} < 7.0\%$ at week 26 (43.2%, 56.6%, and 18.0%, respectively; $p < 0.001$ for both canagliflozin doses) and week 52 (39.4%, 52.6%, and 18.7%, respectively).

Significant improvements from baseline in FPG were observed at week 26 with canagliflozin 100 and 300 mg compared with placebo; differences in LS mean changes vs. placebo were –1.2 and –1.9 mmol/l, respectively ($p < 0.001$ for both canagliflozin doses; Figure 2B). Reductions in FPG with canagliflozin 100 and 300 mg compared with placebo were sustained over 52 weeks (Figure 2B), with differences in LS mean changes (95% CI) vs. placebo of –1.6 mmol/l (–2.1, –1.1) and –2.1 mmol/l (–2.6, –1.6) for canagliflozin 100 and 300 mg, respectively, at week 52. Maximal reductions in FPG with both canagliflozin doses were seen at week 6, with subsequent small increases through week 52 that were similar to the increases seen with placebo. Consistent with the extent of HbA_{1c} and FPG reductions across groups, fewer patients treated with canagliflozin 100 and 300 mg compared with placebo met glycaemic rescue criteria and initiated rescue medication or were discontinued before week 52 (12.7%, 7.7%, and 34.6%, respectively).

Other efficacy end-points

At week 26, canagliflozin 100 and 300 mg significantly reduced body weight from baseline compared with placebo, with LS mean per cent changes relative

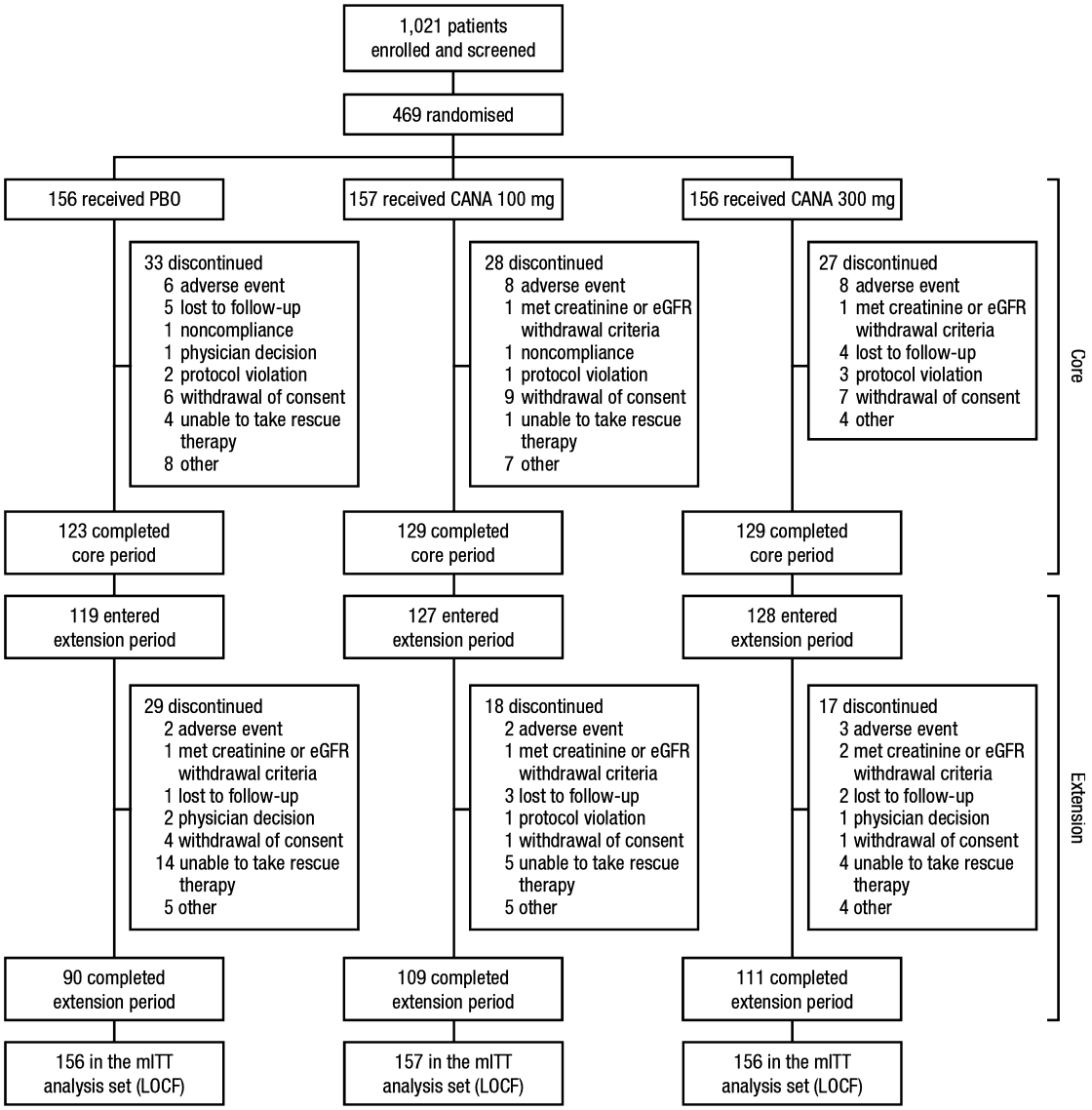


Figure 1 Study diagram. PBO, placebo; CANA, canagliflozin; eGFR, estimated glomerular filtration rate; mITT, modified intent-to-treat; LOCF, last observation carried forward

to placebo of –1.4% (–1.1 kg) and –2.0% (–1.7 kg), respectively ($p < 0.001$ for both canagliflozin doses; Figure 3). Reductions in body weight with canagliflozin 100 and 300 mg compared with placebo were sustained over 52 weeks of treatment (Figure 3), with differences in LS mean per cent changes (95% CI) vs. placebo of –1.3% (–2.1, –0.5) and –2.2% (–3.0, –1.4) for canagliflozin 100 and 300 mg, respectively, at week 52. Weight loss occurred most rapidly with both canagliflozin doses through week 12, with a continued gradual decrease through week 52 with canagliflozin 300 mg and minimal further reduction observed with canagliflozin 100 mg. A small, progressive decrease from baseline in body weight was seen with placebo over the 52-week treatment period.

Reductions from baseline in systolic BP at week 26 were seen across treatment groups, with numerically greater, but non-statistically significant reductions with canagliflozin 100 and 300 mg (difference in LS mean changes vs. placebo of –2.2 and –1.6 mmHg, respectively; Table 4). At 52 weeks, canagliflozin 100 and 300 mg were associated with differences in LS mean changes (95% CI) vs. placebo of –3.7 mmHg (–6.2, –1.3) and –3.0 mmHg (–5.5, –0.5), respectively (Table 5). Reductions in diastolic BP were also seen with canagliflozin 100 and 300 mg relative to placebo at week 52; no notable changes in pulse rate were seen across treatment groups (0.9, –1.2, and –0.4 beats per minute for canagliflozin 100 and 300 mg and placebo, respectively).

Table 2 Baseline demographic and disease characteristics*

	PBO (n = 156)	CANA 100 mg (n = 157)	CANA 300 mg (n = 156)	Total (n = 469)
Gender, n (%)				
Men	76 (48.7)	76 (48.4)	87 (55.8)	239 (51.0)
Women	80 (51.3)	81 (51.6)	69 (44.2)	230 (49.0)
Age (years)	56.8 ± 8.3	57.4 ± 10.5	56.1 ± 8.9	56.8 ± 9.3
Race, n (%)†				
White	128 (82.1)	132 (84.1)	127 (81.4)	387 (82.5)
Black or African American	10 (6.4)	5 (3.2)	11 (7.1)	26 (5.5)
Asian	2 (1.3)	2 (1.3)	0	4 (0.9)
Other‡	16 (10.3)	18 (11.5)	18 (11.5)	52 (11.1)
HbA_{1c} (%)	8.1 ± 0.9	8.1 ± 0.9	8.1 ± 0.9	8.1 ± 0.9
FPG (mmol/l)	9.4 ± 2.2	9.6 ± 2.3	9.3 ± 2.1	9.5 ± 2.2
Body weight (kg)	91.2 ± 22.6	93.8 ± 22.6	93.5 ± 22.0	92.8 ± 22.4
BMI (kg/m^2)	32.7 ± 6.8	33.3 ± 6.3	33.2 ± 6.3	33.1 ± 6.5
Duration of T2DM (years)	10.3 ± 6.7	9.0 ± 5.7	9.4 ± 6.4	9.6 ± 6.3

PBO, placebo; CANA, canagliflozin; FPG, fasting plasma glucose; BMI, body mass index; T2DM, type 2 diabetes mellitus; SD, standard deviation.

*Data are mean ± SD unless otherwise indicated.

†Percentages may not total 100.0% because of rounding.

‡Includes American Indian or Alaska Native, Native Hawaiian or other Pacific islander, multiple, other, or not reported.

Canagliflozin 100 and 300 mg showed numerical increases in HDL-C and decreases in triglycerides relative to placebo at week 26, but these differences did not reach statistical significance (Table 4). A numerical increase in low-density lipoprotein cholesterol (LDL-C) was observed for canagliflozin 300 mg compared with canagliflozin 100 mg and placebo at week 26, with a smaller per cent increase in non–HDL-C and no notable per cent change in the LDL-C/HDL-C ratio. At week 52, increases from baseline in HDL-C and triglycerides were seen with both canagliflozin doses compared with placebo (Table 5). Changes in HDL-C at week 52 were similar to those seen at week 26, with a slightly larger per cent increase seen with canagliflozin at week 52 relative to week 26. At week 52, an increase in LDL-C compared with placebo was observed with canagliflozin 300 mg, with an increase in non–HDL-C that was smaller than that observed with LDL-C; no notable changes in LDL-C or non–HDL-C were seen with canagliflozin 100 mg relative to placebo. A larger increase in the per cent change in LDL-C from baseline from week 26 to week 52 was seen with canagliflozin 300 mg compared with canagliflozin 100 mg and placebo. The ratio of LDL-C/HDL-C was slightly decreased with canagliflozin 100 mg relative to placebo, with minimal change seen with canagliflozin 300 mg.

Glucose-related FS-MMTT end-points

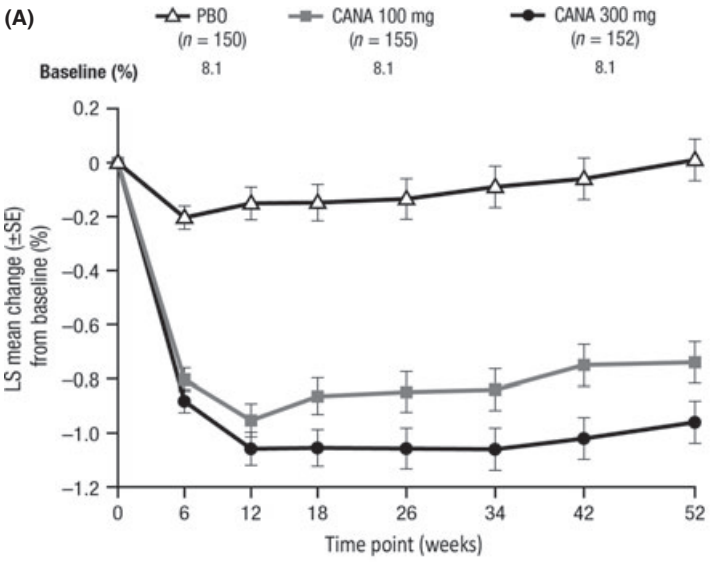
In the subset of patients who underwent the FS-MMTT, dose-related reductions were observed in 2-h PPG at week 26 with canagliflozin compared with placebo (Table 6). Relative to placebo, reductions from baseline in both the total AUC_G and ΔAUC_G were observed with both canagliflozin groups.

Indices of β-cell function

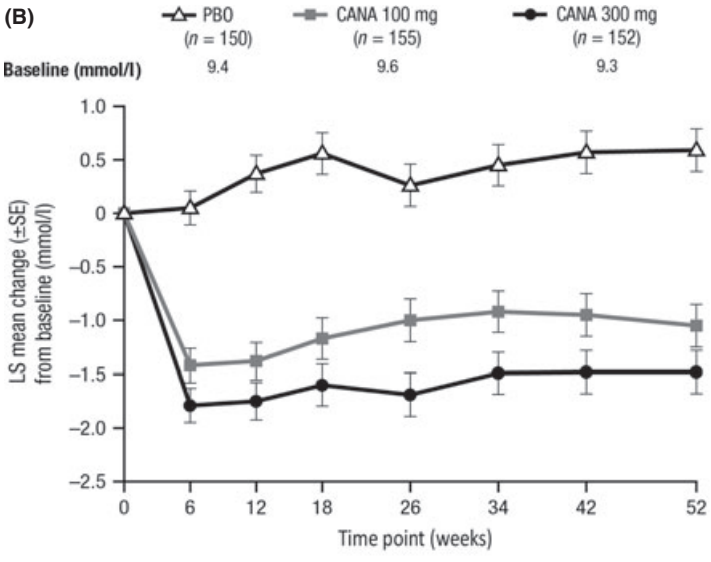
At week 26, improvements in β-cell function were observed with both canagliflozin doses compared with placebo. Canagliflozin was associated with increases in HOMA2-%B among patients who participated in the FS-MMTT (Table 6). Minimal changes from baseline in AUC_C were seen across groups. Numerical increases in the ratio of AUC_C to AUC_G were seen with canagliflozin 100 and 300 mg compared with placebo.

Safety and tolerability

The overall incidence of AEs was similar across treatment groups over the 52-week treatment period (Table 7). The incidence of AEs leading to study discontinuation was slightly higher with canagliflozin compared with placebo; serious AE rates were higher with placebo than with both doses of canagliflozin. During the extension period, overall incidences of



	Week 26		Week 52	
	LS mean change, %	Difference vs PBO, % (95% CI)	LS mean change, %	Difference vs PBO, % (95% CI)
PBO	−0.13		0.01	
CANA 100 mg	−0.85	−0.71 (−0.90, −0.52)*	−0.74	−0.75 (−0.95, −0.55)
CANA 300 mg	−1.06	−0.92 (−1.11, −0.73)*	−0.96	−0.97 (−1.17, −0.77)



	Week 26		Week 52	
	LS mean change, mmol/l	Difference vs PBO, mmol/l (95% CI)	LS mean change, mmol/l	Difference vs PBO, mmol/l (95% CI)
PBO	0.2		0.6	
CANA 100 mg	−1.0	−1.2 (−1.7, −0.7)*	−1.1	−1.6 (−2.1, −1.1)
CANA 300 mg	−1.7	−1.9 (−2.4, −1.4)*	−1.5	−2.1 (−2.6, −1.6)

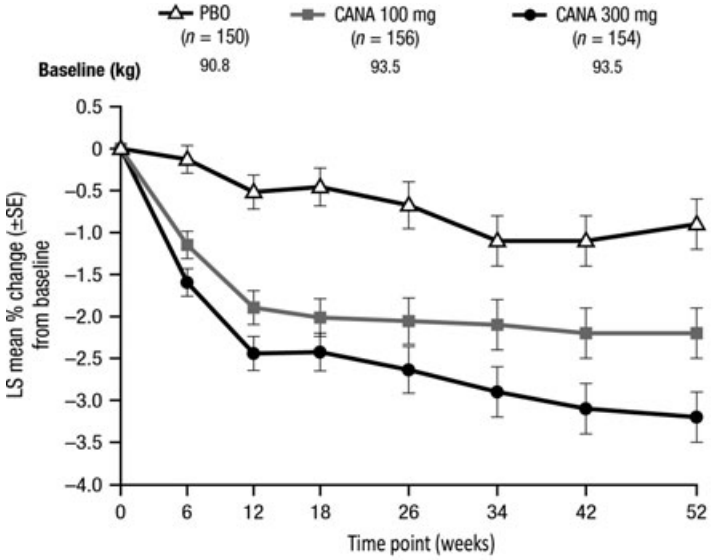
Figure 2 Effects on glycaemic parameters (LOCF). Changes in HbA_{1c} (A) and FPG (B). LOCF, last observation carried forward; FPG, fasting plasma glucose; PBO, placebo; CANA, canagliflozin; LS, least squares; SE, standard error; CI, confidence interval. *$p < 0.001$

AEs were higher with canagliflozin 100 and 300 mg compared with placebo (Table 8). Incidences of AEs leading to study discontinuation during the extension period were low and similar across groups; serious AE rates were higher with placebo relative to canagliflozin 100 and 300 mg. Only one serious AE

Table 3 Summary of changes from baseline in HbA_{1c} at week 26 in baseline HbA_{1c} subgroups (LOCF)

	PBO	CANA 100 mg	CANA 300 mg
Baseline HbA_{1c} < 8.0%, n	74	73	74
Mean ± SD baseline (%)	7.4 ± 0.3	7.3 ± 0.4	7.4 ± 0.3
LS mean ± SE change	–0.02 ± 0.10	–0.47 ± 0.09	–0.67 ± 0.09
Difference vs. PBO (95% CI)		–0.45 (–0.69, –0.21)	–0.64 (–0.88, –0.40)
Baseline HbA_{1c} ≥ 8.0% to < 9.0%, n	48	51	49
Mean ± SD baseline (%)	8.4 ± 0.3	8.4 ± 0.3	8.4 ± 0.3
LS mean ± SE change	–0.12 ± 0.12	–1.02 ± 0.13	–1.30 ± 0.12
Difference vs. PBO (95% CI)		–0.90 (–1.21, –0.58)	–1.18 (–1.49, –0.87)
Baseline HbA_{1c} ≥ 9.0%, n	28	31	29
Mean ± SD baseline (%)	9.5 ± 0.7	9.6 ± 0.4	9.6 ± 0.5
LS mean ± SE change	–0.44 ± 0.22	–1.55 ± 0.22	–1.59 ± 0.24
Difference vs. PBO (95% CI)		–1.11 (–1.68, –0.53)	–1.15 (–1.74, –0.56)

LOCF, last observation carried forward; PBO, placebo; CANA, canagliflozin; SD, standard deviation; LS, least squares; SE, standard error; CI, confidence interval.



	Week 26		Week 52	
	LS mean % change	Difference vs PBO, % (95% CI)	LS mean % change	Difference vs PBO, % (95% CI)
PBO	–0.7		–0.9	
CANA 100 mg	–2.1	–1.4 (–2.1, –0.7)*	–2.2	–1.3 (–2.1, –0.5)
CANA 300 mg	–2.6	–2.0 (–2.7, –1.3)*	–3.2	–2.2 (–3.0, –1.4)
	LS mean change, kg	Difference vs PBO, kg (95% CI)	LS mean change, kg	Difference vs PBO, kg (95% CI)
PBO	–0.8		–1.0	
CANA 100 mg	–1.9	–1.1 (–1.8, –0.3)	–2.0	–1.0 (–1.8, –0.2)
CANA 300 mg	–2.5	–1.7 (–2.5, –1.0)	–3.1	–2.1 (–2.9, –1.2)

Figure 3 Per cent change in body weight (LOCF). LOCF, last observation carried forward; PBO, placebo; CANA, canagliflozin; LS, least squares; SE, standard error; CI, confidence interval. *p < 0.001

was considered by the investigator as drug-related in this study, a serious AE of UTI that led to a hospitalisation in a patient in the canagliflozin 300 mg group.

Over 52 weeks, both canagliflozin doses were associated with higher rates of AEs consistent with genital mycotic infections in women and men compared with placebo (Table 7). These were generally

Table 4 Summary of changes from baseline in blood pressure and fasting plasma lipids at week 26 (LOCF)

	PBO	CANA 100 mg	CANA 300 mg
Systolic BP, n	150	156	154
Mean ± SD baseline (mmHg)	130.1 ± 13.7	130.4 ± 13.5	130.8 ± 12.8
LS mean ± SE change	–2.7 ± 1.0	–4.9 ± 1.0	–4.3 ± 1.0
Difference vs. PBO (95% CI)		–2.2 (–4.7, 0.2)*	–1.6 (–4.1, 0.9)*
Diastolic BP, n	150	156	154
Mean ± SD baseline (mmHg)	79.0 ± 8.3	78.2 ± 8.3	78.9 ± 8.1
LS mean ± SE change	–1.7 ± 0.6	–2.9 ± 0.6	–2.3 ± 0.6
Difference vs. PBO (95% CI)		–1.1 (–2.7, 0.4)†	–0.5 (–2.1, 1.0)†
Triglycerides, n	134	145	142
Mean ± SD baseline (mmol/l)	2.2 ± 1.5	2.1 ± 1.3	2.3 ± 1.5
LS mean ± SE change	0.12 ± 0.09	0.02 ± 0.09	–0.07 ± 0.09
Median (IQR) per cent change	0.3 (–18.5, 28.1)	–2.3 (–21.1, 19.7)	–3.4 (–26.4, 32.7)
LS mean ± SE per cent change	11.6 ± 4.2	5.4 ± 4.2	8.5 ± 4.2
Difference vs. PBO (95% CI)		–6.2 (–16.9, 4.5)*	–3.1 (–13.8, 7.7)*
LDL-C, n	134	145	139
Mean ± SD baseline (mmol/l)	2.8 ± 1.0	2.7 ± 1.1	2.6 ± 0.9
LS mean ± SE change	0.00 ± 0.06	–0.02 ± 0.06	0.11 ± 0.06
Median (IQR) per cent change	0.2 (–12.8, 12.3)	1.9 (–9.4, 16.9)	5.3 (–10.0, 21.4)
LS mean ± SE per cent change	3.3 ± 2.5	3.8 ± 2.5	7.8 ± 2.5
Difference vs. PBO (95% CI)		0.5 (–5.8, 6.8)†	4.6 (–1.8, 10.9)†
HDL-C, n	135	145	141
Mean ± SD baseline (mmol/l)	1.2 ± 0.3	1.2 ± 0.3	1.1 ± 0.3
LS mean ± SE change	0.02 ± 0.02	0.06 ± 0.02	0.06 ± 0.02
Median (IQR) per cent change	1.8 (–6.7, 10.3)	3.6 (–3.8, 14.5)	6.9 (–2.3, 15.4)
LS mean ± SE per cent change	3.1 ± 1.3	5.7 ± 1.3	6.6 ± 1.3
Difference vs. PBO (95% CI)		2.6 (–0.8, 6.0)*	3.5 (0.1, 7.0)*
LDL-C/HDL-C, n	134	145	139
Mean ± SD baseline (mol/mol)	2.4 ± 0.9	2.4 ± 1.1	2.4 ± 0.9
LS mean ± SE change	–0.03 ± 0.05	–0.14 ± 0.05	–0.04 ± 0.05
Median (IQR) per cent change	0.6 (–15.8, 14.3)	–4.4 (–17.4, 10.6)	–2.0 (–16.1, 13.8)
LS mean ± SE per cent change	1.9 ± 2.5	–0.8 ± 2.5	2.2 ± 2.5
Difference vs. PBO (95% CI)		–2.7 (–8.9, 3.6)†	0.3 (–6.0, 6.6)†
Non–HDL-C, n	133	145	141
Mean ± SD baseline (mmol/l)	3.8 ± 1.2	3.6 ± 1.3	3.7 ± 1.1
LS mean ± SE change	0.02 ± 0.07	–0.05 ± 0.06	0.09 ± 0.06
Median (IQR) per cent change	0.0 (–11.6, 10.1)	–0.9 (–8.1, 10.9)	2.0 (–9.2, 16.0)
LS mean ± SE per cent change	2.9 ± 1.9	1.5 ± 1.8	5.6 ± 1.8
Difference vs. PBO (95% CI)		–1.4 (–6.1, 3.3)†	2.7 (–2.0, 7.4)†

LOCF, last observation carried forward; PBO, placebo; CANA, canagliflozin; BP, blood pressure; SD, standard deviation; LS, least squares; SE, standard error; CI, confidence interval; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; NS, not significant.

*p = NS vs. PBO.

†Statistical comparison vs. PBO not performed (not prespecified).

mild to moderate in severity and resulted in study discontinuation in very few patients (three women and one man); most of these events were reported during the first 26 weeks of treatment. All canagliflozin-treated men with genital mycotic infections were uncircumcised, and 3 of the 11 men had a prior history of balanitis/balanoposthitis. A prior history of genital mycotic infection was also more common in women in the canagliflozin groups with a genital mycotic infection AE (36%) compared with women who received canagliflozin and did not have such an AE (17%). Genital mycotic infections were generally treated with antifungal therapies (topical and/or oral), either prescribed by the healthcare provider or self-initiated by the patient, without interruption of study drug. Incidences of UTIs were similar across treatment groups over 52 weeks.

Table 5 Summary of changes from baseline in blood pressure and fasting plasma lipids at week 52 (LOCF)

	PBO	CANA 100 mg	CANA 300 mg
Systolic BP, n	150	156	154
Mean ± SD baseline (mmHg)	130.1 ± 13.7	130.4 ± 13.5	130.8 ± 12.8
LS mean ± SE change	0.1 ± 1.0	–3.7 ± 1.0	–2.9 ± 1.0
Difference vs. PBO (95% CI)		–3.7 (–6.2, –1.3)	–3.0 (–5.5, –0.5)
Diastolic BP, n	150	156	154
Mean ± SD baseline (mmHg)	79.0 ± 8.3	78.2 ± 8.3	78.9 ± 8.1
LS mean ± SE change	–0.7 ± 0.6	–2.2 ± 0.6	–1.7 ± 0.6
Difference vs. PBO (95% CI)		–1.6 (–3.2, 0.1)	–1.1 (–2.7, 0.5)
Triglycerides, n	134	145	144
Mean ± SD baseline (mmol/l)	2.2 ± 1.5	2.1 ± 1.3	2.3 ± 1.5
LS mean ± SE change	0.03 ± 0.10	0.04 ± 0.10	–0.14 ± 0.10
Median (IQR) per cent change	–1.2 (–18.7, 22.7)	5.3 (–19.0, 24.8)	0.2 (–27.6, 23.7)
LS mean ± SE per cent change	4.7 ± 4.6	8.5 ± 4.6	6.7 ± 4.5
Difference vs. PBO (95% CI)		3.8 (–7.8, 15.4)	2.0 (–9.6, 13.6)
LDL-C, n	134	145	144
Mean ± SD baseline (mmol/l)	2.8 ± 1.0	2.7 ± 1.1	2.6 ± 0.9
LS mean ± SE change	0.05 ± 0.06	0.01 ± 0.06	0.22 ± 0.06
Median (IQR) per cent change	0.2 (–12.9, 12.3)	3.6 (–11.2, 17.9)	6.7 (–5.0, 27.6)
LS mean ± SE per cent change	5.4 ± 2.8	4.8 ± 2.8	13.3 ± 2.8
Difference vs. PBO (95% CI)		–0.6 (–7.7, 6.5)	7.9 (0.8, 15.0)
HDL-C, n	135	145	144
Mean ± SD baseline (mmol/l)	1.2 ± 0.3	1.2 ± 0.3	1.1 ± 0.3
LS mean ± SE change	0.03 ± 0.02	0.07 ± 0.01	0.09 ± 0.01
Median (IQR) per cent change	0.0 (–7.0, 10.3)	5.4 (–2.2, 14.3)	7.3 (–2.0, 16.0)
LS mean ± SE per cent change	3.3 ± 1.3	6.6 ± 1.3	8.2 ± 1.3
Difference vs. PBO (95% CI)		3.2 (–0.1, 6.5)	4.9 (1.6, 8.2)
LDL-C/HDL-C, n	134	145	144
Mean ± SD baseline (mol/mol)	2.4 ± 0.9	2.4 ± 1.1	2.4 ± 0.9
LS mean ± SE change	0.00 ± 0.06	–0.15 ± 0.06	0.03 ± 0.05
Median (IQR) per cent change	0.3 (–17.0, 14.3)	–3.3 (–17.7, 13.3)	1.5 (–12.2, 17.8)
LS mean ± SE per cent change	3.7 ± 2.7	–0.3 ± 2.7	5.1 ± 2.6
Difference vs. PBO (95% CI)		–4.0 (–10.8, 2.8)	1.4 (–5.4, 8.2)
Non–HDL-C, n	133	145	144
Mean ± SD baseline (mmol/l)	3.8 ± 1.2	3.6 ± 1.3	3.7 ± 1.1
LS mean ± SE change	0.07 ± 0.07	–0.02 ± 0.07	0.14 ± 0.07
Median (IQR) per cent change	–0.2 (–9.8, 10.6)	0.8 (–9.2, 14.7)	4.9 (–10.3, 22.0)
LS mean ± SE per cent change	3.9 ± 2.1	2.5 ± 2.1	7.5 ± 2.1
Difference vs. PBO (95% CI)		–1.5 (–6.9, 3.9)	3.6 (–1.8, 9.0)

LOCF, last observation carried forward; PBO, placebo; CANA, canagliflozin; BP, blood pressure; SD, standard deviation; LS, least squares; SE, standard error; CI, confidence interval; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

Canagliflozin 100 and 300 mg were associated with higher rates of AEs reflecting osmotic diuresis [e.g. pollakiuria (increased urine frequency), polyuria (increased urine volume)] over 52 weeks (Table 7). Incidences of these events were low (< 4% per specific AE) and led to few study discontinuations. Incidences of AEs possibly related to volume depletion (e.g. postural dizziness, orthostatic hypotension) were low and similar across treatment groups. More patients treated with canagliflozin 100 and 300 mg than placebo had ≥ 1 documented hypoglycaemia episode (33.8%, 36.5% and 17.9%, respectively) over 52 weeks of treatment (Table 7); differences (95% CI) vs. placebo were 15.8% (5.6, 26.0) for canagliflozin 100 mg and 18.6% (8.3, 28.9) for canagliflozin 300 mg. One patient in each treatment group experienced a severe hypoglycaemia event.

Overall, there were only minor differences seen in mean per cent changes in laboratory parameters with canagliflozin compared with placebo over

Table 6 Summary of changes from baseline in glucose-related FS-MMTT end-points and indices of β-cell function at week 26 (LOCF)*

	PBO	CANA 100 mg	CANA 300 mg
Two-hour PPG, n†	38	46	38
Mean ± SD baseline (mmol/l)	15.5 ± 3.4	16.5 ± 3.7	16.0 ± 4.0
LS mean ± SE change	–1.1 ± 0.6	–2.6 ± 0.6	–3.1 ± 0.6
Difference vs. PBO (95% CI)		–1.5 (–3.0, –0.1)	–2.1 (–3.6, –0.5)
$AUC_{G(0–3\ h)}$, n†	34	41	36
Mean ± SD baseline (mmol/l·h)	41.4 ± 8.2	44.0 ± 9.3	43.3 ± 8.9
LS mean ± SE change	–4.3 ± 1.4	–6.3 ± 1.3	–9.2 ± 1.4
Difference vs. PBO (95% CI)		–2.0 (–5.5, 1.6)	–4.9 (–8.5, –1.3)
$\Delta AUC_{G(0–3\ h)}$, n†	34	41	36
Mean ± SD baseline (mmol/l·h)	13.6 ± 4.5	14.5 ± 4.7	14.6 ± 4.8
LS mean ± SE change	–1.8 ± 0.8	–2.5 ± 0.8	–3.3 ± 0.8
Difference vs. PBO (95% CI)		–0.8 (–2.8, 1.2)	–1.6 (–3.6, 0.5)
HOMA2-%B, n	129	133	133
Mean ± SD baseline	55.4 ± 38.1	51.3 ± 32.3	53.0 ± 28.0
LS mean ± SE change	–1.0 ± 4.8	12.3 ± 4.9	25.9 ± 4.8
Difference vs. PBO (95% CI)		13.3 (1.1, 25.5)	26.9 (14.7, 39.1)
$AUC_{C(0–3\ h)}$, n†	33	41	36
Mean ± SD baseline (nmol/l·h)	4.9 ± 2.0	5.3 ± 2.4	4.9 ± 2.5
LS mean ± SE change	–0.4 ± 0.2	–0.1 ± 0.2	–0.3 ± 0.2
Difference vs. PBO (95% CI)		0.3 (–0.2, 0.8)	0.1 (–0.4, 0.7)
AUC_C/AUC_G ratio, n†	33	40	35
Mean ± SD baseline (pmol/mmol)	123.1 ± 51.6	131.7 ± 79.8	122.5 ± 72.3
LS mean ± SE change	–3.4 ± 10.6	23.7 ± 10.5	24.0 ± 11.1
Difference vs. PBO (95% CI)		27.1 (–0.2, 54.4)	27.4 (–0.7, 55.6)

FS-MMTT, frequently-sampled mixed-meal tolerance test; LOCF, last observation carried forward; PBO, placebo; CANA, canagliflozin; PPG, postprandial glucose; SD, standard deviation; LS, least squares; SE, standard error; CI, confidence interval; AUC_G, glucose area under the curve; ΔAUC_G, incremental glucose area under the curve; HOMA, Homeostasis Model Assessment; AUC_C, C-peptide area under the curve.

*Statistical comparison for CANA 100 and 300 mg vs. PBO not performed (not prespecified).

†Assessed in patients who participated in the FS-MMTT.

52 weeks (Table 9). Canagliflozin 100 and 300 mg were associated with moderate reductions from baseline in alanine aminotransferase (–3.8% and –9.7%, respectively), while a modest increase was seen with placebo (6.6%). Moderate reductions in gamma glutamyl transferase were also observed with canagliflozin 100 and 300 mg compared with an increase seen with placebo (–12.3%, –8.6%, and 36.0%, respectively). Small increases in serum creatinine were seen with canagliflozin 300 mg relative to canagliflozin 100 mg and placebo (7.7%, 2.5%, and 2.8%, respectively), with commensurate decreases observed in eGFR (–5.8%, –1.6%, and –1.9%, respectively). Moderate increases in blood urea nitrogen were observed for canagliflozin 100 and 300 mg compared with placebo (14.5%, 17.5%, and 5.5%, respectively). Decreases in serum urate were seen with canagliflozin 100 and 300 mg compared with placebo (–8.8%, –9.4%, and 0.7%, respectively). Small increases in haemoglobin were observed with canagliflozin 100 and 300 mg compared with a slight decrease seen with placebo (4.2%, 4.4%, and –1.6%, respectively). No meaningful changes from baseline were observed in serum electrolytes, including chloride, potassium, sodium, or phosphate (Table 9). A small to moderate increase in magnesium was observed with canagliflozin 100 and 300 mg compared with a slight decrease seen with placebo (7.1%, 9.7%, and –1.1%, respectively).

Discussion

Over time, many T2DM patients require a combination of therapies, and eventually insulin, to maintain glycaemic control (2). Some currently available OADs are associated with adverse effects, including weight gain and increased risk of hypoglycaemia that can limit efficacy. In this study of

Table 7 Summary of overall safety and selected AEs over 52 weeks*

Patients, n (%)	PBO (n = 156)	CANA 100 mg (n = 157)	CANA 300 mg (n = 156)
Any AE	111 (71.2)	106 (67.5)	114 (73.1)
AEs leading to discontinuation	7 (4.5)	11 (7.0)	12 (7.7)
AEs related to study drug†	24 (15.4)	41 (26.1)	57 (36.5)
Serious AEs	13 (8.3)	7 (4.5)	8 (5.1)
Deaths	0	0	0
Selected AEs			
UTI	12 (7.7)	13 (8.3)	13 (8.3)
Genital mycotic infection			
Men‡,§	1 (1.3)	6 (7.9)	5 (5.7)
Women¶,**	4 (5.0)	15 (18.5)	13 (18.8)
Osmotic diuresis-related AEs††	3 (1.9)	9 (5.7)	11 (7.1)
Volume-related AEs‡‡	3 (1.9)	1 (0.6)	6 (3.8)
Documented hypoglycaemia episodes§§	28 (17.9)	53 (33.8)	57 (36.5)
Severe episodes	1 (0.6)	1 (0.6)	1 (0.6)

AE, adverse event; PBO, placebo; CANA, canagliflozin; UTI, urinary tract infection.
*All AEs are reported for regardless of rescue medication; hypoglycaemia episodes are reported for prior to rescue medication.
†Possibly, probably, or very likely related to study drug, as assessed by investigators.
‡PBO, n = 76; CANA 100 mg, n = 76; CANA 300 mg, n = 87.
§Including balanitis, balanitis candida, and balanoposthitis.
¶PBO, n = 80; CANA 100 mg, n = 81; CANA 300 mg, n = 69.
**Including vaginal infection, vulvitis, vulvovaginal candidiasis, vulvovaginal mycotic infection, and vulvovaginitis.
††Including dry mouth, nocturia, pollakiuria, polyuria, thirst, and urine output increased.
‡‡Including dizziness postural, hypotension, orthostatic hypotension, and syncope.
§§Including biochemically documented episodes (≤ 3.9 mmol/l) with or without symptoms and severe episodes (i.e. requiring the assistance of another individual or resulting in seizure or loss of consciousness).

patients with T2DM inadequately controlled with metformin plus sulphonylurea, treatment with canagliflozin 100 and 300 mg improved glycaemic control and reduced body weight compared with placebo over 52 weeks.

The reductions in HbA_{1c} seen with canagliflozin 100 and 300 mg relative to placebo over 52 weeks in a patient population with baseline HbA_{1c} values reflecting only mild to moderate hyperglycaemia suggest clinically valuable efficacy (22). HbA_{1c} and FPG profiles over time demonstrated sustained effects of canagliflozin over the 52-week treatment period. Canagliflozin also provided reductions compared with placebo in 2-h PPG, AUC_G, and ΔAUC_G at week 26 in patients who underwent the FS-MMTT. Improvements in glycaemic control have also been observed with other SGLT2 inhibitors (18,23–25).

In addition, canagliflozin 100 and 300 mg showed greater body weight reduction compared with placebo over 52 weeks. While body composition measurements were not performed in this study, analyses conducted in other Phase 3 studies in patients with T2DM showed that approximately two-thirds of the reduction in body mass seen with canagliflozin was from fat mass and one-third was from lean body mass (9,26). In clinical studies of weight loss, modest reductions in body weight have been associated with favourable improvements in cardiovascular risk factors, including lipids, BP, and inflammatory markers (27). While the mechanism of weight loss with canagliflozin remains to be fully determined, it is likely related to the loss of calories associated with UGE.

Canagliflozin was also associated with a decrease in systolic BP and an increase in HDL-C compared with placebo over 52 weeks; only slight changes from baseline were seen in triglycerides across treatment groups. Canagliflozin 300 mg was associated with an increase in LDL-C compared with placebo at week 52, with an increase in non–HDL-C that was smaller than that observed with LDL-C; similar changes in LDL-C and non–HDL-C were seen with canagliflozin 100 mg and placebo. Minimal changes in LDL-C/HDL-C ratio were seen with canagliflozin 300 mg; a slight decrease was seen with canagliflozin 100 mg relative to placebo. While the mechanism of LDL-C increase with canagliflozin is unknown, it may reflect downstream metabolic effects of UGE, as well as modest haemoconcentration resulting from canagli-

Table 8 Summary of overall safety and selected AEs during the 26-week double-blind extension period (weeks 26–52)*

Patients, n (%)	PBO (n = 156)	CANA 100 mg (n = 157)	CANA 300 mg (n = 156)
Any AE	53 (44.5)	64 (50.4)	72 (56.3)
AEs leading to discontinuation	2 (1.7)	2 (1.6)	3 (2.3)
AEs related to study drug†	4 (3.4)	11 (8.7)	21 (16.4)
Serious AEs	6 (5.0)	3 (2.4)	2 (1.6)
Deaths	0	0	0
Selected AEs			
UTI	4 (3.4)	4 (3.1)	5 (3.9)
Genital mycotic infection			
Men‡,§	0	1 (1.6)	3 (4.2)
Women¶,**	0	4 (6.2)	2 (3.5)
Osmotic diuresis-related AEs††	0	1 (0.8)	1 (0.8)
Volume-related AEs‡‡	1 (0.8)	1 (0.8)	3 (2.3)
Documented hypoglycaemia episodes§§	10 (9.7)	28 (22.4)	34 (27.2)
Severe episodes	0	0	1 (0.8)

AE, adverse event; PBO, placebo; CANA, canagliflozin; UTI, urinary tract infection.
*All AEs are reported for regardless of rescue medication; hypoglycaemia episodes are reported for prior to rescue medication.
†Possibly, probably or very likely related to study drug, as assessed by investigators.
‡PBO, n = 61; CANA 100 mg, n = 62; CANA 300 mg, n = 71.
§Including balanitis.
¶PBO, n = 58; CANA 100 mg, n = 65; CANA 300 mg, n = 57.
**Including vulvitis, vulvovaginal candidiasis, and vulvovaginal mycotic infection.
††Including dry mouth and urine output increased.
‡‡Including dizziness postural, hypotension, and syncope.
§§Including biochemically documented episodes (≤ 3.9 mmol/l) with or without symptoms and severe episodes (i.e. requiring the assistance of another individual or resulting in seizure or loss of consciousness).

flozin's osmotic diuretic effect (which has been reported with diuretic agents) (28). The clinical implications of changes in glycaemic control, body weight, BP, and lipids with canagliflozin are being assessed in the ongoing CANagliflozin cardioVascular Assessment Study (CANVAS). In a meta-analysis of cardiovascular events across the canagliflozin Phase 3 clinical trial program, no increase in cardiovascular risk was observed with canagliflozin treatment (29).

Progressive β-cell dysfunction is believed to be a critical factor in the pathogenesis of hyperglycaemia in T2DM; since glucotoxicity further reduces β-cell dysfunction, a vicious cycle ensues that contributes to this progressive loss of function (30). By decreasing hyperglycaemia through a non–insulin-dependent mechanism, canagliflozin may indirectly improve β-cell function, but whether this will translate into a reduction in the rate of progression of T2DM requires further study. In this study, canagliflozin was associated with improvements in measures of β-cell function (HOMA2-%B and AUC_C/AUC_G ratio) compared with placebo at week 26. These findings are consistent with improvements in measures of β-cell function expected with glucose-lowering therapy and observed in previous studies evaluating canagliflozin in patients with T2DM (5,31–33). The improvements in indices of β-cell function with canagliflozin were because of stable C-peptide concentrations in the presence of decreased plasma glucose concentrations, similar to observations with other antidiabetic agents known to increase β-cell function (34–36).

Canagliflozin 100 and 300 mg were generally well tolerated over 52 weeks, consistent with previous reports (5). Canagliflozin was associated with higher rates of genital mycotic infections; these were generally mild or moderate in severity, treated by antifungal therapies, and led to few study discontinuations. Because of its mechanism of action, canagliflozin treatment results in osmotic diuresis; incidences of AEs related to osmotic diuresis (e.g. pollakiuria, polyuria) were low in this study but were increased with canagliflozin compared with placebo. However, AEs related to volume depletion (e.g. postural dizzi-

Table 9 Mean per cent changes in clinical laboratory parameters from baseline to week 52

Parameter	PBO	CANA 100 mg	CANA 300 mg
ALT, n	88	107	108
Mean baseline (U/l)	28.6	29.4	29.7
Mean (SD) per cent change	6.6 ± 48.2	–3.8 ± 31.5	–9.7 ± 33.2
BUN, n	89	108	109
Mean baseline (mmol/l)	5.6	5.5	5.6
Mean (SD) per cent change	5.5 ± 24.5	14.5 ± 29.0	17.5 ± 29.3
Chloride	89	108	109
Mean baseline (mmol/l)	101.6	101.4	101.5
Mean (SD) per cent change	0.1 ± 2.9	0.6 ± 2.6	0.6 ± 2.3
Creatinine	89	108	109
Mean baseline (μmol/l)	72.9	70.3	71.3
Mean (SD) per cent change	2.8 ± 12.2	2.5 ± 11.8	7.7 ± 20.5
eGFR, n	89	108	109
Mean baseline (ml/min/1.73 m^2)	87.4	91.0	91.9
Mean (SD) per cent change	–1.9 ± 12.9	–1.6 ± 13.7	–5.8 ± 14.5
Magnesium, n	89	108	109
Mean baseline (mmol/l)	0.8	0.8	0.8
Mean (SD) per cent change	–1.1 ± 7.8	7.1 ± 10.3	9.7 ± 9.5
Phosphate, n	89	108	109
Mean baseline (mmol/l)	1.2	1.2	1.2
Mean (SD) per cent change	4.6 ± 15.0	2.2 ± 14.6	4.2 ± 14.5
Potassium, n	89	108	109
Mean baseline (mmol/l)	4.4	4.4	4.4
Mean (SD) per cent change	1.7 ± 9.9	1.3 ± 10.0	0.6 ± 8.7
Sodium, n	89	108	109
Mean baseline (mmol/l)	139.4	139.6	139.5
Mean (SD) per cent change	0.7 ± 2.4	0.7 ± 1.9	0.5 ± 1.8
Urate, n	89	108	109
Mean baseline (μmol/l)	332.9	322.3	340.1
Mean (SD) per cent change	0.7 ± 20.2	–8.8 ± 20.4	–9.4 ± 17.5
Haemoglobin, n	86	105	107
Mean baseline (g/l)	142.4	140.1	141.4
Mean (SD) per cent change	–1.6 ± 6.0	4.2 ± 5.7	4.4 ± 5.8

PBO, placebo; CANA, canagliflozin; ALT, alanine aminotransferase; SD, standard deviation; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.

ness, hypotension) were generally low and similar across treatment groups. Consistent with the small decrease in fluid volume with canagliflozin, a moderate increase in blood urea nitrogen and a smaller change in serum creatinine were seen. The overall safety and tolerability findings observed with canagliflozin were generally consistent with those seen with other SGLT2 inhibitors (18,23–25).

An increased incidence of hypoglycaemia relative to placebo was seen with canagliflozin, but the rate of severe events was not increased. This was not unexpected, as prior studies have shown an increase in hypoglycaemia events when antihyperglycaemic agents that are not generally associated with hypoglycaemia are added to treatment regimens associated with hypoglycaemia, including sulphonylurea and insulin therapy (21,37–40). In patients with T2DM, canagliflozin has been shown to reduce RT_G to approximately 4.4–5.0 mmol/l (80–90 mg/dl) (5,41), a range that is above the threshold for hypoglycaemia [≤ 3.9 mmol/l (70 mg/dl)]. Other Phase 3 studies conducted in patients with T2DM have shown a low incidence of hypoglycaemia with canagliflozin when not used in combination with agents that are associated with hypoglycaemia (6,7,9,10). In a study comparing canagliflozin 300 mg with sitagliptin 100 mg (an agent considered to be associated with a low hypoglycaemia risk) in patients with T2DM on background metformin and sulphonylurea, a similar incidence of documented hypoglycaemia was seen with the two agents, despite a 0.4% greater reduction in HbA_{1c} seen with canagliflozin vs. sitagliptin (8). In

practice, it will be important for clinicians to consider the risk of hypoglycaemia if canagliflozin is added to the combination of metformin and a sulphonylurea and recommend appropriate glucose monitoring with consideration of lowering the dose of sulphonylurea if hypoglycaemia occurs.

One limitation of this study was the lack of an active comparator group, but a separate Phase 3 study has evaluated the efficacy of canagliflozin 300 mg vs. sitagliptin 100 mg in patients on background metformin plus sulphonylurea (8). In addition, this study enrolled patients inadequately controlled on metformin plus sulphonylurea with a reasonably wide range of baseline HbA_{1c} ($\geq$ 7.0% to $\leq$ 10.5%); thus, these results may not be generalisable to patients on other background antihyperglycaemic agents or those with milder or more severe hyperglycaemia at baseline. Longer term studies are also needed to evaluate the durability of effects associated with canagliflozin treatment.

In conclusion, canagliflozin 100 and 300 mg improved glycaemic control, reduced body weight, and were generally well tolerated compared with placebo over 52 weeks in patients with T2DM inadequately controlled with metformin plus sulphonylurea. Canagliflozin may therefore provide a new treatment option for this patient population. Results from ongoing Phase 3 studies will provide greater insight into the long-term efficacy and safety of canagliflozin in various T2DM treatment settings.

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Author contributions

J.W., G.C., P.H., G.G., C.M., F.V., S.B., and G.M. contributed to the conduct of the study and the acquisition, analysis, and interpretation of data, and reviewed and approved the manuscript. K.U. and W.C. contributed to the design and conduct of the study and the acquisition, analysis, and interpretation of data, and reviewed and approved the manuscript. G.L. contributed to the analysis and interpretation of data, and reviewed and approved the manuscript.

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