

Efficacy and safety of titrated canagliflozin in patients with type 2 diabetes mellitus inadequately controlled on metformin and sitagliptin

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Aims: To evaluate the efficacy and safety of titrated canagliflozin, a sodium glucose co-transporter 2 inhibitor, in patients with type 2 diabetes mellitus (T2DM) inadequately controlled on metformin and sitagliptin.

Methods: In this randomized, double-blind study, patients with T2DM (N=218) on metformin ≥ 1500 mg/day and sitagliptin 100 mg received canagliflozin 100 mg or placebo. After 6 weeks, the canagliflozin dose was increased from 100 to 300 mg (or from placebo to matching placebo) if all of the following criteria were met: baseline estimated glomerular filtration rate ≥ 70 ml/min/1.73 m²; fasting self-monitored blood glucose ≥ 5.6 mmol/l (≥ 100 mg/dl); and no volume depletion-related adverse events (AEs) within 2 weeks before dose increase. Endpoints included change in glycated haemoglobin (HbA1c) at week 26 (primary); proportion of patients achieving HbA1c $< 7.0\%$; and changes in fasting plasma glucose (FPG), body weight and systolic blood pressure (SBP). Safety was assessed using AE reports.

Results: Overall, 85.4% of patients were titrated to canagliflozin 300 mg or matching placebo (mean \pm standard deviation time to titration 6.2 ± 0.8 weeks). At week 26, canagliflozin (pooled 100 and 300 mg) demonstrated superiority in HbA1c reduction versus placebo (-0.91% vs. -0.01% ; $p < 0.001$). Canagliflozin provided significant reductions in FPG, body weight and SBP compared with placebo ($p < 0.001$). The overall AE incidence was 39.8 and 44.4% for canagliflozin and placebo, respectively. Canagliflozin was associated with an increased incidence of genital mycotic infections.

Conclusions: Titrated canagliflozin significantly improved HbA1c, FPG, body weight and SBP, and was generally well tolerated over 26 weeks in patients with T2DM as add-on to metformin and sitagliptin.

Keywords: canagliflozin, sitagliptin, sodium glucose co-transporter, titration, triple therapy, type 2 diabetes mellitus

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Introduction

Metformin is the standard first-line therapy for the treatment of type 2 diabetes mellitus (T2DM); however, patients often require combination therapy to achieve and maintain glycaemic control because of the progressive nature of the disease [1]. Dipeptidyl peptidase-4 (DPP-4) inhibitors, particularly sitagliptin, are widely used in combination with metformin to manage T2DM in dual-therapy regimens [2,3]. Treatment escalation after dual oral therapy remains somewhat controversial, as a key clinical decision is whether to add a third oral agent or proceed to injectable agents (e.g. insulin, glucagon-like peptide-1 receptor agonists) [1,4]. The optimum treatment strategy should be individualized based on the efficacy and safety/tolerability profile of pharmacological agents, as well as

patient preferences and comorbidities, with the goal of improving glycaemic control and minimizing potential adverse effects (e.g. hypoglycaemia, weight gain) [1,4].

Sodium glucose co-transporter 2 (SGLT2) inhibitors lower blood glucose by decreasing the renal threshold for glucose and increasing urinary glucose excretion, which results in a mild osmotic diuresis and a net caloric loss [5,6]. SGLT2 inhibitors have been shown to reduce glycated haemoglobin (HbA1c) and plasma glucose levels, and to provide additional benefits of body weight and blood pressure (BP) reduction, with a low inherent risk of hypoglycaemia [5,6]. The insulin-independent mechanism of SGLT2 inhibitors makes them particularly suitable for use in dual- and triple-therapy regimens and differentiates them from other classes of antihyperglycaemic agents, such as DPP-4 inhibitors, which stimulate insulin release and lower glucagon release from the pancreas by increasing active glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide levels [7]. Titration to higher doses of SGLT2 inhibitors may be required if more intensive glycaemic control is needed [8–10]; however, studies evaluating the efficacy of dose titration with SGLT2 inhibitor treatment have yet to be reported.

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Canagliflozin is an SGLT2 inhibitor that has been shown to improve glycaemic control and reduce body weight and BP, with a favourable tolerability profile in patients with T2DM as monotherapy or in dual or triple combination therapy involving a variety of background antihyperglycaemic agents [11–24], including DPP-4 inhibitors [25]. Notably, all previous phase III studies of canagliflozin used a parallel-arm design that did not include a dose-titration protocol; however, based on the observed dose-dependent difference in volume depletion-related adverse events (AEs), the practical approach of initiating treatment at a lower dose of canagliflozin and then increasing to a higher dose (as needed) was considered. The objective of the present study was to evaluate the efficacy and safety of canagliflozin when administered using a dose-advancement titration algorithm in patients with T2DM inadequately controlled on metformin and sitagliptin.

Materials and Methods

Study Design and Patients

This randomized, double-blind, parallel-group, multicentre study was conducted at 47 study centres in five countries from 21 February 2014 to 2 September 2015. The study consisted of a 3-week pretreatment phase, including a 1-week screening period and a 2-week single-blind placebo run-in period, followed by a 26-week double-blind treatment phase and 2 weeks of post-treatment follow-up for all patients. Eligible patients were aged 18–75 years with T2DM, who were inadequately controlled (HbA1c ≥ 7.5 to $\leq 10.5\%$) on stable combination therapy with maximum or near-maximum effective doses of metformin (i.e. ≥ 1500 mg/day; mean dose 1984 mg/day) and sitagliptin 100 mg/day administered ≥ 12 weeks before screening. Patients were excluded if they had a history of diabetic ketoacidosis or type 1 diabetes; had fasting self-monitored blood glucose (SMBG) levels ≥ 15.0 mmol/l (≥ 270 mg/dl) at baseline; had myocardial infarction, unstable angina, a revascularization procedure or cerebrovascular accident ≤ 12 weeks before screening; had a history of New York Heart Association Class III or IV cardiac disease; had uncontrolled hypertension; had an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m² or serum creatinine ≥ 124 μ mol/l (≥ 1.4 mg/dl) in men or ≥ 115 μ mol/l (≥ 1.3 mg/dl) in women; were taking loop diuretics; or were taking any antihyperglycaemic agent other than metformin and sitagliptin ≤ 12 weeks before screening. Patients were discontinued from the study if they had repeated fasting SMBG values meeting prespecified discontinuation criteria [SMBG > 15 mmol/l (> 270 mg/dl) after day 1 up to week 6, SMBG > 13.3 mmol/l (> 240 mg/dl) after week 6 up to week 12, and SMBG > 11.1 mmol/l (> 200 mg/dl) after week 12 up to week 26; values were confirmed with a central laboratory fasting plasma glucose (FPG) measurement].

This study was conducted in accordance with the ethical principles that comply with the Declaration of Helsinki and was consistent with Good Clinical Practice and applicable regulatory requirements. Approval was obtained from institutional review boards and independent ethics committees for each

participating centre. Patients provided informed written consent before participation.

Randomization, Blinding and Titration

Patients were randomized (1 : 1) to receive canagliflozin 100 mg or placebo once daily using a computer-generated randomization schedule prepared by or under supervision of the sponsor prior to initiation of the study (Figure 1). Randomization was balanced using permuted blocks and stratified by HbA1c at screening (HbA1c < 8.0 or $\geq 8.0\%$). FPG and HbA1c values were masked to the study sites and to the sponsor, unless an FPG value met specific glycaemic criteria for discontinuation.

At week 6, patients increased their canagliflozin dose from 100 to 300 mg or from placebo to matching placebo if they met all of the following criteria: baseline eGFR ≥ 70 ml/min/1.73 m²; fasting SMBG ≥ 5.6 mmol/l (≥ 100 mg/dl), documented by ≥ 2 measurements within the previous 2 weeks; and no volume depletion-related AEs (e.g. hypotension, postural dizziness, orthostatic hypotension) within 2 weeks before the dose increase. Patients who did not meet these criteria at week 6 remained on canagliflozin 100 mg or matching placebo, and were reassessed approximately every 2 weeks up to week 18 to determine eligibility for dose titration. Patients who experienced hyperglycaemia before 6 weeks of treatment with canagliflozin or matching placebo increased their dose early, if they met the titration criteria.

Endpoints and Assessments

The primary efficacy endpoint was change from baseline in HbA1c at week 26. Secondary endpoints at week 26 included the proportion of patients achieving HbA1c $< 7.0\%$, changes from baseline in FPG and systolic BP, and change from baseline in body weight. Additional exploratory endpoints at week 26 included the proportion of patients with HbA1c $< 8.0\%$ and HbA1c $> 9.0\%$; change from baseline in diastolic BP; the proportion of patients with BP $< 140/90$ mmHg and BP $< 130/80$ mmHg; and change from baseline in fasting plasma lipids, including triglycerides, HDL cholesterol, LDL cholesterol, LDL cholesterol/HDL cholesterol ratio and non-HDL cholesterol.

Overall safety and tolerability were assessed using AE reports, safety laboratory tests and vital signs measurements. The incidence of documented hypoglycaemia [i.e. concurrent fingerstick or plasma glucose ≤ 3.9 mmol/l (≤ 70 mg/dl) with or without symptoms or severe episodes (i.e. requiring assistance from another person or resulting in seizure or loss of consciousness)] was also assessed. Patients were instructed to record information on the signs and symptoms of hypoglycaemia, as well as associated SMBG measurements, if available, and routine fasting SMBG measurements in a diary card.

Statistical Analyses

The primary hypothesis for the present study was that canagliflozin (pooled data for patients who remained on canagliflozin 100 mg and those who increased their canagliflozin dose to 300 mg) was superior to placebo in

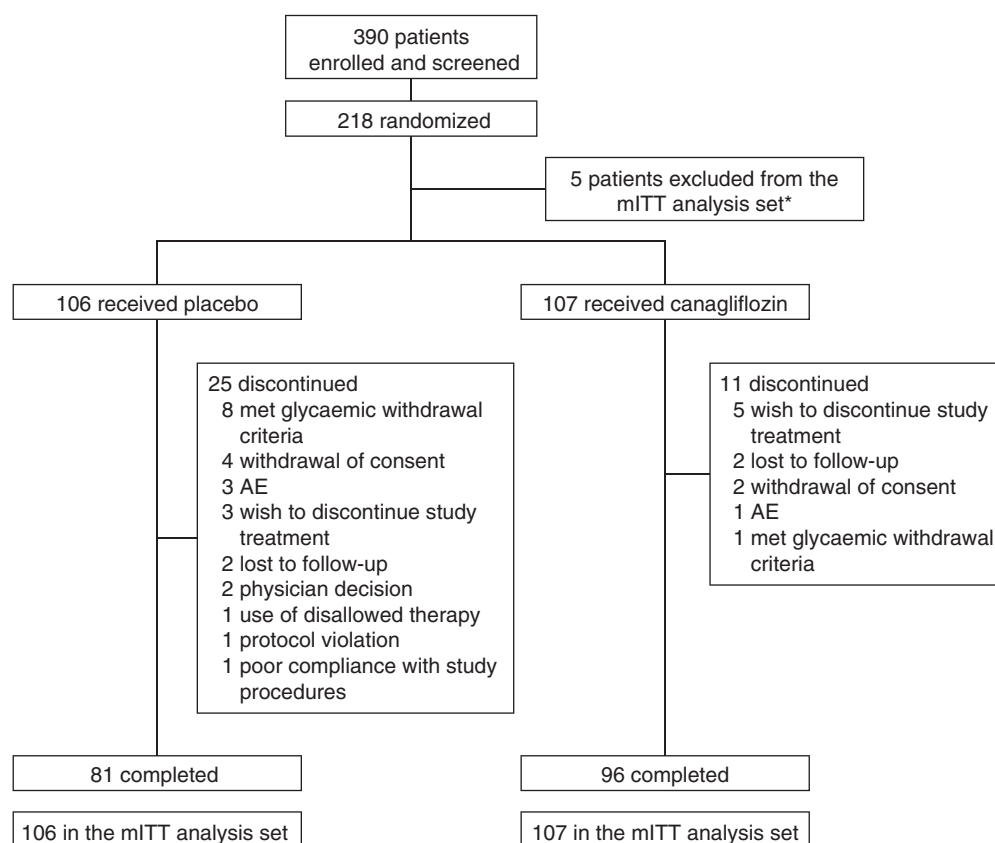


Figure 1. Study flow diagram. AE, adverse event; mITT, modified intention-to-treat. *One patient was randomized at two different sites and was withdrawn from the study. Three patients were excluded from the mITT analysis set due to potential misconduct and Good Clinical Practice compliance issues; these patients were included in the safety analysis.

reducing HbA1c from baseline to week 26. Sample size was determined based on demonstrating the statistical superiority of canagliflozin in lowering HbA1c compared with placebo. A total of 86 patients per treatment group were estimated to be required to achieve 90% power, with an assumed group difference of 0.5% and an assumed standard deviation of 1.0% using a two-sample, two-sided *t*-test, with a type I error rate of 0.05.

Approximately 100 patients were planned for inclusion in each treatment group to enlarge the safety database with respect to adding canagliflozin treatment with metformin and sitagliptin.

Efficacy and safety analyses were conducted using the modified intention-to-treat (mITT) analysis set (i.e. all patients who were randomized and received ≥ 1 dose of double-blind study drug). The primary efficacy endpoint of change from baseline in HbA1c was analysed using a mixed-model for repeated measures with a restricted maximum likelihood approach. This analysis was based on observed data that included treatment, stratification factor (i.e. HbA1c < 8.0 or ≥ 8.0 % at screening), visit and treatment-by-visit interaction as fixed categorical effects, and baseline and baseline-by-visit interaction as continuous fixed covariates. An unstructured covariance was used to model the within-patient errors. Changes from baseline in FPG, body weight and BP were analysed with a mixed-model for repeated measures similar to the primary efficacy endpoint.

Changes from baseline in lipids were analysed using analysis of covariance, with treatment and the stratification factor as fixed effects and the corresponding baseline value as a covariate; given the skewed nature of the distribution of the change in triglycerides, treatment comparisons were evaluated based on the Wilcoxon rank-sum test. Missing lipid data were imputed using the last observation carried forward approach, as lipid variables were only collected at baseline and week 26. Least squares (LS) mean differences and 95% confidence intervals (CIs) were estimated for the changes in HbA1c, FPG, body weight, BP and lipids at week 26 for canagliflozin (pooled 100 and 300 mg) versus placebo. The Hodges–Lehmann difference in median values for triglycerides was also estimated.

The binary endpoints of the proportion of patients with HbA1c < 7.0 %, HbA1c < 8.0 %, HbA1c > 9.0 %, BP $< 140/90$ mmHg and BP $< 130/80$ mmHg were analysed longitudinally using a generalized linear mixed model that included treatment, stratification factor, visit and treatment-by-visit interaction as fixed categorical effects, and baseline and baseline-by-visit interaction as continuous fixed covariates. An unstructured covariance was used to model the within-patient errors. Odds ratios (ORs) and 95% CIs were estimated at week 26 for canagliflozin (pooled 100 and 300 mg) versus placebo. Safety analyses included all reported AEs with onset

Table 1. Baseline demographic and disease characteristics.*

	Placebo (n = 106)	Canagliflozin (n = 107)	Total (N = 213)
Sex, n (%)			
Male	55 (51.9)	66 (61.7)	121 (56.8)
Female	51 (48.1)	41 (38.3)	92 (43.2)
Age, years	57.5 ± 10.1	57.4 ± 9.3	57.4 ± 9.7
Race, n (%)†			
White	77 (72.6)	80 (74.8)	157 (73.7)
Black/African-American	16 (15.1)	6 (5.6)	22 (10.3)
Asian	12 (11.3)	20 (18.7)	32 (15.0)
Other‡	1 (0.9)	1 (0.9)	2 (0.9)
HbA1c, %	8.4 ± 0.8	8.5 ± 0.9	8.5 ± 0.8
Baseline HbA1c, n (%)			
<8.0%	29 (27.4)	32 (29.9)	61 (28.6)
≥8.0%	77 (72.6)	75 (70.1)	152 (71.4)
FPG			
mmol/l	10.0 ± 2.1	10.3 ± 2.6	10.2 ± 2.3
mg/dl	180.4 ± 37.8	185.5 ± 46.2	183.0 ± 42.2
Body weight, kg	90.0 ± 19.3	94.1 ± 21.8	92.1 ± 20.7
BMI, kg/m ²	31.7 ± 5.5	32.3 ± 5.8	32.0 ± 5.7
eGFR, ml/min/1.73 m ²	89.6 ± 16.2	91.4 ± 14.6	90.5 ± 15.4
Duration of T2DM, years	10.1 ± 5.9	9.8 ± 5.4	9.9 ± 5.7

BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; s.d., standard deviation; T2DM, type 2 diabetes mellitus.

*Data are mean ± s.d. unless otherwise indicated.

†Percentages may not total 100.0% due to rounding.

‡Includes Native Hawaiian or other Pacific Islander and other.

during the treatment phase (i.e. treatment-emergent AEs), and laboratory results included data up to within 2 days after the last dose of study drug.

Results

Patient Disposition

A total of 218 patients were randomized and received ≥1 dose of study drug. One patient was randomized twice at two different sites (once to placebo and once to canagliflozin) and was excluded from the mITT and safety analysis sets. Three patients were excluded from the mITT analysis set because of potential site misconduct and Good Clinical Practice compliance issues, but were included in the safety analysis. Of 213 patients in the mITT analysis set, 177 (83.1%) completed 26 weeks of treatment (Figure 1). Overall, a greater proportion of patients discontinued from the placebo group (23.6%; n = 25) compared with the canagliflozin group (10.3%; n = 11). The most common reasons for discontinuation were glycaemic withdrawal criteria (4.2%; n = 9), patient wish to discontinue treatment (3.8%; n = 8) and withdrawal of consent (2.8%; n = 6). A greater proportion of patients in the placebo group (7.5%; n = 8) met glycaemic withdrawal criteria versus the canagliflozin group (0.9%; n = 1). Baseline demographic and disease characteristics were generally similar in the treatment groups (Table 1). Patients had a mean age of 57.4 years and a mean duration of T2DM of 9.9 years, and 57% (n = 121) were men. The mean baseline HbA1c was 8.5%, with 71.4% (n = 152) having baseline HbA1c levels ≥8.0%. The mean body mass index was 32.0 kg/m², and the mean eGFR was 90.5 ml/min/1.73 m².

A total of 182 patients (85.4%) increased their canagliflozin dose from 100 to 300 mg (90.7%; n = 97) or increased from placebo to matching placebo (80.2%; n = 85). The mean time to dose increase (± standard deviation) was 6.2 ± 0.8 weeks; most patients (82.6%; n = 176) had a dose increase from canagliflozin 100 to 300 mg or from placebo to matching placebo by week 8, with only six patients (2.8%) increasing to canagliflozin 300 mg or matching placebo after week 8. Overall, 31 patients (14.6%) did not increase their dose, with a greater proportion of these in the placebo group (19.8%; n = 21) than in the canagliflozin group (9.3%; n = 10). The most common reasons for not increasing the dose were the presence of a baseline eGFR <70 ml/min/1.73 m² and early study discontinuation.

Efficacy

Glycaemic Efficacy. At week 26, canagliflozin (pooled 100 and 300 mg) was found to be superior in HbA1c reduction compared with placebo (Figure 2A). The LS mean changes in HbA1c with canagliflozin and placebo were −0.91 and −0.01%, respectively [difference vs. placebo (95% CI) of −0.89% (−1.19, −0.59); p < 0.001]. In the canagliflozin group, the greatest reductions in HbA1c were observed at week 12, with an additional small decrease through week 26. There were no discernable HbA1c changes over time in the placebo group.

A greater proportion of patients achieved HbA1c <7.0% at week 26 with canagliflozin compared with placebo [32.3 and 12.2%, respectively; OR (95% CI) of 4.5 (1.9, 10.9); p = 0.001; Figure 2B]. Likewise, a greater proportion of patients achieved HbA1c <8.0% with canagliflozin versus placebo [70.8 and 39.0%, respectively; OR (95% CI) of 5.6 (2.7, 11.4);

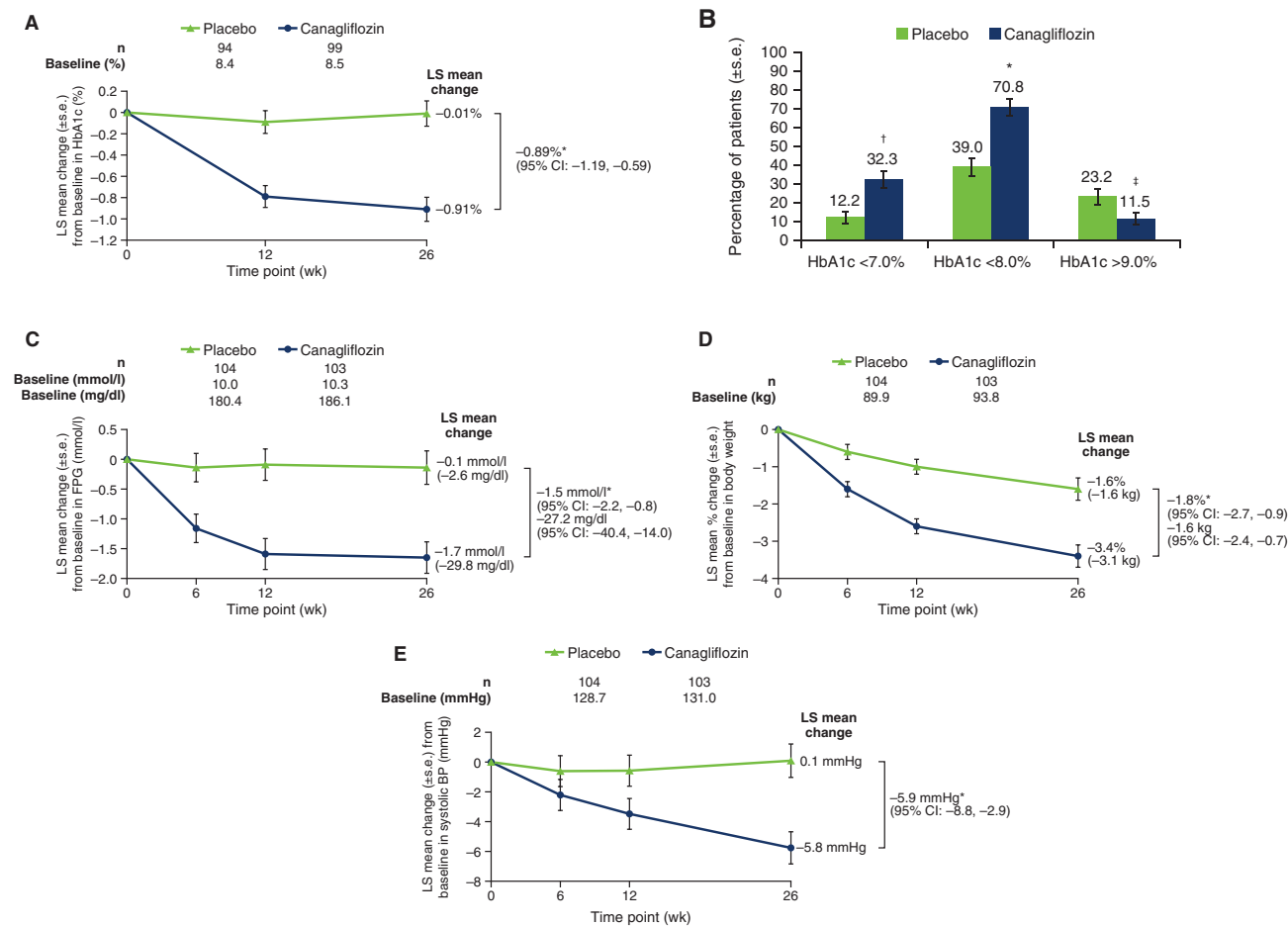


Figure 2. (A) Change from baseline in glycated haemoglobin (HbA1c) over 26 weeks. (B) Proportion of patients with HbA1c <7.0, <8.0 and >9.0% at 26 weeks. (C) Change from baseline in fasting plasma glucose (FPG) over 26 weeks. (D) Change from baseline in body weight over 26 weeks. (E) Change from baseline in systolic blood pressure (BP) over 26 weeks. CI, confidence interval; LS, least squares; s.e., standard error. * $p < 0.001$ versus placebo. † $p = 0.001$ versus placebo. ‡ $p = 0.002$ versus placebo.

$p < 0.001$]. A smaller proportion of patients had an HbA1c level >9.0% at week 26 with canagliflozin versus placebo [11.5 and 23.2%, respectively; OR (95% CI) of 0.3 (0.1, 0.6); $p = 0.002$].

Canagliflozin provided significant reductions in FPG compared with placebo at week 26 [LS mean changes of -1.7 and -0.1 mmol/l (-29.8 and -2.6 mg/dl), respectively; $p < 0.001$; Figure 2C]. The greatest reductions in FPG with canagliflozin occurred at week 6, with a further small decrease at week 12 that attained a plateau through week 26. There were no discernable changes in FPG over time with placebo.

Body Weight and Blood Pressure. Significant reductions in body weight were seen with canagliflozin compared with placebo at week 26 (LS mean changes of -3.4 and -1.6 , respectively; $p < 0.001$; Figure 2D). The pattern of body weight reduction over time was similar in both treatment groups, with no apparent plateau at week 26; however, the magnitude of reduction was greater with canagliflozin than with placebo.

Significant reductions in systolic BP were seen with canagliflozin compared with placebo at week 26 (LS mean changes of -5.8 and 0.1 mmHg, respectively; $p < 0.001$;

Figure 2E). In the canagliflozin group, a progressive and steady decline in systolic BP was observed over 26 weeks, with no plateau. No discernable change in systolic BP over time was seen in the placebo group. At week 26, changes in diastolic BP were -3.3 and -0.2 mmHg with canagliflozin and placebo, respectively ($p = 0.002$). A greater proportion of patients achieved the endpoint of BP <140/90 mmHg [86.5 vs. 78.3%; OR (95% CI) of 2.8 (1.2, 6.5)] and BP <130/80 mmHg [54.2 vs. 32.5%; OR (95% CI) of 3.6 (1.7, 7.5)] with canagliflozin versus placebo.

Fasting Plasma Lipids. No meaningful differences were observed in mean changes from baseline in fasting cholesterol (LDL cholesterol and HDL cholesterol) and triglycerides with canagliflozin relative to placebo (Table S1, Supporting Information). Increases in LDL cholesterol (LS mean changes from baseline of 15.0% vs. 7.2%) and HDL cholesterol (5.4% vs. 2.5%) were seen with canagliflozin versus placebo at week 26. Increases from baseline in triglycerides were smaller with canagliflozin (9.8%) than with placebo (14.8%). Changes from baseline in non-HDL cholesterol were similar with canagliflozin (9.2%) and placebo (8.6%).

Safety and Tolerability

The overall incidence of AEs at week 26 was 39.8% (n = 43) and 44.4% (n = 48) for the canagliflozin and placebo groups, respectively. The incidence of AEs leading to discontinuation was low for both groups [0.9% (n = 1) and 2.8% (n = 3) for canagliflozin and placebo, respectively]. The incidence of AEs related to the study drug (possibly, probably or very likely related to study drug, as assessed by investigators) was 11.1% (n = 12) with canagliflozin and 8.3% (n = 9) with placebo. The incidence of serious AEs was 1.9% (n = 2) in both groups. No deaths were reported in the study.

The incidences of selected AEs of interest at week 26, including those related to the mechanism of SGLT2 inhibition, are summarized in Table 2. The incidence of female genital mycotic infections was higher with canagliflozin than with placebo [12.2% (n = 5) vs. 2.0% (n = 1)]. One man (1.5%) experienced a genital mycotic infection with canagliflozin, and no men experienced a genital mycotic infection with placebo. Most of the genital mycotic infections were mild and did not lead to study discontinuation. The incidence of urinary tract infections was 1.9% (n = 2) in both groups. None were serious, and no upper urinary tract infections were reported. One woman in the canagliflozin group discontinued the medication because of a genital mycotic infection occurring concomitantly with a urinary tract infection that was not considered to be related to the study drug. The incidence of osmotic diuresis-related AEs (e.g. thirst, increased urine frequency and volume) was 5.6% (n = 6) and 3.7% (n = 4) with canagliflozin and placebo, respectively. Osmotic diuresis-related AEs were mild, and most were regarded as related to the study drug; none led to study discontinuation. The incidence of volume depletion-related AEs (e.g. dehydration, dizziness postural) was low in both groups [0.9% (n = 1) and 1.9% (n = 2) with canagliflozin and placebo, respectively]. No fractures were reported with canagliflozin, whereas one fracture was reported in a patient receiving placebo (crush injury to the finger). The incidence of documented hypoglycaemia was 3.7% (n = 4) and 1.9% (n = 2) with canagliflozin and placebo, respectively. There were no reports of severe hypoglycaemia or ketone-related AEs (e.g. diabetic ketoacidosis, ketosis) in either group.

Changes from baseline in laboratory variables over 26 weeks were consistent with the expected profile of canagliflozin (Table S2, Supporting Information). Increases in haemoglobin (+4.4% vs. +0.2%), blood urea nitrogen (+15.9% vs. +2.9%) and serum creatinine (+2.3% vs. -1.4%), with commensurate decreases in eGFR (-1.6% vs. +1.4%) and serum urate (-3.1% vs. +1.9%), were seen with canagliflozin versus placebo. Greater reductions were observed with canagliflozin versus placebo in alanine aminotransferase (-12.0% vs. -3.2%) and aspartate aminotransferase (-6.3% vs. -2.1%). In addition, canagliflozin was associated with reductions in alkaline phosphatase and gamma-glutamyl transferase (-2.1% and -14.3%) compared with increases for placebo (+1.8 and +6.4%). An increase in total bilirubin was observed with canagliflozin versus placebo (+12.0% vs. -0.7%). Canagliflozin was also associated with increases in serum magnesium (+11.3% vs. -0.8%) and serum phosphate (+4.4% vs. +0.2%) compared with placebo; changes in serum calcium were similar with canagliflozin and placebo

Table 2. Summary of selected adverse events over 26 weeks.

Patients, n (%)	Placebo (n = 108)	Canagliflozin (n = 108)
UTIs	2 (1.9)	2 (1.9)
Genital mycotic infections		
Male [†]	0	1 (1.5)
Female ^{‡,§}	1 (2.0)	5 (12.2)
Osmotic diuresis-related AEs	4 (3.7)	6 (5.6)
Volume depletion-related AEs¶	2 (1.9)	1 (0.9)
Fracture AEs#	1 (0.9)	0
Ketone-related AEs	0	0
Hypoglycaemia episodes		
Documented hypoglycaemia**	2 (1.9)	4 (3.7)
Severe hypoglycaemia	0	0

AE, adverse event; UTI, urinary tract infection.

*Placebo, n = 57; canagliflozin, n = 67.

[†]Including balanoposthitis.

[‡]Placebo, n = 51; canagliflozin, n = 41.

[§]Including genital infection female, genital infection fungal, vulvovaginal candidiasis and vulvovaginal mycotic infection.

||Including dry mouth, pollakiuria, polyuria and thirst.

¶Including dehydration and dizziness postural.

#Including crush injury to the finger.

**Includes biochemically documented episodes [fingerstick or plasma glucose \leq 3.9 mmol/l (\leq 70 mg/dl)] with or without symptoms and severe episodes (i.e. requiring assistance from another person or resulting in seizure or loss of consciousness).

(+0.1% and -0.4%). There were no differences in laboratory variables meeting predefined limits of change criteria, except for haemoglobin, where a greater proportion of patients met the predefined limits of change criterion of a \geq 20 g/l increase from baseline with canagliflozin [6.5% (n = 6)] versus placebo (0%).

Discussion

In the present study of patients with T2DM inadequately controlled on metformin and sitagliptin, administration of canagliflozin using a dose-advancement algorithm throughout a 26-week period was followed by significant reductions in HbA1c and FPG, as well as clinically important weight loss and systolic BP reduction. The improvements in glycaemic control, body weight and BP seen with canagliflozin were consistent with previous reports [11–14,16–19,21–25], including triple therapy studies of canagliflozin as an addition to metformin plus sulphonylurea or metformin plus pioglitazone [15,20]. This suggests that canagliflozin can provide robust glycaemic efficacy, despite being added to an existing dual therapy regimen.

Another SGLT2 inhibitor, dapagliflozin, has been evaluated in combination with metformin and sitagliptin [26]; the placebo-subtracted change in HbA1c was -0.4% (baseline, 7.8%) with dapagliflozin 10 mg at 24 weeks. The HbA1c lowering provided by canagliflozin in this triple therapy regimen is of clinical importance and is consistent with observations of canagliflozin 300 mg in other “add-on” studies with a similar design and patient population [13,20]. This is probably attributable to the high proportion of patients (>90%) who

increased their canagliflozin dose to 300 mg, most within the first 8 weeks of treatment. A greater proportion of patients achieved HbA1c <7.0 and <8.0%, and a lower proportion had HbA1c >9.0% with canagliflozin treatment, consistent with diabetes-related quality measures for “good” and “poor” glycaemic control, as recommended by the National Committee for Quality Assurance Healthcare Effectiveness Data and Information Set (HEDIS) [27]. Clinically important FPG reductions were seen by week 6 (before dose advancement), with further decreases through to week 12. Body weight and systolic BP reductions with canagliflozin treatment were progressive over time, with further decreases observed between weeks 12 and 26, suggesting that the response had not yet plateaued. A greater proportion of patients achieved BP <140/90 mmHg (per HEDIS criteria) and BP <130/80 mmHg with canagliflozin versus placebo at week 26.

Titration of canagliflozin was generally well tolerated. The incidence of overall AEs and AEs leading to discontinuation with the addition of canagliflozin was similar to that seen with metformin and sitagliptin, further supporting the favourable safety/tolerability profile of canagliflozin as a triple therapy partner. Notably, the incidence of hypoglycaemia was low despite triple therapy with maximum or near-maximum effective doses of metformin and sitagliptin; this was not surprising because of the low inherent risk of hypoglycaemia with canagliflozin when added to agents not associated with hypoglycaemia. There was an increased incidence of genital mycotic infections among women treated with canagliflozin, which is related to the increased urinary glucose excretion observed with SGLT2 inhibition [28]. Most genital mycotic infections were considered to be mild in intensity and did not lead to discontinuation. The incidence of urinary tract infections was low and balanced between treatment groups.

The incidence of volume depletion-related AEs was numerically smaller in the canagliflozin group compared with placebo, and lower than that generally reported in other studies of canagliflozin [29]. While the present study was relatively small in size and the number of volume depletion-related AEs was too limited to draw definitive conclusions, these findings suggest that starting patients on canagliflozin 100 mg and increasing to the 300 mg dose may lead to a reduced occurrence of volume depletion-related AEs and an overall improved safety/tolerability profile.

The present study was the first to evaluate the efficacy and safety of canagliflozin when administered using a step-wise titration from 100 to 300 mg in patients with T2DM, consistent with recommendations provided in the canagliflozin prescribing information [8]. Findings from the present study show that the efficacy of canagliflozin was not diminished with titration in eligible patients (i.e. baseline eGFR ≥ 70 ml/min/1.73 m², fasting SMBG ≥ 5.6 mmol/l and no volume depletion-related AEs <2 weeks before dose increase). The titration algorithm used in this study offers one option for canagliflozin dose advancement, but others are being evaluated. The ongoing CANVAS-R trial (CANagliflozin cardioVascular Assessment Study renal endpoints; ClinicalTrials.gov Identifier: NCT01989754), in patients with T2DM and a history or

high risk of cardiovascular disease, uses an alternate titration algorithm and may provide an opportunity to achieve maximum efficacy while mitigating potential tolerability issues with long-term canagliflozin treatment.

In summary, titrated canagliflozin provided robust and significant improvements in glycaemic control, body weight and BP compared with placebo over 26 weeks in patients with T2DM inadequately controlled on metformin and sitagliptin. Canagliflozin was generally well tolerated, with a higher incidence of genital mycotic infections related to the mechanism of SGLT2 inhibition. The insulin-independent mechanism of SGLT2 inhibitors is distinct from other classes of antihyperglycaemic agents; thus, canagliflozin has the potential to be used in combination with a wide range of other agents in patients with T2DM at different stages of the disease. Overall, findings from this study support the use of canagliflozin in patients with T2DM inadequately controlled on metformin and sitagliptin.

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Conflict of Interest

H. W. R. has served as a consultant and speaker for AstraZeneca, Boehringer Ingelheim, Bidel, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi and Regeneron and has received research support from AstraZeneca, Bidel, Bristol-Myers Squibb, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi and Regeneron. J. S. has attended advisory boards and/or speaker's bureaus for Takeda, Bayer, Novartis, Merck Sharp & Dohme, Amgen, AstraZeneca, Bristol-Myers Squibb, Novo Nordisk, Sanofi Aventis, Berlin-Chemie, Eli Lilly, Boehringer Ingelheim, Merck, Roche, Ipsen, Pfizer, Janssen and LifeScan, and has received research support from Takeda, Novartis, Merck Sharp & Dohme, Amgen, GlaxoSmithKline, Novo Nordisk, Sanofi Aventis, Ipsen, Pfizer, Janssen, Servier, Eli Lilly, Apitope, Intarcia and Roche. N. A. has served on a national advisory board for Janssen Canada for canagliflozin and has no other financial disclosures. A. C., A. F. and M. A. are full-time employees of Janssen Research & Development, LLC. M. P. is a full-time employee of Janssen Scientific Affairs, LLC.

H. W. R., J. S. and N. A. contributed to the conduct of the study and the interpretation of data, and drafted, reviewed and approved the manuscript. A. C., A. F. and M. P. contributed to the analysis and interpretation of data and drafted, reviewed and approved the manuscript. M. A. contributed to the design and conduct of the study and the acquisition, analysis and interpretation of data, and drafted, reviewed and approved the manuscript.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Summary of changes from baseline in fasting plasma lipids at week 26 (LOCF).*

Table S2. Mean changes in clinical laboratory parameters at week 26.*

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