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ORIGINAL RESEARCH

Efficacy and Safety of Canagliflozin Used in Conjunction with Sulfonylurea in Patients with Type 2 Diabetes Mellitus: A Randomized, Controlled Trial

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ABSTRACT

Introduction: The efficacy and safety of canagliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, was evaluated in patients with type 2 diabetes mellitus (T2DM) inadequately controlled on sulfonylurea monotherapy.

Methods: The CANagliflozin cardioVascular Assessment Study (CANVAS) is a double-blind, placebo-controlled cardiovascular outcomes study that randomized participants to placebo or canagliflozin 100 or 300 mg once daily in addition to routine therapy. Participants in the CANVAS trial are men and women aged ≥30 years with T2DM and a history or high risk of cardiovascular disease, and inadequate glycemic control (glycated hemoglobin [HbA1c] ≥7.0% and ≤10.5%) on current

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On behalf of the CANVAS trial collaborative group.

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antihyperglycemic therapies. The primary objective of this prespecified substudy was to assess change from baseline to 18 weeks in HbA1c among patients on sulfonylurea monotherapy.

Results: Of the 4330 patients enrolled in CANVAS, 127 met the entry criteria for the sulfonylurea monotherapy substudy (placebo, $n = 45$; canagliflozin 100 mg, $n = 42$; canagliflozin 300 mg, $n = 40$). At 18 weeks, placebo-subtracted changes (95% confidence interval) in HbA1c were −0.74% (−1.15, −0.33; $P < 0.001$) and −0.83% (−1.24, −0.42; $P < 0.001$) with canagliflozin 100 and 300 mg, respectively. Relative to placebo, canagliflozin 100 and 300 mg also decreased fasting plasma glucose (FPG; −2.1 mmol/L [−3.0, −1.2] and −2.7 mmol/L [−3.6, −1.7], respectively). Body weight was lower with canagliflozin 300 mg (–1.8% [−3.2, −0.4]; $P = 0.014$) but unchanged with canagliflozin 100 mg (−0.4% [−1.8, 1.0]; $P = 0.557$). Canagliflozin 300 mg increased hypoglycemia episodes compared to canagliflozin 100 mg and placebo (15%, 0%, and 4.4%, respectively). Adverse events (AEs) of male and female genital mycotic infections, pollakiuria, and thirst were more common with canagliflozin.

Conclusions: Canagliflozin added to ongoing sulfonylurea monotherapy produced improvements in HbA1c, FPG, and body weight, with an increased incidence of AEs consistent with the mechanism of action of SGLT2 inhibition.

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Keywords: Canagliflozin; Cardiovascular disease; SGLT2 inhibitor; Sulfonylureas; Type 2 diabetes

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a progressive disease that often requires combination therapy with antihyperglycemic agents (AHAs) to achieve and maintain glycemic control [1]. Metformin is the most widely recommended initial monotherapy approach, but some patients are started first with sulfonylureas either for intolerance to metformin or because of physician and/or patient preferences despite the known adverse effects, such as hypoglycemia and weight gain [1]. As the sulfonylurea glucose-lowering effects are not sustained, many patients fail to achieve individualized glycemic targets and will need additional therapy [2, 3]. Accordingly, the availability of new agents that can lower blood glucose levels with good safety and tolerability, without increasing hypoglycemia risk and ideally neutralizing the sulfonylurea-induced weight gain, may have significant potential in the future management of the condition.

Canagliflozin is a sodium glucose co-transporter 2 (SGLT2) inhibitor approved in the United States and elsewhere as an adjunct to diet and exercise to improve glycemic control in adults with T2DM [4–17]. Treatment produces significant urinary glucose loss with beneficial effects on glycemic control, body weight, and blood pressure (BP) [5–17]. Small increases in low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) have been observed, with the ratio remaining unchanged [5–17].

Canagliflozin is not associated with hypoglycemia when used in isolation, although rates may be increased when used in conjunction with insulin or insulin secretagogues [5–17]. The risks of genital mycotic infections and lower urinary tract

infections, but not upper urinary tract infections, are elevated with canagliflozin [18, 19].

This report defines the effects of canagliflozin on indicators of glycemia, safety, and tolerability compared to placebo in a subset of patients who were on background sulfonylurea monotherapy in a prespecified substudy of the CANagliflozin cardioVascular Assessment Study (CANVAS).

METHODS

Overall Design of the CANVAS Trial

CANVAS is a randomized, double-blind, placebo-controlled, parallel-group, multicenter trial. A total of 4330 individuals have been randomized to placebo, canagliflozin 100 mg or canagliflozin 300 mg (Janssen Pharmaceuticals, Inc.; Titusville, NJ, USA) [20].

Objectives and Specific Hypotheses for the Sulfonylurea Substudy

The prespecified CANVAS sulfonylurea substudy was designed to determine the effects of canagliflozin when used in addition to sulfonylurea monotherapy on efficacy, safety, and tolerability in patients with T2DM with inadequate glycemic control at 18 weeks without compromising the masked study design of the entire study cohort. The objectives of the substudy were to assess the changes in glycated hemoglobin (HbA1c) and effects on safety and tolerability with canagliflozin 100 and 300 mg compared to placebo at 18 weeks. A greater reduction in HbA1c with each dose of canagliflozin compared to placebo was the primary hypothesis to be tested.

Secondary objectives of the substudy were to assess the effects of canagliflozin 100 and 300 mg compared to placebo on body weight, fasting plasma glucose (FPG), proportion of participants reaching HbA1c <7.0%, systolic and diastolic BP, fasting plasma lipids (i.e., triglycerides, HDL-C, LDL-C, total cholesterol, and LDL-C to HDL-C ratio) at 18 weeks. Prespecified hypotheses were evaluated for effects on body weight, FPG, proportion of participants reaching HbA1c <7.0%, systolic BP, triglycerides, and HDL-C.

Recruitment

Patient recruitment methods for CANVAS (ClinicalTrials.gov Identifier: NCT01032629) have been previously described [20].

Participant Inclusion and Exclusion Criteria

Participants in the CANVAS trial are men and women aged ≥30 years with T2DM with inadequate glycemic control (HbA1c ≥7.0% and ≤10.5%) on current antihyperglycemic therapies and at increased risk of cardiovascular disease [20]. The specific inclusion and exclusion criteria and the overall CANVAS trial design (including screening and run-in procedures, randomization, and follow-up procedures) have been previously published [20].

The subset included in the sulfonylurea substudy are the participants who were taking minimum or above specified doses of sulfonylurea monotherapy at baseline, specifically glipizide 20 mg, glipizide extended release 10 mg, glyburide/glibenclamide 10 mg, glimepiride 4 mg, gliclazide 160 mg, or gliclazide modified release (MR) 60 mg (i.e., at

least half the maximum labeled dose of sulfonylurea).

Background Drug Treatments

Participants were required to have stable background sulfonylurea monotherapy for 8 weeks prior to screening and to continue on the same sulphonylurea dose if at all possible for 18 weeks to allow for the evaluation of short-term effects of canagliflozin on biomarkers while participants were on stable background therapy. Criteria for the initiation of glycemic rescue therapy have been published [20]. In summary, glycemic rescue therapy was either up-titration of current sulfonylurea or the stepwise addition of non-insulin AHA(s), and then insulin therapies, instituted by investigators using local guidelines for glycemic targets.

Outcomes

The primary efficacy outcome for this substudy was change in HbA1c from baseline to week 18. The secondary efficacy outcomes evaluated at week 18 were body weight, FPG, proportion of participants reaching HbA1c <7.0%, systolic BP, triglycerides, and HDL-C.

Adverse events (AEs), including preidentified AEs of interest (i.e., genital mycotic infections, urinary tract infections, and AEs related to osmotic diuresis and reduced intravascular volume) were recorded. Hypoglycemia episodes were also reported and were defined as biochemically documented (concurrent finger-stick or plasma glucose ≤3.9 mmol/L, irrespective of symptoms) and severe (i.e., requiring the assistance of another individual or resulting in seizure or loss of consciousness).

Statistical Analyses

Efficacy and safety analyses were performed using the modified intent-to-treat population, consisting of all randomized patients who received ≥1 dose of study drug. The last observation carried forward approach was used to impute missing efficacy data. An analysis of covariance model including treatment as a fixed effect and corresponding baseline value as a covariate was used for primary and continuous secondary endpoints. Least squares means and 2-sided 95% confidence intervals (CIs) were calculated for the comparison of each canagliflozin dose versus placebo. A logistic regression model with treatment as a factor and baseline HbA1c as a covariate was used for the analysis of the proportion of patients reaching HbA1c <7.0%. A prespecified, hierarchical testing sequence was used to evaluate the prespecified 18-week hypotheses and estimate *P* values. For endpoints that were not prespecified for hypothesis testing, point estimates and 95% CIs are provided in lieu of *P* values. For patients who received rescue therapy, the last post-baseline value prior to the initiation of rescue therapy was used for analysis. Finally, the efficacy analyses were repeated for all CANVAS trial participants who recorded use of any sulfonylurea dose in monotherapy at baseline (data not shown, but conclusions not different). Data for other outcomes remain blinded. Statistical analyses were performed using SAS, version 9.2 (Cary, NC, USA).

Compliance with Ethics

The study is being conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013, and is consistent with Good Clinical

Practice. Regulatory approval for the conduct of the trial was obtained in each country, and ethics approval was received for every site prior to initiation. Informed consent was obtained from all patients included in the CANVAS trial.

RESULTS

During a recruitment period of 15 months, 7691 individuals were screened and 4330 were randomized (Fig. 1). The CANVAS trial participants who met the inclusion criteria for this sulfonylurea substudy (sulfonylurea monotherapy at the prespecified minimum doses) were 127 individuals, of whom 119 (93.7%) completed the 18-week treatment period. A further 88 patients at baseline were receiving sulfonylurea monotherapy at less than the prespecified doses; when the total sulfonylurea-taking population was analyzed,

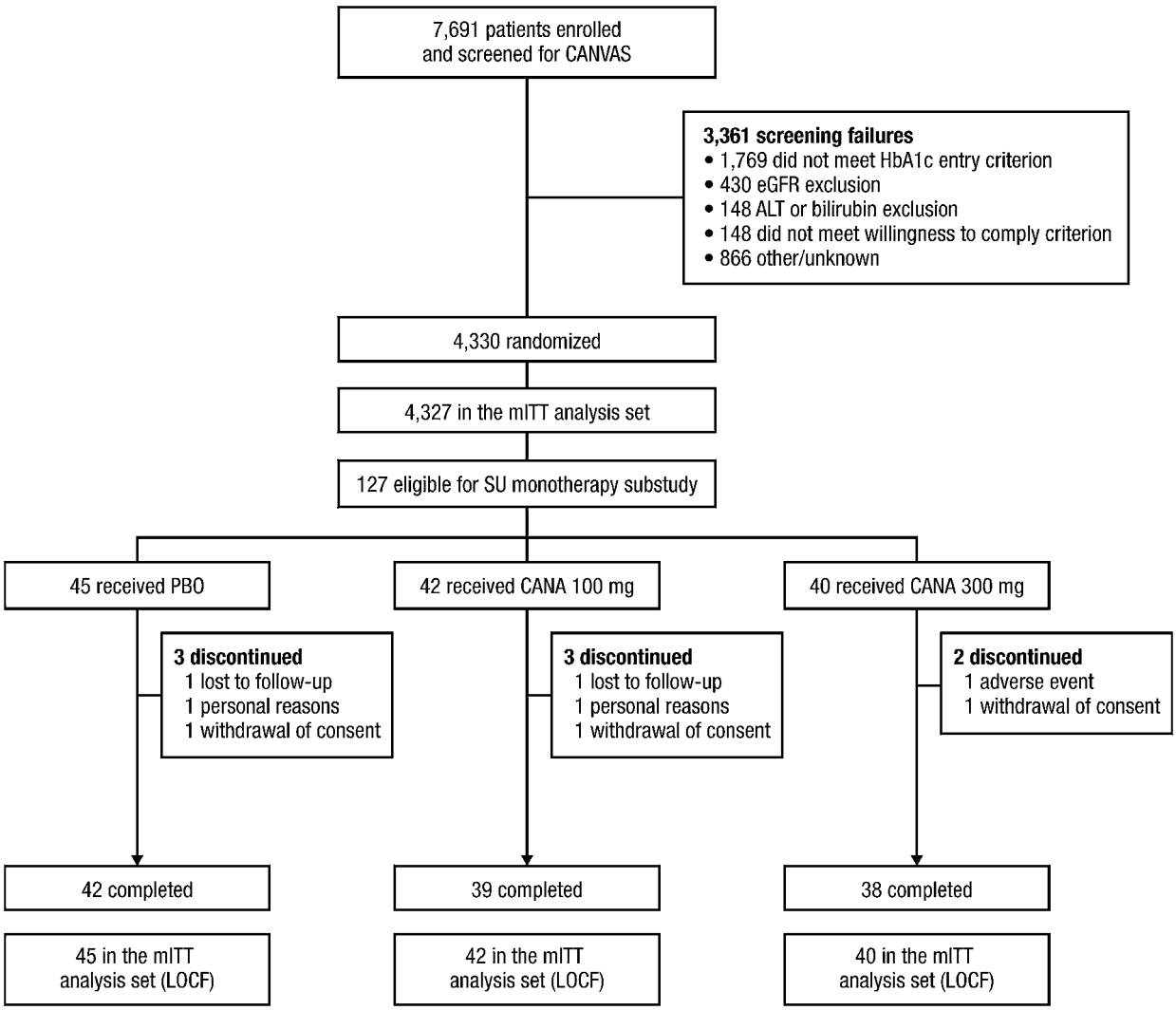

Fig. 1 Study flow diagram. *ALT* alanine aminotransferase, *CANA* canagliflozin, *CANVAS* CANagliflozin cardioVascular Assessment Study, *eGFR* estimated glomerular filtration rate, *LOCF* last observation carried forward, *mITT* modified intent-to-treat, *PBO* placebo, *SU* sulfonylurea

the conclusions were the same as from the predefined analysis (data not shown). Amongst the 127 patients in the primary analysis, 45 were assigned to placebo, 42 to canagliflozin 100 mg, and 40 to canagliflozin 300 mg. No patients in the canagliflozin 300 mg group required rescue therapy in the first 18 weeks, while 4.8% (2 patients) of the canagliflozin 100 mg group and 17.8% (8 patients) of the placebo group did.

Baseline Characteristics of Participants

Baseline demographic and disease characteristics were generally similar across treatment groups (Table 1). At entry to the study, mean age was 64.8 years, HbA1c was 8.4%, body mass index was 29.9 kg/m^2, and the median duration of diabetes was 10.2 years. The estimated glomerular filtration rate (eGFR) was 69.3 mL/min/1.73 m^2 and FPG was 10.0 mmol/L. The most common

Table 1 Baseline demographic and disease characteristics

Characteristic	Study population			
	PBO (n = 45)	CANA 100 mg (n = 42)	CANA 300 mg (n = 40)	Total (n = 127)
Sex, n (%)				
Male	26 (58)	24 (57)	22 (55)	72 (57)
Female	19 (42)	18 (43)	18 (45)	55 (43)
Mean ± SD age, years	64.8 ± 7.8	64.1 ± 7.5	65.5 ± 7.8	64.8 ± 7.7
Race, n (%)[a]				
White	34 (76)	30 (71)	31 (78)	95 (75)
Black or African American	1 (2)	0	0	1 (1)
Asian	9 (20)	12 (29)	8 (20)	29 (23)
Other[b]	1 (2)	0	1 (3)	2 (2)
Mean ± SD body weight, kg	85.2 ± 19.3	83.7 ± 17.4	79.9 ± 19.5	83.0 ± 18.7
Mean ± SD BMI, kg/m^2	30.7 ± 6.1	30.2 ± 5.0	28.7 ± 6.2	29.9 ± 5.8
Mean ± SD eGFR, mL/min/1.73 m^2	68.8 ± 18.8	71.5 ± 18.4	67.7 ± 18.7	69.3 ± 18.6
Mean ± SD duration of T2DM, years	11.4 ± 6.7	10.6 ± 5.9	8.4 ± 6.2	10.2 ± 6.4
Mean ± SD HbA1c, %	8.5 ± 1.13	8.3 ± 0.82	8.2 ± 1.01	8.4 ± 1.00
Mean ± SD FPG, mmol/L	10.3 ± 2.68	10.1 ± 2.67	9.7 ± 2.28	10.0 ± 2.55
Microvascular complications, n (%)	18 (40)	15 (36)	22 (55)	55 (43)

BMI body mass index, *CANA* canagliflozin, *eGFR* estimated glomerular filtration rate, *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin, *PBO* placebo, *SD* standard deviation, *T2DM* type 2 diabetes mellitus

[a] Percentages may not total 100% due to rounding

[b] Including other

Table 2 Effects of canagliflozin on primary and secondary outcomes

	Treatment difference, 95% CI			
	CANA 100 mg vs PBO		CANA 300 mg vs PBO	
HbA1c, %[a]	−0.74	−1.15 to −0.33	−0.83	−1.24 to −0.42
% change in body weight[b]	−0.4	−1.8 to 1.0	−1.8	−3.2 to −0.4
FPG, mmol/L	−2.1	−3.0 to −1.2	−2.7	−3.6 to −1.7
Proportion with HbA1c <7.0%, %	20.0	2.5 to 37.5	28.3	9.5 to 47.1
Systolic BP, mmHg	−0.10	−6.45 to 6.25	−1.77	−8.21 to 4.67
% change in HDL-C	2.7	−5.3 to 10.7	0.9	−7.1 to 8.8
% change in triglycerides	−13.0	−28.5 to 2.6	12.0	−3.0 to 27.1
% change in LDL-C	−1.1	−13.3 to 11.1	3.7	−8.5 to 15.9

BP blood pressure, *CANA* canagliflozin, *CI* confidence interval, *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin, *PBO* placebo, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol

[a] Both doses vs PBO, $P < 0.001$

[b] CANA 100 mg vs PBO, $P = 0.557$; CANA 300 mg vs PBO, $P = 0.014$

sulfonylurea therapies were glimepiride (35%), glyburide/glibenclamide (29%), and gliclazide MR (27%).

Effects of Canagliflozin on Efficacy Outcomes

Both doses of canagliflozin significantly reduced the primary outcome of HbA1c relative to placebo at week 18 (placebo-subtracted changes [95% CI] of −0.74% [−1.15, −0.33; $P < 0.001$] and −0.83% [−1.24, −0.42; $P < 0.001$] with canagliflozin 100 and 300 mg, respectively; Table 2; Fig. 2) and a higher proportion of patients treated with canagliflozin 100 and 300 mg achieved HbA1c <7.0% versus placebo (25.0% and 33.3% vs 5.0%, respectively). FPG was also lower with both doses (Fig. 3; Table 2). There was also a statistically significant reduction in the secondary outcome of body weight with canagliflozin 300 mg but not canagliflozin 100 mg (Fig. 4; Table 2). There were no notable differences detected in systolic BP with canagliflozin 100 or 300 mg (Table 2). Clear effects on blood lipids were not apparent, with large CIs about most estimates (Fig. 5).

Effects of Canagliflozin on Safety and Tolerability Outcomes

AEs were reported for 66.7%, 26.2%, and 45.0% of participants treated with placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively (Table 3). The corresponding figures for serious AEs were 8.9%, 0%, and 7.5%, respectively, with no specific serious AE terms reported in more than 1 patient in any group. AEs leading to discontinuation of treatment were numerically similar with canagliflozin 300 mg compared to canagliflozin 100 mg and placebo. Genital mycotic infections were more common with canagliflozin compared with placebo for women (5.6% [1/18], 5.6% [1/18], and 0% [0/19] with canagliflozin 100 and 300 mg and placebo, respectively), and no genital mycotic infections were reported in men across groups;

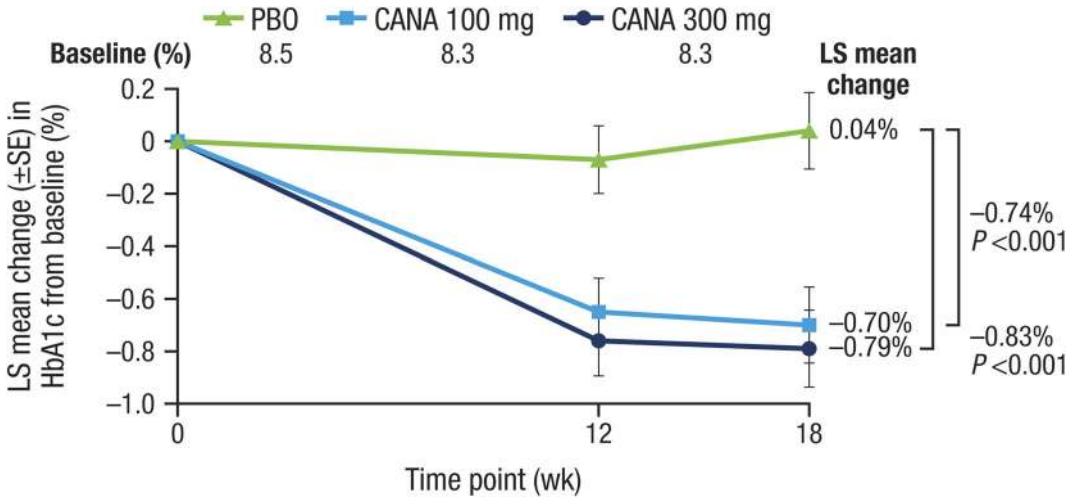

Fig. 2 Effects of canagliflozin on HbA1c (LOCF). *CANA* canagliflozin, *HbA1c* glycated hemoglobin, *LOCF* last observation carried forward, *LS* least squares, *PBO* placebo, *SE* standard error, *wk* week

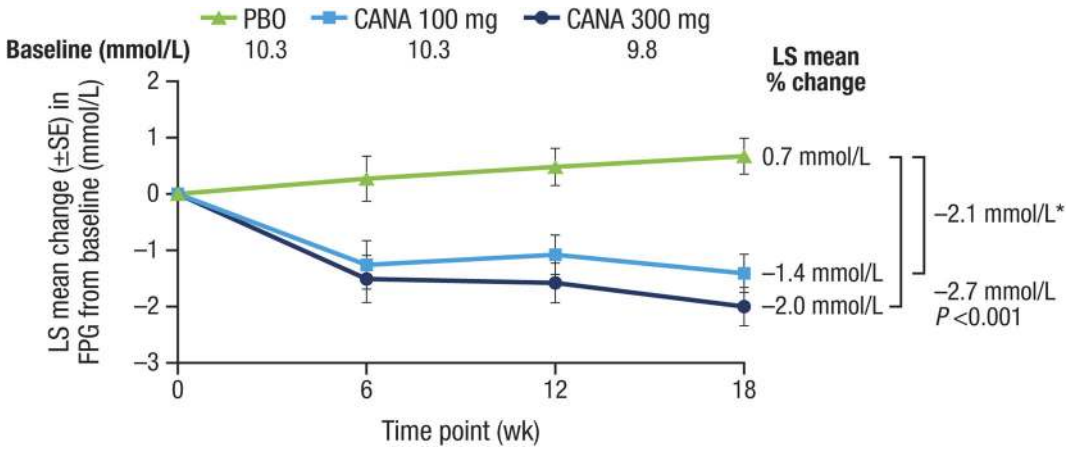

Fig. 3 Effects of canagliflozin on FPG (LOCF). *CANA* canagliflozin, *FPG* fasting plasma glucose, *LOCF* last observation carried forward, *LS* least squares, *PBO* placebo, *SE* standard error, *wk* week. *Asterisk* Not statistically significant vs PBO based on the hypothesis testing sequence (nominal $P < 0.001$)

there was no evidence of an increased rate of upper or lower urinary tract infection. AEs attributable to volume depletion, such as postural hypotension and dizziness, were more common with active treatment compared to placebo. The rates of documented hypoglycemia were greater with canagliflozin than placebo, and there were no cases defined as severe hypoglycemia reported across treatment groups (Table 3). Small to moderate mean percent changes from baseline in serum creatinine were observed with canagliflozin 100 and 300 mg and placebo (4.1%, 9.9%, and 5.7%, respectively). The largest increase in serum creatinine occurred by week 6 in both the canagliflozin 100 and 300 mg groups, and the levels were trending toward baseline by week 18. Similar but reciprocal differences in

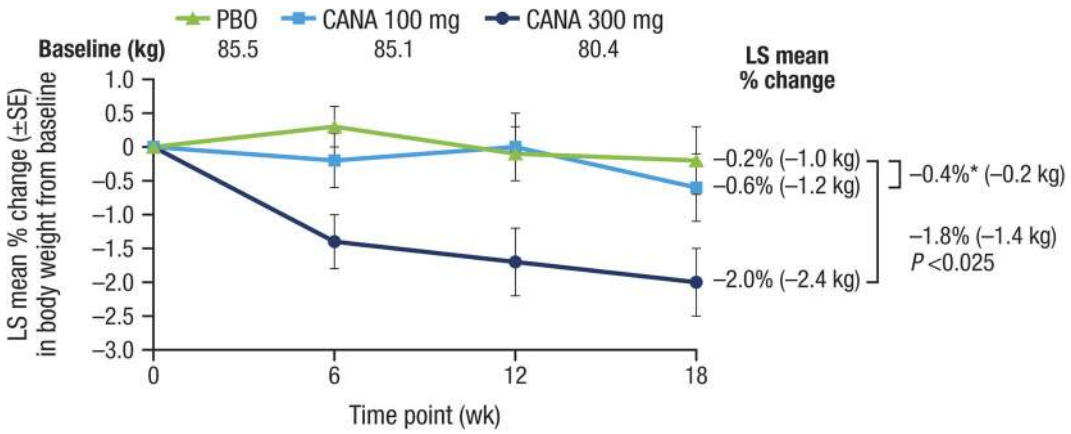

Fig. 4 Effects of canagliflozin on body weight (LOCF). *CANA* canagliflozin, *LOCF* last observation carried forward, *LS* least squares, *PBO* placebo, *SE* standard error, *wk* week. *Asterisk* Not statistically significant vs PBO

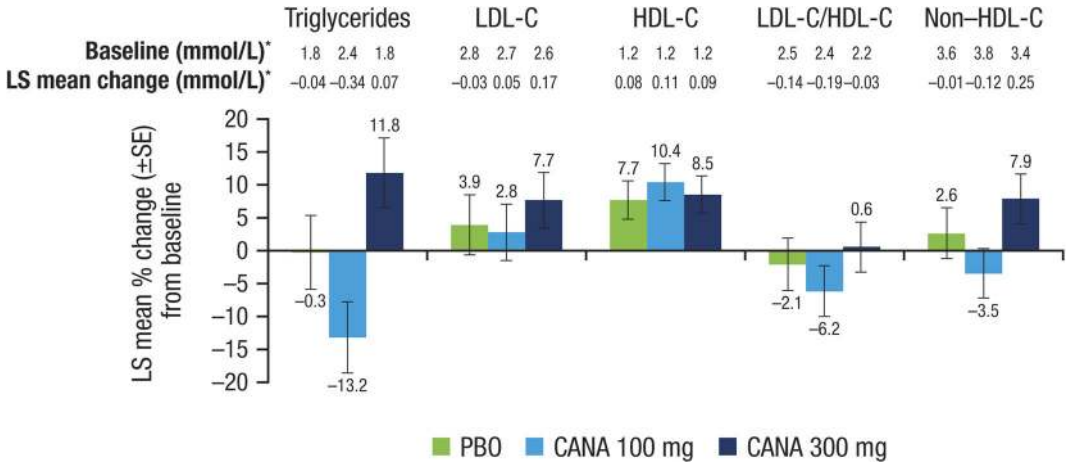

Fig. 5 Effects of canagliflozin on fasting plasma lipids (LOCF). *CANA* canagliflozin, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *LOCF* last observation carried forward, *LS* least squares, *PBO* placebo, *SE* standard error. *Asterisk* Units of mol/mol for LDL-C/HDL-C

the mean percent change from baseline in eGFR were observed with canagliflozin 100 and 300 mg and placebo (−2.5%, −9.6%, and −4.7%, respectively).

DISCUSSION

The addition of canagliflozin to background sulfonylurea monotherapy was efficacious, with further placebo-adjusted decreases of HbA1c of −0.74% and −0.83% for canagliflozin 100 and 300 mg, respectively, at 18 weeks. Furthermore, the reductions in HbA1c were accompanied by a significant decrease in body weight for the 300-mg dose (−1.8%) although not for the 100-mg dose. Canagliflozin 100 mg has been associated with consistent weight loss in other Phase 3 studies [5–17], with significant weight loss observed with canagliflozin 100 mg versus placebo (–1.4%) in the 26-week study as add-on

Table 3 Overall safety and selected adverse events

	Patients, *n* (%)		
	PBO (*n* = 45)	**CANA 100 mg (*n* = 42)**	**CANA 300 mg (*n* = 40)**
Any AEs	30 (66.7)	11 (26.2)	18 (45.0)
AEs causing discontinuation	0	1 (2.4)	1 (2.5)
AEs related to study drug[a]	8 (17.8)	3 (7.1)	6 (15.0)
Serious AEs	4 (8.9)[b]	0	3 (7.5)[c]
Deaths	0	0	0
AEs of special interest			
Genital mycotic infections			
Male	0	0	0
Female[d,e]	0	1 (5.6)	1 (5.6)
Urinary tract infections	1 (2.2)	1 (2.4)	1 (2.5)
Osmotic diuresis-related events			
Pollakiuria	0	1 (2.4)	2 (5.0)
Polyuria	1 (2.2)	1 (2.4)	0
Volume-related events			
Postural dizziness	0	0	0
Orthostatic hypotension	0	0	0
Documented hypoglycemia[f,g]	2 (4.4)	0	6 (15.0)
Severe hypoglycemia	0	0	0

AE adverse event, *CANA* canagliflozin, *PBO* placebo

[a] Possibly, probably, or very likely related to study drug, as assessed by investigators

[b] Including asthma, atrioventricular block second degree, blood creatinine increased, diabetes mellitus, flank pain, and hyperglycemia

[c] Including angina pectoris, ankle fracture, colon cancer metastatic, and coronary artery disease

[d] The proportions of female genital mycotic infections were calculated using the number of female patients in each treatment group, as follows: PBO, $n = 19$; CANA 100 mg, $n = 18$; CANA 300 mg, $n = 18$

[e] Including vaginal infection and vulvovaginitis

[f] All documented hypoglycemia episodes are reported for prior to rescue therapy

[g] Documented hypoglycemia included episodes that were biochemically documented ($\leq$3.9 mmol/L) or severe (i.e., requiring the assistance of another individual or resulting in seizure or loss of consciousness)

to metformin plus sulfonylurea [6]. Thus, it seems unlikely that the addition of canagliflozin to the background of a sulfonylurea alone would diminish the extent of weight loss and suggests that the modest reduction in body weight with canagliflozin 100 mg in this study is likely an outlying estimate. Changes in BP, while not significant, were in a similar direction to those observed in other reports [5–17]. Effects on lipid metabolism were also inconsistent and nonsignificant, but the overall pattern appeared to be similar to

that reported previously in larger, better powered studies with small increases in LDL-C [5–17]. Importantly, there was no change in the LDL-C/HDL-C ratio with either canagliflozin 300 or 100 mg.

The observed additive glycemic effects of canagliflozin on top of sulfonylurea are anticipated on the basis of its complementary mechanism of action, and while the efficacy of sulfonylurea is dependent on adequate pancreatic insulin-secretory capacity, this is not the case with the SGLT2 inhibitors. For this reason, it is hypothesized that canagliflozin will be an effective treatment choice at most stages of the disease, and in combination with other glucose-lowering therapies. The 300-mg dose of canagliflozin was associated with numerically greater effects on several parameters compared with the 100-mg dose, including a modest increase in the percentage of patients achieving a target HbA1c <7.0% (placebo-subtracted differences of 28.3% vs 20.0%, respectively).

We and others have previously reported that the additional efficacy effects of the 300-mg over the 100-mg dose were achieved at the expense of an increased risk of drug-related AEs [5–17]. By contrast, (almost certainly as the result of the much smaller study numbers), osmotic diuresis-related (e.g., polyuria, pollakiuria, thirst) and volume-related AEs (e.g., postural dizziness, orthostatic hypotension, hypotension, syncope, presyncope) were similar in all treatment groups, with no difference between the 2 canagliflozin doses. We should not, however, conclude that the combination of canagliflozin with a sulfonylurea provides a protective effect against these side effects, and identifying patients potentially susceptible to AEs will be an important component of a patient-centered approach to diabetes management. At the same time, it reinforces the impression that serious adverse effects are relatively uncommon with this compound.

The other AEs observed with canagliflozin were those generally recognized for SGLT2 inhibitors [21]. Genital mycotic infections were more common with canagliflozin than placebo. As has been reported, they were generally mild or moderate in intensity, were managed with usual therapies, and treatment was continued [19]. There was no evidence of an increased rate of either upper or lower urinary tract infections, although this is a recognized potential complication with this drug class in larger datasets [21]. The observed decline in eGFR is likely to be hemodynamic in origin and was not associated with an excess of renal AEs. The small size of the decline in eGFR and the other favorable metabolic effects suggest that the net impact of canagliflozin on renal outcomes is unlikely to be harmful.

The primary weakness of this study is the relatively small sample size. This almost certainly reflects a decrease in the use of sulfonylureas as initial therapy in general, and the small proportion of diabetic patients managed on sulfonylurea monotherapy. As such, the confidence intervals about many estimates are wide, and, while the point estimates of effects sometimes appear different to those reported in prior studies, it is difficult to know whether this reflects real differences in efficacy and safety or chance. In this context, these substudy findings are best interpreted in the context of the broader experience with canagliflozin in this and other patient groups. The conduct of the analyses at 18 weeks provides estimates of short-term effects only, with the long-term impact of canagliflozin in this group remaining to be established.

CONCLUSION

Canagliflozin appears to offer significant and clinically meaningful benefits when used in conjunction with sulfonylureas with a similar class-effect AE profile. Overall, findings from this study support the efficacy and safety of canagliflozin as add-on to sulfonylurea monotherapy in patients with T2DM and cardiovascular risk.

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