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Efficacy and Safety of Twice-Daily Treatment With Canagliflozin, a Sodium Glucose Co-Transporter 2 Inhibitor, Added on to Metformin Monotherapy in Patients With Type 2 Diabetes Mellitus

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ABSTRACT

Aim: To evaluate the efficacy/safety of canagliflozin twice daily (BID) compared with placebo in patients with type 2 diabetes mellitus (T2DM) on metformin.

Methods: In this 18-week, randomised, double-blind, placebo-controlled study, patients (N=279) at 60 centres in 7 countries received canagliflozin 50 or 150 mg or placebo BID. The pre-specified primary endpoint was change from baseline in HbA_{1c} at Week 18. Pre-specified secondary endpoints included proportion of patients reaching HbA_{1c} <7.0%, change in fasting plasma glucose (FPG) and percent change in body weight; changes in systolic blood pressure (BP) and fasting plasma lipids were also evaluated. Adverse events (AEs) were recorded throughout the study.

Results: From a mean baseline HbA_{1c} of 7.6% (60 mmol/mol), canagliflozin 50 and 150 mg BID significantly reduced HbA_{1c} compared with placebo at Week 18 (–0.45%, –0.61%, –0.01% [–5, –7, –0.1 mmol/mol], respectively; P <0.001). More patients achieved HbA_{1c} <7.0% with canagliflozin than placebo (P <0.05). Relative to placebo, both canagliflozin doses significantly lowered FPG and body weight (P <0.001), and reduced systolic BP. Overall AE incidence was 35.5%, 40.9%, 36.6% with canagliflozin 50 and 150 mg BID and placebo, respectively. Canagliflozin was associated with increased incidences of urinary tract infections, female genital mycotic infections, and osmotic diuresis-related AEs; these led to few discontinuations. The incidence of documented hypoglycaemia was low across groups.

Conclusions: Canagliflozin 50 and 150 mg BID provided significant glycaemic efficacy and body weight reduction, and were generally well tolerated in patients with T2DM on background metformin.

Clinicaltrials.gov Identifier: NCT01340664

Keywords: type 2 diabetes mellitus; sodium glucose co-transporter 2 (SGLT2) inhibitor; canagliflozin; metformin; twice daily (BID)

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic disease that often requires combination therapy with antihyperglycaemic agents (AHAs) as the disease progresses [1-3]. Metformin is the standard first-line pharmacologic therapy for patients who do not achieve and maintain adequate glycaemic control with diet and exercise alone [2]. Metformin is a biguanide that reduces hepatic glucose production and improves peripheral insulin sensitivity; immediate-release (IR) formulations of metformin are typically administered twice daily (BID) [4]. For patients on metformin monotherapy who require better glycaemic control, several classes of AHAs may be added as dual therapy; however, some of these agents are associated with adverse effects such as weight gain or hypoglycaemia [2]. Of note, the HbA_{1c}-lowering efficacy of oral AHAs has been shown to be impacted by patients' baseline HbA_{1c} values, with greater HbA_{1c} lowering observed in patients with higher baseline HbA_{1c} [5].

Canagliflozin is a sodium glucose co-transporter 2 (SGLT2) inhibitor developed for the treatment of adult patients with T2DM [6-15]. Canagliflozin reduces plasma glucose in individuals with hyperglycaemia by inhibiting renal glucose reabsorption and increasing urinary glucose excretion, and is associated with a mild osmotic diuresis. In Phase 3 studies in patients with T2DM, once-daily (QD) doses of canagliflozin 100 and 300 mg provided glycaemic improvements and reductions in body weight and systolic blood pressure (BP), and were generally well tolerated as monotherapy and in combination with a variety of other AHAs [7-13,15]. This 18-week, Phase 2 study evaluated the efficacy and safety of canagliflozin BID dosing compared with placebo as add-on therapy in patients with T2DM inadequately controlled

with metformin monotherapy, to support the development of a fixed-dose combination of canagliflozin and metformin IR.

PATIENTS, MATERIALS, AND METHODS

Patients and study design

This was a randomised, double-blind, placebo-controlled, Phase 2 study conducted at 60 centres in 7 countries (ClinicalTrials.gov Identifier: NCT01340664). The study consisted of a 2-week, single-blind, placebo run-in period; an 18-week, double-blind, treatment period; and a 30-day, post-treatment, follow-up period. Eligible patients were men and women with T2DM aged 18 to 80 years who had inadequate glycaemic control (HbA_{1c} ≥7.0% [53 mmol/mol] and ≤10.5% [91 mmol/mol]) on metformin monotherapy at protocol-specified doses (≥2,000 mg/day, or ≥1,500 mg/day if unable to tolerate a higher dose) for ≥8 weeks prior to screening. Patients also had fasting plasma glucose (FPG) <15 mmol/L at Week –2, and fasting fingerstick glucose ≥6.1 and <15 mmol/L on Day 1.

Patients were excluded from the study if they had repeated FPG and/or fasting self-monitored blood glucose ≥15.0 mmol/L during the pretreatment phase; history of type 1 diabetes or diabetic ketoacidosis; history of cardiovascular disease (including myocardial infarction, unstable angina, revascularisation procedure, or cerebrovascular accident) within 3 months before screening; uncontrolled hypertension; treatment with a peroxisome proliferator-activated receptor γ agonist, insulin, another SGLT2 inhibitor, or any other AHA (except metformin monotherapy) within 12 weeks before screening; or estimated glomerular filtration rate (eGFR) <55 mL/min/1.73 m^2 (or

<60 mL/min/1.73 m^2 if based upon restriction in local metformin label) or serum creatinine ≥124 µmol/L (men) or ≥115 µmol/L (women).

Eligible patients first entered the single-blind, placebo run-in period, during which they received placebo capsules matching the double-blind study drug. Patients were instructed to take placebo BID, with 1 capsule given with the morning meal and 1 given with the evening meal, along with metformin at each meal. Patients took the last dose of single-blind placebo the day before the baseline (Day 1) visit. Patients who met all enrolment criteria were then randomised to receive canagliflozin 50 or 150 mg or placebo BID in a 1:1:1 ratio. Randomisation was balanced using permuted blocks and was stratified according to whether the patient's HbA_{1c} value at Week –2 was <8.0% or ≥8.0%. During the double-blind period, patients took their first dose of canagliflozin 50 or 150 mg or placebo on Day 1 at the study centre. The last dose of the double-blind period was taken with the evening meal on the day prior to the Week 18 visit. After randomisation, HbA_{1c} and FPG values were masked to study centres; FPG values were unmasked if they met specific glycaemic withdrawal criteria (>15.0 mmol/L after Day 1 through Week 6, >13.3 mmol/L after Week 6 through Week 12, and >11.1 mmol/L after Week 12 through Week 18).

This study was conducted in accordance with ethical principles that comply with the Declaration of Helsinki, and are consistent with Good Clinical Practices and applicable regulatory requirements. The study protocol and amendments were approved by institutional review boards at participating institutions. All participants provided written informed consent prior to participation.

Endpoints and assessments

The pre-specified primary endpoint was change from baseline in HbA_{1c} at Week 18. Pre-specified secondary endpoints at Week 18 included change in FPG, percent change in body weight, and the proportion of patients achieving HbA_{1c} <7.0% (53 mmol/mol). It was noted that ~20% of patients who were eligible for the trial (based on HbA_{1c} ≥7.0% at Week –2) had a baseline HbA_{1c} <7.0%; therefore, a pre-specified sensitivity analysis was performed to assess change in HbA_{1c} in patients with baseline HbA_{1c} ≥7.0% (53 mmol/mol). Changes in systolic and diastolic BP and percent changes in fasting plasma lipids (including triglycerides, high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], LDL-C/HDL-C ratio, and non–HDL-C) were also assessed.

Safety was evaluated based on adverse event (AE) reports, safety laboratory tests, vital sign measurements, 12-lead electrocardiograms, and physical examinations. AEs pre-specified for additional data collection included urinary tract infections (UTIs) and genital mycotic infections. Assessment of documented hypoglycaemia episodes included biochemically documented episodes (concurrent fingerstick or plasma glucose ≤3.9 mmol/L with or without symptoms) and severe episodes (ie, those requiring the assistance of another individual or resulting in seizure or loss of consciousness).

Statistical analyses

Sample size determination was based on the primary objective of demonstrating the superiority of canagliflozin 150 mg BID versus placebo in lowering HbA_{1c} at Week 18. Using a 2-sample, 2-sided *t*-test with a type I error rate of 0.05, and assuming a group difference of 0.5% and a

common standard deviation (SD) of 1.0%, 85 patients per group were estimated to be required to achieve 90% power. Sample size was expanded to 90 patients per group to account for potential patients with missing HbA_{1c} values at study endpoint.

Efficacy analyses were performed using the modified intent-to-treat (mITT) population, consisting of all randomised patients who received ≥1 dose of study drug. The last observation carried forward (LOCF) approach was used to impute missing efficacy data. Safety analyses were performed on the same population analysed according to the predominant treatment received; in this study, the safety analysis set was identical to the mITT analysis set.

Primary and continuous secondary efficacy endpoints were assessed using an analysis of covariance (ANCOVA) model with treatment and stratification factors (ie, whether or not HbA_{1c} at screening was ≥8.0%) as fixed effects and the corresponding baseline value as a covariate. Least squares (LS) mean differences between treatment groups and the associated 2-sided 95% confidence intervals (CIs) were estimated based on this model. A mixed model for repeated measures (MMRM) based on restricted maximum likelihood was also pre-specified as a sensitivity analysis for the primary efficacy analysis, in order to assess the data longitudinally. The categorical secondary efficacy endpoint (ie, proportion of patients reaching HbA_{1c} <7.0% [53 mmol/mol]) was analysed using a logistic regression model including terms for treatment and stratification factor, and adjusting for baseline HbA_{1c} as a covariate. A pre-specified, hierarchical testing sequence was implemented to strongly control overall type I error due to multiplicity. All statistical tests were interpreted at a 2-sided significance level of 0.05, and *P* values are reported for pre-specified comparisons only.

RESULTS

Patient disposition and baseline characteristics

A total of 279 patients were randomised, all of whom received ≥1 dose of study drug and were included in the mITT analysis set; of these, 251 (90%) completed 18 weeks of treatment (**Figure 1**). The rate of study discontinuation before Week 18 was 8.6%, 14.0%, and 7.5% with canagliflozin 50 and 150 mg BID and placebo, respectively. The 3 most common reasons for discontinuation were AEs (2.9%), withdrawal of consent (2.2%), and other (1.8%). Baseline demographic and disease characteristics were generally similar across groups (**Table 1)**. Notably, 22.2% of patients had HbA_{1c} <7.0% (53 mmol/mol) at baseline, despite the inclusion criteria of HbA_{1c} ≥7.0% (53 mmol/mol) and ≤10.5% (91 mmol/mol).

Efficacy

Glycaemic parameters

From a mean baseline HbA_{1c} of 7.6% (60 mmol/mol), canagliflozin 50 and 150 mg BID significantly reduced HbA_{1c} from baseline compared with placebo at Week 18, with differences in LS mean changes of −0.44% (−5 mmol/mol) and −0.60% (−7 mmol/mol), respectively (*P* <0.001 for both; **Figures 2A and 2B**). The pre-specified MMRM analysis showed similar changes in HbA_{1c}. Significantly higher proportions of patients achieved HbA_{1c} <7.0% (53 mmol/mol) at Week 18 with canagliflozin 50 and 150 mg BID compared with placebo (47.8%, 57.1%, and 31.5%, respectively; *P* <0.05 and *P* <0.001 vs placebo, respectively). In the pre-specified sensitivity analysis in patients with baseline HbA_{1c} ≥7.0%, canagliflozin 50 and 150 mg BID reduced HbA_{1c} compared with placebo (differences in LS mean changes of –0.5% [–6 mmol/mol] and –0.7% [–8 mmol/mol]; **Figure 2C**).

Both canagliflozin doses significantly reduced FPG compared with placebo (differences in LS mean changes of −1.3 mmol/L for both; *P* <0.001; **Figure 2D**). The median reductions in FPG were –0.7 and –1.2 mmol/L with canagliflozin 50 and canagliflozin 150 mg BID, while a median increase in FPG was seen with placebo (0.3 mmol/L).

Body weight, BP, and lipids

Relative to placebo, canagliflozin 50 and 150 mg BID significantly reduced body weight at Week 18 (differences in LS mean changes of −2.2% and −2.6%, respectively; *P* <0.001; **Figure 2E**). Changes from baseline in BP and fasting plasma lipids at Week 18 are presented in **Table 2**. Canagliflozin 50 and 150 mg BID lowered systolic BP compared with placebo at Week 18 (differences in LS mean changes of −5.4 and −5.7 mmHg, respectively). Diastolic BP was also reduced with both canagliflozin doses versus placebo, with minimal changes in pulse rate observed across groups (mean changes of 0.9, 1.4, and 0.0 beats per minute with canagliflozin 50 and 150 mg BID and placebo, respectively). Canagliflozin 150 mg BID was associated with an LS mean percent increase in triglycerides compared with canagliflozin 50 mg BID and placebo. A median percent decrease in triglycerides was seen with canagliflozin 150 mg BID, suggesting that the change in LS means may be influenced by outliers; canagliflozin 50 mg BID was associated with a modest median percent increase in triglycerides relative to the placebo. A larger increase in HDL-C was also seen with canagliflozin 150 mg BID compared with canagliflozin 50 mg BID and placebo. Minimal changes were observed with canagliflozin versus placebo in LDL-C and non–HDL-C. Canagliflozin 150 mg BID was associated with a decrease in LDL-C/HDL-C ratio compared with canagliflozin 50 mg BID and placebo.

Safety

The overall incidence of AEs was 35.5%, 40.9%, and 36.6% with canagliflozin 50 and 150 mg BID and placebo, respectively, over 18 weeks (**Table 3**). The incidence of serious AEs was low across groups (0%, 3.2%, and 1.1% with canagliflozin 50 and 150 mg BID and placebo, respectively). The incidence of AEs leading to discontinuation was 1.1% (1 patient), 7.5% (7 patients), and 0% with canagliflozin 50 and 150 mg BID and placebo, respectively. In the canagliflozin 150 mg BID group, 2 patients discontinued the study due to AEs of vulvovaginal pruritus; no other individual specific AE term led to discontinuation in more than 1 patient.

Canagliflozin 50 and 150 mg BID were associated with a higher incidence of urinary tract infections (UTIs; 4.3% for both) compared with placebo (2.2%). Most UTIs in canagliflozin-treated patients were mild and only 1 led to study discontinuation; 1 (1.1%) patient in the canagliflozin 150 mg BID group who had an indwelling urinary catheter reported an upper UTI (pyelonephritis) that was a serious AE. Canagliflozin 50 mg BID was associated with a higher incidence of genital mycotic infections in females than canagliflozin 150 mg BID and placebo (11.3%, 2.0%, and 4.3%, respectively); most events with canagliflozin were mild or moderate in intensity and none led to discontinuation. Two males reported genital mycotic infections: 1 (2.5%) in the canagliflozin 50 mg BID group and 1 (2.2%) in the placebo group. The incidence of AEs related to osmotic diuresis (eg, pollakiuria [increased urine frequency]) was 7.5% with canagliflozin 150 mg BID, with none reported in the other groups; all events were mild and none led to discontinuation. No AEs related to volume depletion (eg, postural dizziness, orthostatic hypotension) were reported.

The incidence of documented hypoglycaemia was low and similar across groups (4.3%, 3.2%, and 3.2% with canagliflozin 50 and 150 mg BID and placebo, respectively). No severe hypoglycaemia events were reported.

Generally, only small differences were observed with canagliflozin relative to placebo in mean percent changes from baseline in laboratory parameters over 18 weeks (**Supplementary Table 1**). Reductions in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were observed with canagliflozin 150 mg BID, whereas increases were seen with canagliflozin 50 mg BID and placebo. Mean percent increases in serum bilirubin and blood urea nitrogen were observed across groups, with relatively higher increases in canagliflozin-treated patients compared with those receiving placebo. Small decreases in eGFR were observed across groups, with commensurate changes seen in serum creatinine. Decreases in serum urate were observed with both canagliflozin doses, whereas minimal change was seen with placebo. Increases in haemoglobin were observed with both canagliflozin doses versus placebo. Median percent changes generally showed similar trends (**Supplementary Table 1**); differences between mean and median changes in some parameters (ie, ALT, AST, and bilirubin) may be related to outliers.

DISCUSSION

This Phase 2 study evaluated the efficacy and safety of canagliflozin BID dosing in patients with T2DM inadequately controlled on maximally effective doses of metformin monotherapy, in support of the development of a fixed-dose combination of canagliflozin and metformin IR. Canagliflozin doses of 50 and 150 mg BID were selected to provide the same total daily doses (ie, 100 and 300 mg QD) as those approved for the treatment of patients with T2DM [6].

Canagliflozin 50 and 150 mg BID provided significant improvements in glycaemic control and reductions in body weight compared with placebo. In the overall patient population with a lower than expected HbA_{1c} at baseline (mean HbA_{1c} of 7.6% [60 mmol/mol]) resulting from the high proportion of patients with HbA_{1c} <7.0%, both canagliflozin doses significantly reduced HbA_{1c}, and a higher proportion of canagliflozin-treated patients achieved HbA_{1c} <7.0% (53 mmol/mol) compared with placebo at Week 18. Reductions in HbA_{1c} from baseline were also seen with canagliflozin versus placebo in a pre-specified sensitivity analysis in patients with baseline HbA_{1c} values ≥7.0% (53 mmol/mol). Both canagliflozin doses were associated with reductions in FPG, body weight, and systolic and diastolic BP. Canagliflozin 150 mg BID was associated with a mean increase in triglycerides; however, a median percent decrease in triglycerides was seen with canagliflozin 150 mg BID, suggesting that the change in LS means may be influenced by outliers. Canagliflozin 150 mg BID was also associated with an increase in HDL-C, compared with canagliflozin 50 mg BID and placebo. No notable differences were observed across treatment groups in LDL-C, whereas dose-related increases in LDL-C have been observed in other Phase 3 studies of canagliflozin [7,9-13,15]. Differences in lipids outcomes relative to other canagliflozin studies may be derived from the small population in the present study.

Overall, efficacy findings with canagliflozin 50 and 150 mg BID in the present study were generally consistent with those observed in Phase 3 studies of canagliflozin 100 and 300 mg QD [7-13,15], with the canagliflozin 150 mg BID dose providing an incremental benefit in HbA_{1c} and body weight reduction relative to the canagliflozin 50 mg BID dose. The lack of a dose-response in FPG changes may reflect an impact of outlying data, as the median reduction in FPG was greater with canagliflozin 150 mg BID than with canagliflozin 50 mg BID (–1.2 vs –0.7

mmol/L). The absence of substantive differences between BID and QD dosing of canagliflozin, at the same total daily doses, was expected based on previous Phase 1 studies that included both BID and QD dosing [16,17].

Of note, the HbA_{1c} reduction reported for the overall population in the present study was lower than that reported in prior Phase 3 studies [7-13,15]. In a meta-analysis of the relationship between baseline glycaemia and HbA_{1c} reduction in published studies of oral AHAs, baseline HbA_{1c} was found to impact HbA_{1c} reductions following AHA treatment, with a greater apparent treatment effect observed with higher baseline HbA_{1c} [5]. Thus, the lesser HbA_{1c} reduction observed in the present 18-week study relative to prior 26-week Phase 3 studies is likely related, in part, to the lower baseline HbA_{1c} in the overall study population. Consistent with this, numerically greater HbA_{1c} reductions were observed with both canagliflozin doses versus placebo when assessed in a subset of patients with baseline HbA_{1c} ≥7.0% (53 mmol/mol). The difference in glycaemic efficacy may also be related to the shorter duration of this study (18 weeks) compared with previous Phase 3 studies (26-52 weeks). Notably, in the overall study population, significantly higher proportions of canagliflozin-treated patients achieved HbA_{1c} <7.0% (53 mmol/mol) compared with patients treated with placebo, demonstrating meaningful glycaemic efficacy with canagliflozin treatment in this population.

Canagliflozin 50 and 150 mg BID were generally well tolerated, with 1 or both doses associated with increased incidences of UTIs, female genital mycotic infections, and AEs related to osmotic diuresis. These AEs were generally mild to moderate in severity, and infrequently led to study discontinuation. Canagliflozin treatment was not associated with an increased incidence of

hypoglycaemia compared with placebo. The safety profile observed for canagliflozin BID dosing in the current study is generally similar to that seen with prior Phase 3 canagliflozin studies [7-13,15].

Despite several potential limitations of the current study, including the relatively small number of patients enrolled in the study, a generally lower baseline HbA_{1c} in this patient population compared with those in Phase 3 studies, and a low representation of some races/ethnicities in the patient population (as a function of study centres), findings were generally consistent with Phase 3 studies of canagliflozin. Longer-term studies of canagliflozin 50 and 150 mg BID in larger and broader patient populations may be helpful for further elucidation of the efficacy and safety of canagliflozin BID dosing regimens. Furthermore, it would be beneficial to include canagliflozin 100 and 300 mg QD arms in future studies to allow for direct comparisons of BID and QD dosing.

In conclusion, canagliflozin BID dosing, at total daily doses of 100 and 300 mg, provided significant glycaemic efficacy. Reductions in HbA_{1c} were modest, consistent with the lower baseline HbA_{1c} in the present study compared with previous Phase 3 studies of canagliflozin. Reductions in body weight and systolic BP were also observed, and canagliflozin BID was generally well tolerated as add-on to metformin monotherapy. Overall, findings from this study indicate a favourable efficacy and safety/tolerability profile of canagliflozin in combination with metformin.

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CONFLICT OF INTEREST

RQ, GC, and GM are full-time employees of Janssen Research & Development, LLC.

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FIGURE LEGENDS

Figure 1. Study flow diagram.

PBO, placebo; CANA, canagliflozin; BID, twice daily; AE, adverse event; eGFR, estimated glomerular filtration rate; mITT, modified intent-to-treat.

Figure 2. Changes in efficacy parameters (LOCF).[a] (A) Change in HbA_{1c} over time, (B) mean HbA_{1c} over time, (C) change in HbA_{1c} at Week 18 in patients with baseline HbA_{1c} ≥7.0%, (D) change in FPG over time, and (E) percent change in body weight over time.

LOCF, last observation carried forward; FPG, fasting plasma glucose; PBO, placebo; CANA, canagliflozin; BID, twice daily; LS, least squares; SE, standard error; CI, confidence interval.

[a]To convert values for HbA_{1c} in % into mmol/mol, subtract 2.15 and multiply by 10.929, or use the conversion calculator at www.HbA1c.nu/eng/.

TABLES

Table 1. Baseline Demographic and Disease Characteristics[a]

Characteristic	PBO (n = 93)	CANA 50 mg BID (n = 93)	CANA 150 mg BID (n = 93)	Total (N = 279)
Sex, n (%)				
Male	46 (49.5)	40 (43.0)	44 (47.3)	130 (46.6)
Female	47 (50.5)	53 (57.0)	49 (52.7)	149 (53.4)
Age, y	57.0 (9.3)	58.6 (8.9)	56.7 (10.3)	57.4 (9.5)
Race, n (%)[b]				
White	73 (78.5)	75 (80.6)	83 (89.2)	231 (82.8)
Black or African American	4 (4.3)	5 (5.4)	1 (1.1)	10 (3.6)
Asian	9 (9.7)	3 (3.2)	6 (6.5)	18 (6.5)
Other[c]	7 (7.5)	10 (10.8)	3 (3.2)	20 (7.2)
HbA_{1c}, % (mmol/mol)	7.7 ± 0.9	7.6 ± 0.9	7.6 ± 0.9	7.6 ± 0.9
	(61 ± 9.8)	(60 ± 9.8)	(60 ± 9.8)	(60 ± 9.8)
Category, n (%)				

<7.0%	20 (21.5)	21 (22.6)	21 (22.6)	62 (22.2)
≥7.0%	73 (78.5)	72 (77.4)	72 (77.4)	217 (77.8)
FPG, mmol/L	9.0 ± 1.9	9.0 ± 2.0	9.1 ± 1.9	9.0 ± 1.9
Body weight, kg	90.5 ± 18.1	91.2 ± 23.9	90.2 ± 19.1	90.6 ± 20.4
BMI, kg/m^2	32.3 ± 5.7	33.0 ± 7.0	32.3 ± 6.8	32.5 ± 6.5
Duration of diabetes, y	7.0 ± 6.4	6.7 ± 4.9	7.3 ± 6.0	7.0 ± 5.8
eGFR, mL/min/ 1.73 m^2	84.8 ± 16.5	86.9 ± 18.0	85.9 ± 15.3	85.9 ± 16.6
Metformin treatment at baseline				
Category, n (%)				
Extended release	24 (26)	20 (22)	15 (16)	59 (21)
Immediate release	69 (74)	73 (78)	78 (84)	220 (79)
Mean daily dose, mg/d	2,131 ± 343.1	2,137 ± 304.1	2,128 ± 341.6	2,132 ± 328.9

PBO, placebo; CANA, canagliflozin; BID, twice daily; FPG, fasting plasma glucose; BMI, body mass index; eGFR, estimated glomerular filtration rate; SD, standard deviation.

[a]Data are mean ± SD unless otherwise indicated.

[b]Percentages may not total 100.0% due to rounding.

[c]Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, and other.

Table 2. Summary of Changes in BP and Fasting Plasma Lipids at Week 18 (LOCF)[a]

Parameter	PBO (n = 93)	CANA 50 mg BID (n = 93)	CANA 150 mg BID (n = 93)
Systolic BP, n	92	90	91
Mean ± SD baseline, mmHg	128.6 ± 11.0	131.1 ± 12.4	128.2 ± 12.0
LS mean ± SE change	3.3 ± 1.1	–2.1 ± 1.1	–2.4 ± 1.1
Difference vs PBO (95% CI)		–5.4 (–8.4, –2.3)	–5.7 (–8.7, –2.6)
Diastolic BP, n	92	90	91
Mean ± SD baseline, mmHg	77.8 ± 7.2	78.1 ± 7.4	78.5 ± 7.7
LS mean change ± SE	1.2 ± 0.7	–1.2 ± 0.7	–1.8 ± 0.7
Difference vs PBO (95% CI)		–2.4 (–4.3, –0.4)	–3.1 (–5.0, –1.1)
Triglycerides, n	88	90	88
Mean ± SD baseline, mmol/L	2.0 ± 1.3	1.9 ± 0.8	2.2 ± 1.7
LS mean ± SE change	–0.06 ± 0.09	–0.02 ± 0.09	0.00 ± 0.09
Median percent change (95% CI)	1.4 (–10.7, 7.7)	4.2 (–3.7, 10.5)	–1.4 (–17.2, 9.7)
LS mean ± SE percent change	6.7 ± 4.8	5.5 ± 4.7	13.7 ± 4.8

Difference vs PBO (95% CI)		–1.2 (–14.3, 12.0)	7.0 (–6.2, 20.3)
LDL-C, n	87	90	88
Mean ± SD baseline, mmol/L	2.6 ± 1.1	2.8 ± 1.0	2.7 ± 0.9
LS mean ± SE change	0.13 ± 0.07	0.18 ± 0.07	0.10 ± 0.07
Median percent change (95% CI)	4.3 (–3.1, 9.4)	3.6 (–0.7, 8.7)	5.1 (–0.7, 10.3)
LS mean ± SE percent change	8.6 ± 3.0	10.4 ± 2.9	7.9 ± 3.0
Difference vs PBO (95% CI)		1.8 (–6.5, 10.1)	–0.7 (–9.0, 7.6)
HDL-C, n	87	90	88
Mean ± SD baseline, mmol/L	1.2 ± 0.3	1.2 ± 0.3	1.3 ± 0.3
LS mean ± SE change	0.03 ± 0.02	0.04 ± 0.02	0.10 ± 0.02
Median percent change (95% CI)	2.3 (–1.5, 6.1)	2.7 (0.0, 6.2)	6.8 (2.9, 10.9)
LS mean ± SE percent change	2.6 ± 1.5	3.8 ± 1.5	8.9 ± 1.5
Difference vs PBO (95% CI)[b]		1.2 (–3.0, 5.5)	6.4 (2.1, 10.6)
LDL-C/HDL-C, n	87	90	88
Mean ± SD baseline, mol/mol	2.2 ± 0.9	2.4 ± 0.9	2.2 ± 0.8
LS mean ± SE change	0.06 ± 0.07	0.12 ± 0.07	–0.06 ± 0.07

Median percent change (95% CI)	2.0 (–0.7, 6.5)	1.4 (–5.4, 7.7)	–3.4 (–7.6, 1.3)
LS mean ± SE percent change	6.6 ± 3.1	8.3 ± 3.1	0.9 ± 3.1
Difference vs PBO (95% CI)		1.6 (–7.0, 10.3)	–5.7 (–14.3, 2.9)
Non–HDL-C, n	87	89	88
Mean ± SD baseline, mmol/L	3.5 ± 1.2	3.7 ± 1.1	3.7 ± 1.1
LS mean ± SE change	0.12 ± 0.09	0.21 ± 0.09	0.11 ± 0.09
Median percent change (95% CI)	2.6 (–3.7, 8.1)	4.1 (–0.9, 8.3)	3.2 (–0.3, 6.5)
LS mean ± SE percent change	5.9 ± 2.7	8.4 ± 2.7	5.9 ± 2.7
Difference vs PBO (95% CI)		2.6 (–5.0, 10.1)[b]	0.1 (–7.5, 7.6)[b]

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

[a]Statistical comparisons versus PBO not performed (not pre-specified).

Table 3. Summary of Overall Safety and Selected AEs Over 18 Weeks

	Patients, n (%)		
	PBO (n = 93)	**CANA 50 mg BID (n = 93)**	**CANA 150 mg BID (n = 93)**
Any AE	34 (36.6)	33 (35.5)	38 (40.9)
AEs leading to discontinuation	0	1 (1.1)[a]	7 (7.5)[b]
AEs related to study drug[c]	2 (2.2)	11 (11.8)	15 (16.1)
Serious AEs	1 (1.1)	0	3 (3.2)
Deaths	0	0	1 (1.1)
Selected AEs			
UTI	2 (2.2)	4 (4.3)	4 (4.3)
Genital mycotic infection			
Male[d,e]	1 (2.2)	1 (2.5)	0
Female[f,g]	2 (4.3)	6 (11.3)	1 (2.0)
Osmotic diuresis-related AEs[h]	0	0	7 (7.5)
Volume depletion AEs	0	0	0

AE, adverse event; PBO, placebo; CANA, canagliflozin; BID, twice daily; UTI, urinary tract infection.

[a]Specific term of headache.

[b]Specific terms included colon cancer (n = 1), dermatitis allergic (n = 1), glomerular filtration rate decreased (n = 1), nephrolithiasis (n = 1), palpitations (n = 1), pyelonephritis (n = 1), and vulvovaginal pruritus (n = 2). One patient experienced 2 AEs (pyelonephritis and nephrolithiasis) that were reported to lead to discontinuation.

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

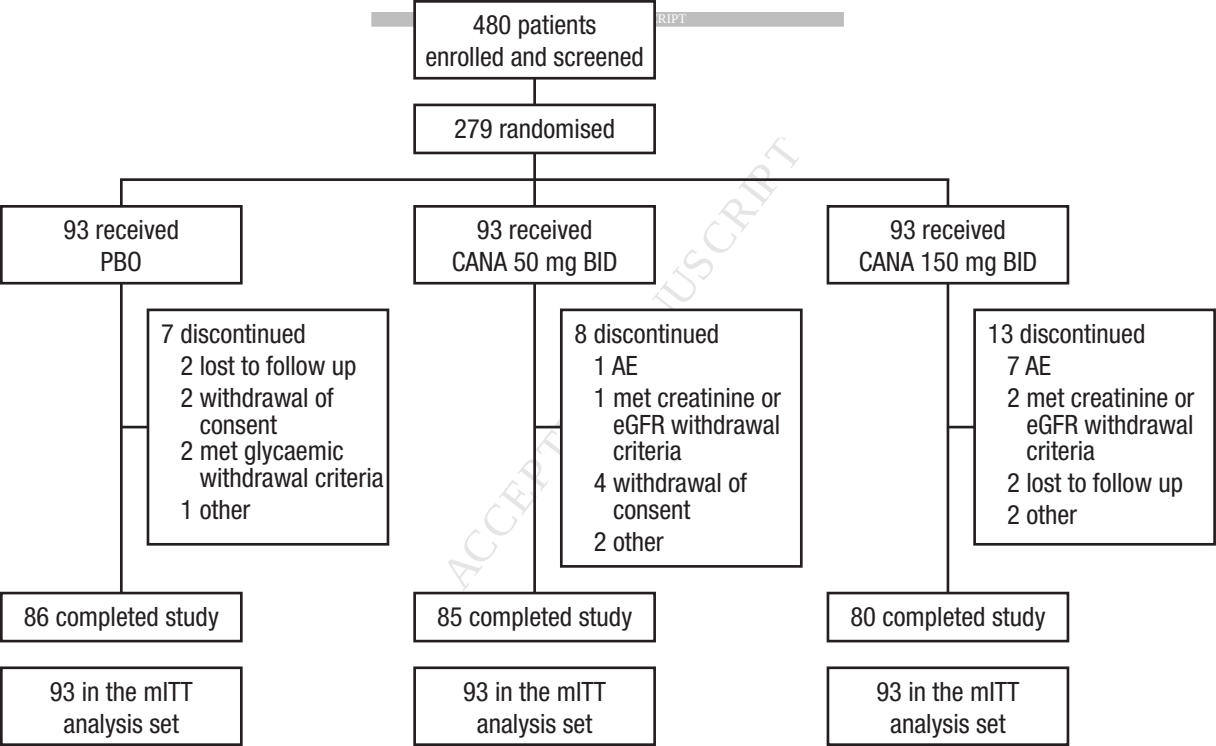
[d]PBO, n = 46; CANA 50 mg BID, n = 40; CANA 150 mg BID, n = 44.

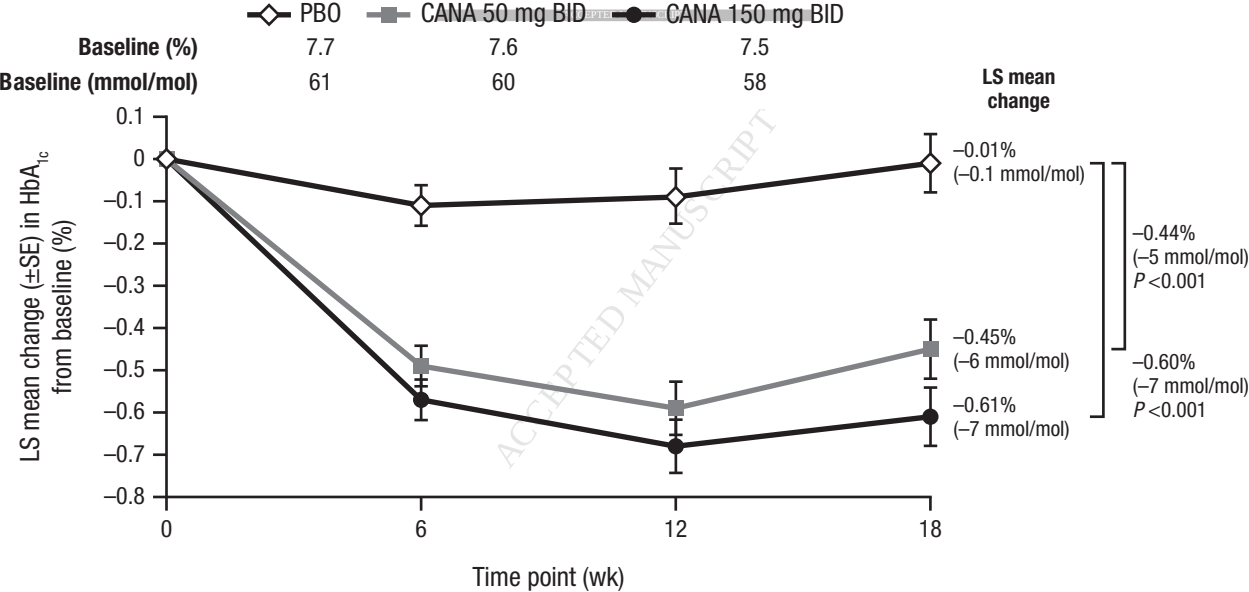
[e]Including balanitis candida and genital infection fungal.

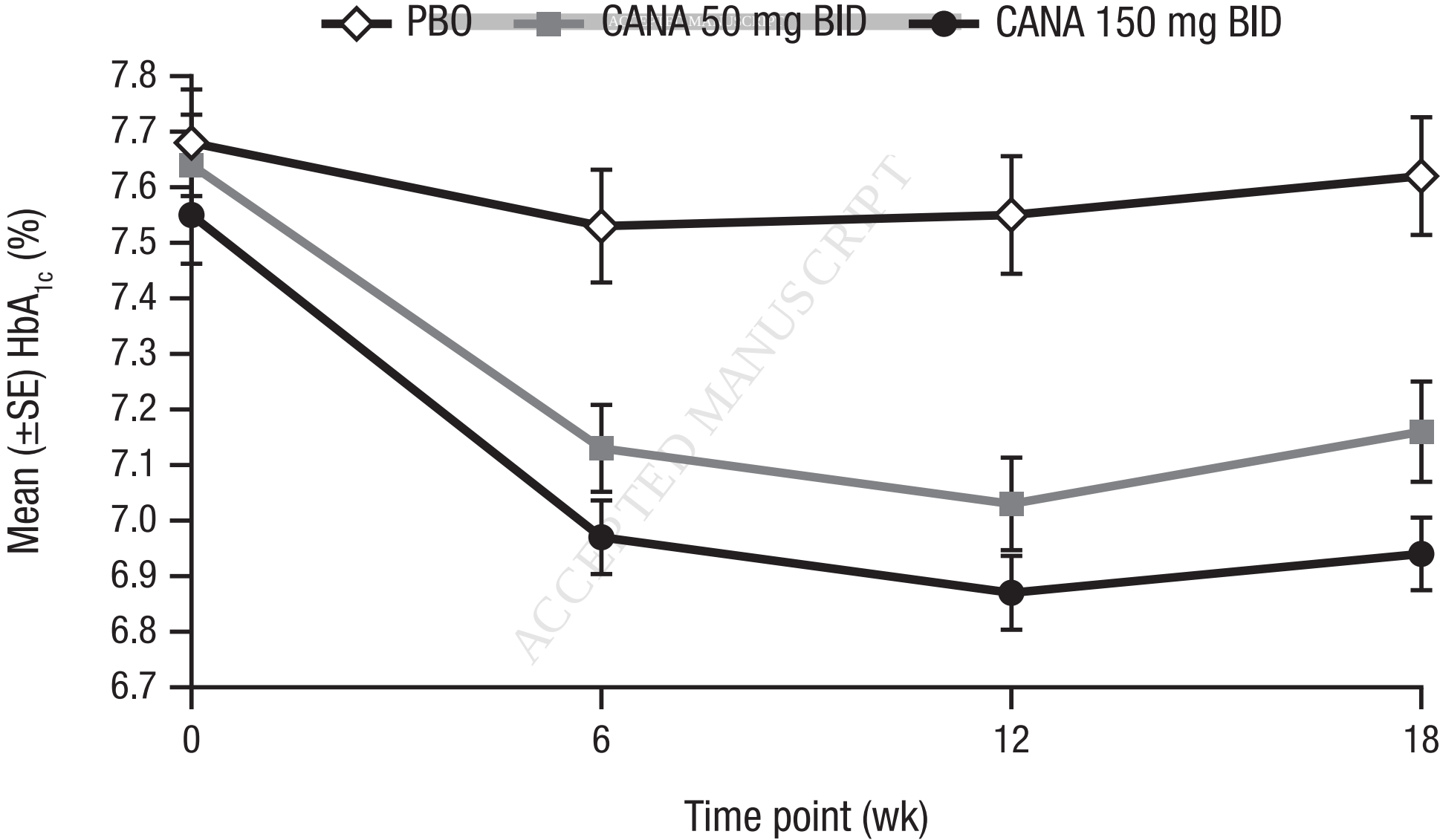
[f]PBO, n = 47; CANA 50 mg BID, n = 53; CANA 150 mg BID, n = 49.

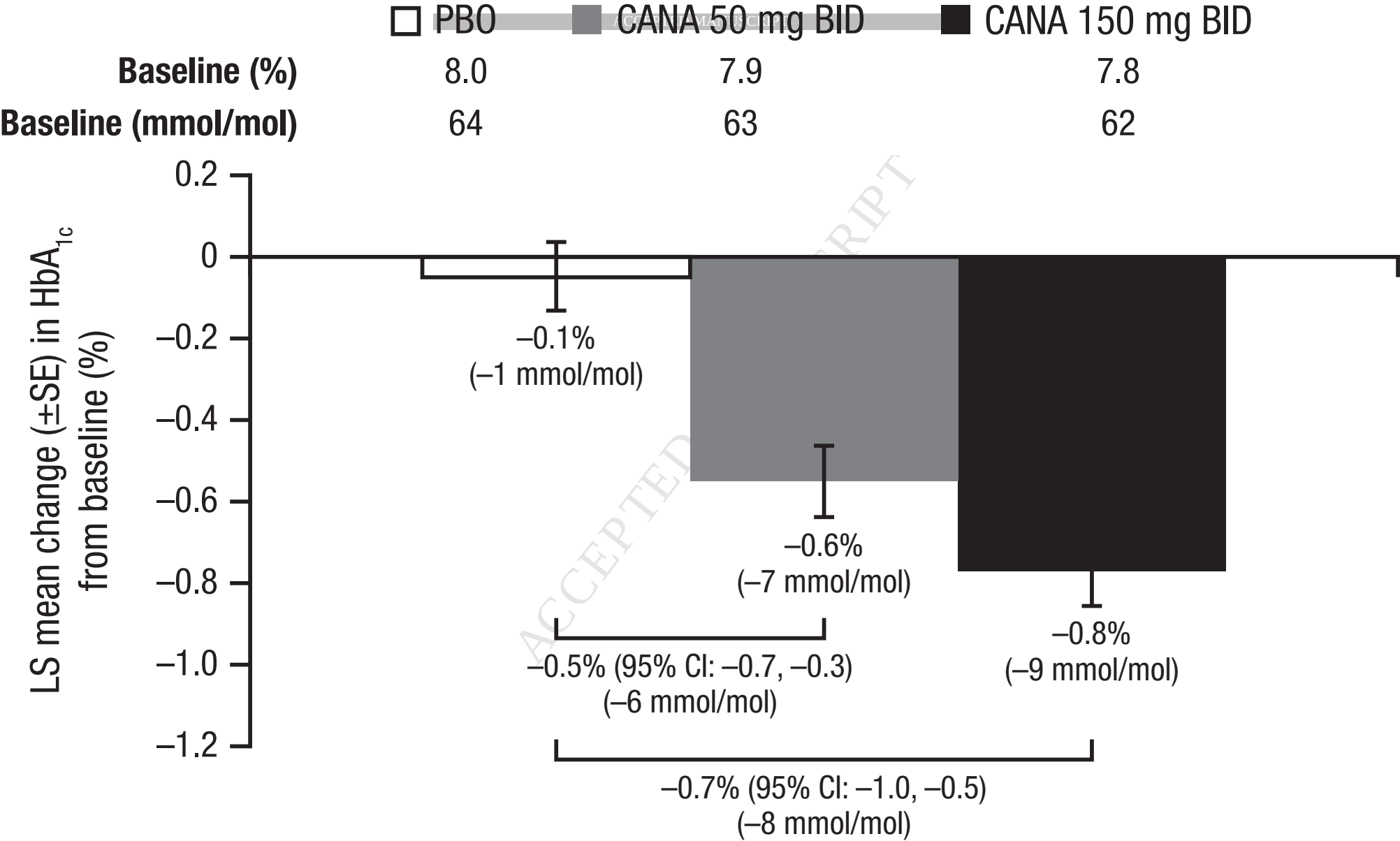
[g]Including vaginal infection, vulvovaginal candidiasis, vulvovaginal mycotic infection, and vulvovaginitis.

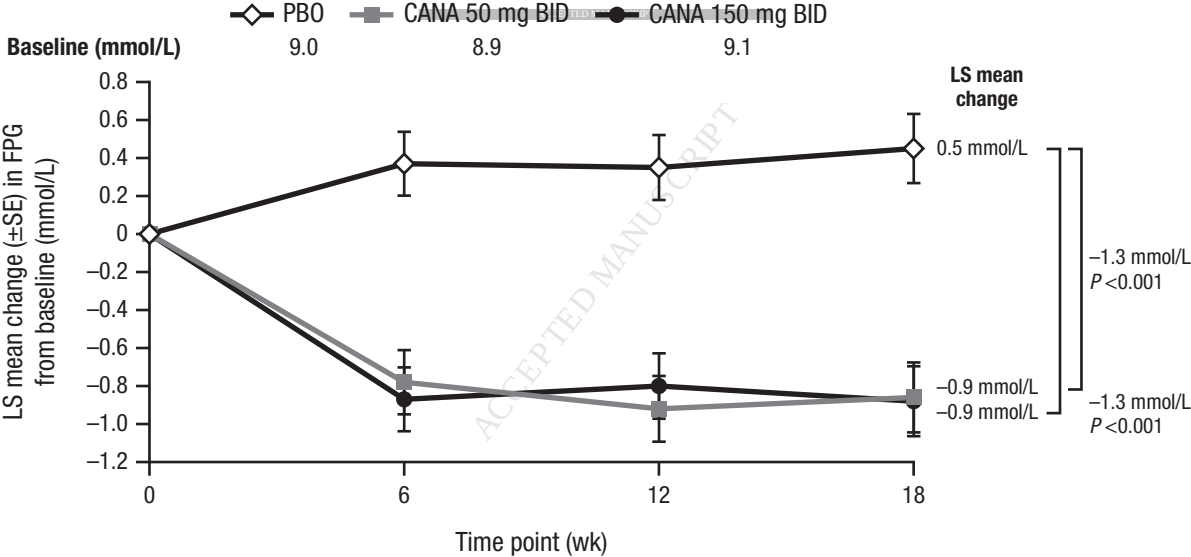
[h]Including dry mouth, micturition urgency, pollakiuria, and thirst.

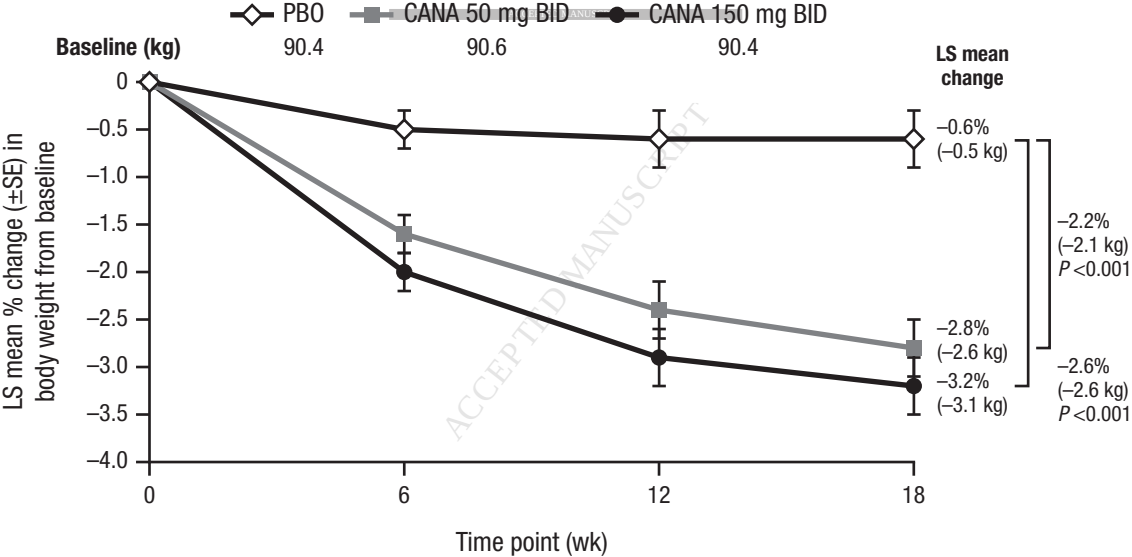

480 patients enrolled and screened
279 randomised
93 received PBO
93 received CANA 50 mg BID
93 received CANA 150 mg BID
7 discontinued
2 lost to follow up
2 withdrawal of consent
2 met glycaemic withdrawal criteria
1 other
8 discontinued
1 AE
1 met creatinine or eGFR withdrawal criteria
4 withdrawal of consent
2 other
13 discontinued
7 AE
2 met creatinine or eGFR withdrawal criteria
2 lost to follow up
2 other
86 completed study
85 completed study
80 completed study
93 in the mITT analysis set
93 in the mITT analysis set
93 in the mITT analysis set


PBO
CANA 50 mg BID
CANA 150 mg BID
Baseline (%) 7.7 7.6 7.5
Baseline (mmol/mol) 61 60 58
LS mean change
0.1
0
−0.1
−0.2
−0.3
−0.4
−0.5
−0.6
−0.7
−0.8
LS mean change (±SE) in HbA1c from baseline (%)
0
6
12
18
Time point (wk)
−0.01% (−0.1 mmol/mol)
−0.45% (−6 mmol/mol)
−0.61% (−7 mmol/mol)
−0.44% (−5 mmol/mol) P <0.001
−0.60% (−7 mmol/mol) P <0.001
ACCEPTED MANUSCRIPT




PBO
CANA 50 mg BID
CANA 150 mg BID
Baseline (%) 8.0 7.9 7.8
Baseline (mmol/mol) 64 63 62
LS mean change (±SE) in HbA1c from baseline (%)
0.2
0
–0.2
–0.4
–0.6
–0.8
–1.0
–1.2
–0.1%
(–1 mmol/mol)
–0.6%
(–7 mmol/mol)
–0.8%
(–9 mmol/mol)
–0.5% (95% CI: –0.7, –0.3)
(–6 mmol/mol)
–0.7% (95% CI: –1.0, –0.5)
(–8 mmol/mol)





Highlights

- Canagliflozin BID was evaluated in patients with type 2 diabetes on metformin.
- Canagliflozin 50 and 150 mg BID significantly reduced HbA_{1c} versus placebo.
- Both doses also lowered fasting plasma glucose, body weight, and blood pressure.
- Efficacy findings were consistent with studies of canagliflozin 100 and 300 mg QD.
- Canagliflozin BID was generally well tolerated, similar to canagliflozin QD.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Summary of Clinical Laboratory Parameters at Baseline and Week 18

Parameter	PBO	CANA 50 mg BID	CANA 150 mg BID
ALT, n	82	80	76
Mean baseline, U/L	27.2	28.6	30.9
Mean ± SD percent change	1.9 ± 37.9	1.7 ± 37.3	–7.7 ± 32.5
Median percent change	–4.2	0.0	–11.3
AST, n	81	80	75
Mean baseline, U/L	22.8	23.8	25.6
Mean ± SD percent change	0.7 ± 27.3	4.6 ± 26.4	–1.2 ± 38.0
Median percent change	0.0	3.3	–7.9
Bilirubin, n	82	80	76
Mean baseline, μmol/L	8.6	8.0	8.8
Mean ± SD percent change	5.4 ± 35.5	7.3 ± 32.2	11.1 ± 41.6
Median percent change	0.0	0.0	0.0
BUN, n	82	81	76

Mean baseline, mmol/L	5.6	5.4	5.4
Mean ± SD percent change	2.0 ± 24.6	11.3 ± 24.8	14.3 ± 31.3
Median percent change	3.4	11.5	12.9
Creatinine, n	82	81	76
Mean baseline, μmol/L	74.8	71.3	73.2
Mean ± SD percent change	1.4 ± 10.7	1.8 ± 11.2	4.7 ± 13.6
Median percent change	1.7	0.0	4.0
eGFR, n	82	81	76
Mean baseline, mL/min/1.73 m^2	84.8	87.2	87.0
Mean ± SD percent change	–0.3 ± 13.0	–0.7 ± 12.1	–3.8 ± 12.2
Median percent change	–1.7	0.0	–4.2
Urate, n	82	81	76
Mean baseline, μmol/L	322.8	310.7	323.8
Mean ± SD percent change	–0.2 ± 17.1	–13.0 ± 15.0	–11.2 ± 27.8
Median percent change	0.9	–15.3	–16.5
Haemoglobin, n	80	79	75

Mean baseline, g/L	139.9	138.8	137.9
Mean ± SD percent change	0.8 ± 4.9	5.6 ± 5.7	8.0 ± 8.2
Median percent change	0.6	6.4	6.7

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