ARTICLE

Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial

F. J. Lavalle-González · A. Januszewicz · J. Davidson · C. Tong · R. Qiu · W. Canovatchel · G. Meininger

Abstract

Aims/hypothesis The aim of this work was to evaluate the efficacy and safety of canagliflozin vs placebo and sitagliptin in patients with type 2 diabetes who were being treated with background metformin.

Methods This randomised, double-blind, four-arm, parallel-group, Phase 3 study was conducted at 169 centres in 22 countries between April 2010 and August 2012. Participants ($N=1,284$) with type 2 diabetes aged ≥18 and ≤80 years who had inadequate glycaemic control (HbA_{1c} ≥7.0% [53 mmol/mol] and ≤10.5% [91 mmol/mol]) on metformin therapy received canagliflozin 100 mg or 300 mg, sitagliptin 100 mg, or placebo ($n=368, 367, 366, 183$, respectively) for a 26 week, placebo- and active-controlled period followed by a 26 week, active-controlled period (placebo group switched to sitagliptin [placebo/sitagliptin]) and were included in the modified intent-to-treat analysis set. Randomisation was performed using a computer-generated schedule; participants, study centres and the sponsor were blinded to group assignment. The primary endpoint was change from baseline in HbA_{1c} at week 26; secondary endpoints included changes in HbA_{1c} (week 52) and fasting plasma glucose (FPG), body weight, and systolic blood pressure (BP; weeks 26 and 52). Adverse events (AEs) were recorded throughout the study.

Results At week 26, canagliflozin 100 mg and 300 mg reduced HbA_{1c} vs placebo (−0.79%, −0.94%, −0.17%, respectively; $p<0.001$). At week 52, canagliflozin 100 mg and 300 mg demonstrated non-inferiority, and canagliflozin 300 mg demonstrated statistical superiority, to sitagliptin in lowering HbA_{1c} (−0.73%, −0.88%,−0.73%, respectively); differences (95% CI) vs sitagliptin were 0% (−0.12, 0.12) and −0.15% (−0.27, −0.03), respectively. Canagliflozin 100 mg and 300 mg reduced body weight vs placebo (week 26: −3.7%, −4.2%, −1.2%, respectively; $p<0.001$) and sitagliptin (week 52: −3.8%, −4.2%, −1.3%, respectively; $p<0.001$). Both canagliflozin doses reduced FPG and systolic BP vs placebo (week 26) and sitagliptin (week 52) ($p<0.001$). Overall AE and AE-related discontinuation rates were generally similar across groups, but higher with canagliflozin 100 mg. Genital mycotic infection and osmotic diuresis-related AE rates were higher with canagliflozin; few led to discontinuations. Hypoglycaemia incidence was higher with canagliflozin.

Conclusions/interpretation Canagliflozin improved glycaemia and reduced body weight vs placebo (week 26) and sitagliptin (week 52) and was generally well tolerated in patients with type 2 diabetes on metformin.

Clinical trial registry ClinicalTrials.gov NCT01106677

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Keywords Canagliflozin · Metformin · Sitagliptin · Sodium glucose co-transporter 2 (SGLT2) inhibitor · Type 2 diabetes mellitus

Abbreviations

AE	Adverse event
AHA	Antihyperglycaemic agent
ANCOVA	Analysis of covariance
DPP-4	Dipeptidyl peptidase-4
eGFR	Estimated GFR
FPG	Fasting plasma glucose
IR	Immediate release
LOCF	Last observation carried forward
LS	Least squares
mITT	Modified intent-to-treat
MMTT	Mixed-meal tolerance test
PPG	Postprandial glucose
SGLT2	Sodium glucose co-transporter 2
SMBG	Self-monitored blood glucose
UGE	Urinary glucose excretion
UTI	Urinary tract infection
XR	Extended release

Introduction

Metformin is the recommended first-line pharmacological therapy for type 2 diabetes but the progressive nature of the disease often necessitates more intensive treatment regimens or combination therapy for patients to achieve and/or maintain glycaemic control [1, 2]. Currently available antihyperglycaemic agents (AHAs) have distinct risk/benefit profiles, which must be considered when choosing an add-on therapy to metformin that meets the needs of each patient [2, 3]. Dipeptidyl peptidase-4 (DPP-4) inhibitors are a class of AHAs that are becoming more commonly used as second agents [2, 4].

Canagliflozin is a sodium glucose co-transporter 2 (SGLT2) inhibitor developed for the treatment of patients with type 2 diabetes [5–10]. Canagliflozin reduces blood glucose by lowering the renal threshold for glucose and increasing urinary glucose excretion (UGE), resulting in a mild osmotic diuresis and a net caloric loss. In a 12 week study, canagliflozin significantly improved glycaemic control and reduced body weight vs placebo in patients with type 2 diabetes on background metformin, with a low incidence of hypoglycaemia [5]. Other SGLT2 inhibitors, dapagliflozin and empagliflozin, have also demonstrated efficacy in lowering HbA_{1c} and body weight with a low risk of hypoglycaemia in patients with type 2 diabetes [11–14]. This 52 week Phase 3 study in patients with type 2 diabetes inadequately controlled with metformin monotherapy evaluated the efficacy and safety of canagliflozin compared with placebo at week 26 and sitagliptin at week 52.

Methods

Participants and study design

This randomised, double-blind, placebo- and active-controlled, Phase 3 study (ClinicalTrials.gov NCT01106677) was conducted at 169 centres in 22 countries. The study consisted of a 2 week single-blind, placebo run-in period, a 26 week placebo- and active-controlled, double-blind treatment period (period I) followed by a 26 week active-controlled, double-blind treatment period (period II) and a 4 week follow-up period.

Eligible participants were men and women with type 2 diabetes, aged ≥18 and ≤80 years, who had inadequate glycaemic control (HbA_{1c} ≥7.0% [53 mmol/mol] and ≤10.5% [91 mmol/mol]) and who were on stable metformin therapy (≥2,000 mg/day [or ≥1,500 mg/day if unable to tolerate higher dose]) for ≥8 weeks and had fasting plasma glucose (FPG) <15 mmol/l at week−2 and fasting fingerstick glucose ≥6.1 mmol/l and <15 mmol/l on day 1. Participants on metformin immediate-release (IR) monotherapy at protocol-specified doses at screening directly entered the placebo run-in period. Those on metformin extended release (XR), metformin IR or XR at below protocol-specified doses or metformin plus sulfonylurea underwent a metformin IR dose titration/dose stable and, if applicable, a sulfonylurea washout period of up to 10 weeks, followed by the placebo run-in period.

The following exclusion criteria were applied: repeated FPG and/or fasting self-monitored blood glucose (SMBG) ≥15.0 mmol/l during the pretreatment phase; history of type 1 diabetes, cardiovascular disease (including myocardial infarction, unstable angina, revascularisation procedure or cerebrovascular accident) in the 3 months before screening or uncontrolled hypertension; treatment with a peroxisome proliferator-activated receptor γ agonist, insulin, another SGLT2 inhibitor or any other AHA (except metformin as monotherapy or in combination with a sulfonylurea) in the 12 weeks before screening; or estimated glomerular filtration rate (eGFR) <55 ml min^{-1} (1.73 $m^2)^{-1}$ (or <60 ml min^{-1} [1.73 $m^2]^{-1}$ if based upon restriction in local label) or serum creatinine ≥124 μmol/l (men) or ≥115 μmol/l (women).

The 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 before taking part in the study.

Randomisation and treatments

During the placebo run-in period, participants received single-blind placebo capsules matching study drug once daily.

Participants were randomised to receive canagliflozin 100 mg or 300 mg, sitagliptin 100 mg or placebo (2:2:2:1) once daily for 26 weeks. The canagliflozin 100 mg and 300 mg once-daily doses were selected based on findings from a dose-ranging, Phase 2 study in patients with type 2 diabetes on background metformin [5]; a 300 mg twice-daily regimen provided only incremental benefits vs the once-daily regimen and was therefore not selected for further development. The use of placebo as a control for the 26 week core treatment period was done in accordance with US Food and Drug Administration and European Medicines Agency regulatory guidelines [15, 16]. The computer-generated randomisation schedule was prepared by the sponsor before the study. Randomisation was balanced using permuted blocks of seven and stratified by whether a participant was on metformin monotherapy or metformin plus sulfonylurea at screening. After randomisation, HbA_{1c} and FPG values were masked to the study centres unless they met glycaemic rescue criteria. After completion of period I, the database was locked and the study was unblinded by the sponsor for regulatory filing; the participants and the study centre and local sponsor personnel remained blinded throughout period II.

Participants who completed period I then entered period II, during which those randomised to canagliflozin (100 or 300 mg) or sitagliptin 100 mg continued on those treatments while those randomised to placebo switched to sitagliptin 100 mg in a blinded fashion. During the double-blind treatment period, glycaemic rescue therapy with glimepiride (added to study drug and background metformin) was initiated if FPG >15.0 mmol/l after day 1 to week 6, >13.3 mmol/l after week 6 to week 12, and >11.1 mmol/l after week 12 to week 26. Glimepiride therapy was also started if HbA_{1c} >8.0% (64 mmol/mol) after week 26.

Endpoints and assessments

The pre-specified primary efficacy endpoint was change in HbA_{1c} from baseline to week 26; change in HbA_{1c} from baseline to week 52 was a key, pre-specified secondary endpoint. Other pre-specified secondary endpoints at week 26 were proportion of participants reaching HbA_{1c} <7.0% (53 mmol/mol), change in FPG, 2 h postprandial glucose (PPG) and systolic BP and per cent change in body weight, triacylglycerol (i.e. triglycerides) and HDL-cholesterol. All participants underwent a mixed-meal tolerance test (MMTT) on day 1 and at week 26 for assessment of 2 h PPG. Change in Apo B was assessed in a subset of participants at week 26 based on availability of paired baseline and week 26 archive samples. Other pre-specified secondary endpoints at week 52 were change in FPG and systolic BP and per cent change in body weight, triacylglycerol and HDL-cholesterol.

Safety and tolerability were evaluated based on adverse event (AE) reports, safety laboratory tests, vital sign measurements, physical examinations, SMBG and 12-lead electrocardiograms. AEs pre-specified for additional data collection included urinary tract infections (UTIs) and genital mycotic infections. Documented episodes of hypoglycaemia included biochemically confirmed episodes (concurrent fingerstick or plasma glucose ≤3.9 mmol/l) and/or severe episodes (i.e. requiring the assistance of another individual or resulting in seizure or loss of consciousness).

Statistical analyses

The primary hypothesis was that canagliflozin 300 mg is statistically superior to placebo in reducing HbA_{1c} from baseline to week 26. Key secondary hypotheses were statistical superiority of canagliflozin 100 mg to placebo in HbA_{1c}-lowering effect at week 26 and non-inferiority of canagliflozin 300 mg or both canagliflozin doses to sitagliptin 100 mg in reducing HbA_{1c} from baseline to week 52. Primary efficacy analysis was performed in the modified intent-to-treat (mITT) population (randomised participants who received ≥1 dose of study drug) using a last observation carried forward (LOCF) approach. Assuming a group difference of 0.5% (5.5 mmol/mol) between canagliflozin and placebo and a common SD of 1.0% (10.9 mmol/mol) for change in HbA_{1c}, and using a two-sample, two-sided t test with a type I error rate of 0.05, an estimated 86 participants per group were required to achieve 90% power to demonstrate statistical superiority of canagliflozin to placebo. To support superiority and non-inferiority objectives for the primary endpoint in the mITT population and for supportive analysis in the per-protocol population (mITT participants who completed the study, did not receive rescue therapy and had no major protocol violations), an estimated 360 randomised participants were needed for each active treatment group and 180 for the placebo group, assuming a 35% discontinuation rate at week 52 and with a 2:2:2:1 randomisation ratio for canagliflozin 100 mg, canagliflozin 300 mg, sitagliptin 100 mg and placebo.

Primary efficacy analyses were performed in the mITT population according to randomised treatment assignment using LOCF to impute missing data; for participants who received rescue therapy, the last post-baseline value before rescue was used. Safety analyses were performed in the same population according to the predominant treatment received; in this study, the mITT and safety populations were identical. Only data from participants randomised to sitagliptin 100 mg on day 1 (i.e. not including participants who switched from placebo to sitagliptin at week 26) were included in efficacy comparisons at week 52. Safety analyses over 52 weeks included participants who received canagliflozin 100 mg or

300 mg or sitagliptin and those who switched from placebo to sitagliptin after 26 weeks (placebo/sitagliptin group).

An analysis of covariance (ANCOVA) model with treatment and stratification factor as fixed effects and corresponding baseline value as a covariate was used to assess primary and continuous secondary endpoints. Least squares (LS) mean differences between groups and two-sided 95% CIs were estimated. The categorical secondary endpoint was analysed with a logistic model with treatment and stratification factor as fixed effects and baseline HbA_{1c} as a covariate. Assessment of non-inferiority of canagliflozin to sitagliptin was based on a pre-specified margin of 0.3% for the upper limit of the two-sided 95% CI for the comparison. If non-inferiority was demonstrated, then superiority was assessed based on an upper bound of the 95% CI around the between-group differences of <0.0%.

Comparisons were performed for canagliflozin vs placebo at week 26 and vs sitagliptin at week 52 based on pre-specified hierarchical testing sequences implemented to strongly control overall type I error due to multiplicity. At week 26, statistical tests were interpreted at a two-sided significance level of 5% for all endpoints except change in systolic BP, HDL-cholesterol and triacylglycerol. These were grouped together into two separate families (one each for canagliflozin 100 mg and 300 mg) and each family was tested using the Hochberg procedure at the 2.5% significance level. Comparisons of canagliflozin with sitagliptin at week 52 were initiated after statistical superiority of canagliflozin 100 mg and 300 mg to placebo in HbA_{1c} lowering at week 26 was established; statistical tests at week 52 were interpreted at a two-sided significance level of 5% for all endpoints. The p values are reported for pre-specified comparisons only.

Results

Participant disposition and baseline characteristics

A total of 1,284 participants were randomised into period I and received ≥1 dose of study drug (mITT analysis set); of 1,119 participants who completed period I, 1,103 entered period II and 1,020 completed 52 weeks of treatment (Fig. 1). The rate of study discontinuation before week 52 was 19.0%, 18.5%, 22.1% and 24.6% with canagliflozin 100 mg, canagliflozin 300 mg, sitagliptin and placebo/sitagliptin, respectively. Over 52 weeks, the percentage of participants who received glycaemic rescue therapy was 14.7%, 9.3%, 18.0% and 25.1% with canagliflozin 100 mg, canagliflozin 300 mg, sitagliptin and placebo/sitagliptin, respectively (OR [95% CI] with canagliflozin 100 mg and 300 mg, respectively, of 0.78 [0.53, 1.16] and 0.46

[0.30, 0.72] vs sitagliptin, and 0.51 [0.33, 0.80] and 0.30 [0.19, 0.49] vs placebo/sitagliptin). Demographic and baseline characteristics were generally similar across groups (Table 1).
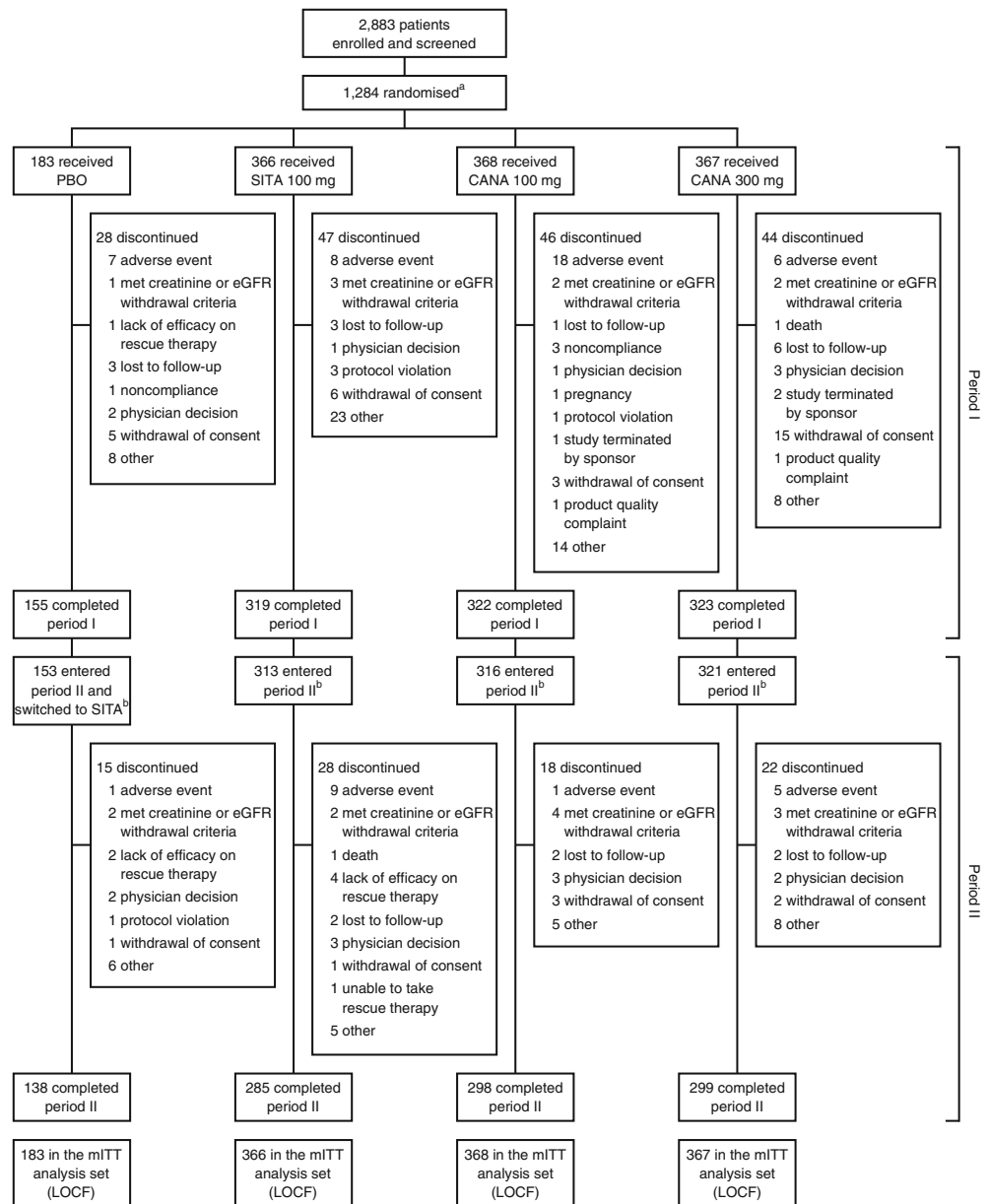
Effect on glycaemic variables

Week 26 (period I only) At week 26, canagliflozin 100 mg and 300 mg significantly reduced HbA_{1c} from baseline compared with placebo (difference in LS mean changes of −0.62% and −0.77% [−6.8 and −8.4 mmol/mol], respectively; $p < 0.001$ for both); the change in HbA_{1c} with sitagliptin was −0.66% (−7.2 mmol/mol) relative to placebo (Fig. 2a; electronic supplementary material [ESM] Table 1). Statistical comparison of canagliflozin with sitagliptin at week 26 was not performed (not pre-specified). A greater proportion of participants treated with canagliflozin 100 mg and 300 mg achieved HbA_{1c} <7.0% (53 mmol/mol) than with placebo (45.5%, 57.8% and 29.8%, respectively; $p = 0.000$ for both); 54.5% of sitagliptin-treated participants achieved HbA_{1c} <7.0% (53 mmol/mol). Both canagliflozin doses significantly reduced FPG and 2 h PPG at week 26 vs placebo ($p < 0.001$ for all; ESM Table 1); FPG and 2 h PPG were also reduced from baseline with sitagliptin.

Week 52 (periods I and II) At 52 weeks, canagliflozin 100 mg and 300 mg demonstrated non-inferiority to sitagliptin 100 mg in HbA_{1c}-lowering effect (upper limit of the 95% CI less than pre-specified margin of 0.3%; Fig. 2b, c; Table 2). Canagliflozin 300 mg demonstrated statistical superiority to sitagliptin in HbA_{1c}-lowering effect (upper limit of the 95% CI less than 0.0%). The difference in LS mean changes (95% CI) for canagliflozin 100 mg and 300 mg vs sitagliptin was 0% (−0.12, 0.12) or 0 mmol/mol (−1.3, 1.3) and −0.15% (−0.27, −0.03) or −1.6 mmol/mol (−3.0, −0.3), respectively. The separation in treatment effect between canagliflozin 300 mg and sitagliptin was observed starting at week 6 and continued through week 52. A higher proportion of participants treated with canagliflozin 300 mg achieved HbA_{1c} <7.0% (53 mmol/mol) compared with those treated with canagliflozin 100 mg or sitagliptin (54.7%, 41.4% and 50.6%, respectively; OR [95% CI] of 1.28 [0.92, 1.76] and 0.66 [0.48, 0.91] with canagliflozin 300 mg and 100 mg vs sitagliptin). The proportion of participants reaching HbA_{1c} <6.5% (48 mmol/mol) was 26.9%, 21.9% and 24.9% for those treated with canagliflozin 300 mg, canagliflozin 100 mg and sitagliptin, respectively (OR 1.14 [0.80, 1.62] and 0.84 [0.59, 1.22], respectively). Over 52 weeks, canagliflozin 100 mg and 300 mg provided greater reductions in FPG than sitagliptin (difference in LS mean changes of −0.5 and −1.0 mmol/l, respectively; $p < 0.001$ for both; Fig. 2d; Table 2), with maximal reductions at 26 weeks across groups.

Fig. 1 Study flow diagram.
[a]Among 2,883 patients enrolled and screened, there were 1,599 screen failures (inclusion/exclusion criteria, $n=1,428$; withdrawal of consent, $n=115$; other, $n=50$; adverse event, $n=6$). [b]Some subjects withdrew from the study after completing period I and did not enter period II. CANA, canagliflozin; PBO, placebo; SITA, sitagliptin

Effect on body weight, BP and lipids

Week 26 (period I only) At week 26, canagliflozin 100 mg and 300 mg significantly reduced body weight compared with placebo ($p<0.001$; ESM Table 1); body weight change was −1.2% with both sitagliptin and placebo. Both canagliflozin doses were associated with significant decreases vs placebo in systolic BP ($p<0.001$ for both; ESM Table 1). Reductions from baseline in diastolic BP were also observed with both canagliflozin doses. Sitagliptin was associated with decreases from baseline in systolic and diastolic BP.

Both canagliflozin doses significantly increased HDL-cholesterol compared with placebo at week 26 ($p<0.001$); no statistically significant changes in triacylglycerol were seen

with canagliflozin relative to placebo (ESM Table 1). Statistical testing was not performed (not pre-specified) for other lipid variables, but 95% CIs for between-group comparisons in these variables are reported in ESM Table 1. Increases from baseline in LDL-cholesterol were seen with canagliflozin and placebo. In a subset of participants with adequate archived samples for analysis of Apo B ($n=586$), increases from baseline of 4.3%, 5.4% and 2.4% were seen with canagliflozin 100 mg and 300 mg and placebo, respectively. Increases from baseline in triacylglycerol, HDL-cholesterol and LDL-cholesterol were observed with sitagliptin.

Week 52 (periods I and II) At week 52, canagliflozin 100 mg and 300 mg significantly reduced body weight compared with

Table 1 Baseline demographics and disease characteristics

Characteristic	PBO/SITA ($n=183$)	SITA 100 mg ($n=366$)	CANA 100 mg ($n=368$)	CANA 300 mg ($n=367$)	Total ($N=1,284$)
Sex, n (%)					
Male	94 (51.4)	172 (47.0)	174 (47.3)	165 (45.0)	605 (47.1)
Female	89 (48.6)	194 (53.0)	194 (52.7)	202 (55.0)	679 (52.9)
Age, years	55.3±9.8	55.5±9.6	55.5±9.4	55.3±9.2	55.4±9.4
Race, n (%)					
White	129 (70.5)	264 (72.1)	252 (68.5)	256 (69.8)	901 (70.2)
Black or African-American	3 (1.6)	13 (3.6)	16 (4.3)	13 (3.5)	45 (3.5)
Asian	30 (16.4)	41 (11.2)	51 (13.9)	60 (16.3)	182 (14.2)
Other[a]	21 (11.5)	48 (13.1)	49 (13.3)	38 (10.4)	156 (12.1)
HbA$_{1c}$, % (mmol/mol)	8.0±0.9 (64±9.8)	7.9±0.9 (63±9.8)	7.9±0.9 (63±9.8)	7.9±0.9 (63±9.8)	7.9±0.9 (63±9.8)
FPG, mmol/l	9.1±2.1	9.4±2.3	9.3±2.3	9.6±2.5	9.4±2.3
Body weight, kg	86.6±22.4	87.7±21.6	88.8±22.2	85.4±20.9	87.2±21.7
BMI, kg/m^2	31.1±6.1	32.0±6.1	32.4±6.4	31.4±6.3	31.8±6.2
Duration of diabetes, years	6.8±5.3	6.8±5.2	6.7±5.4	7.1±5.4	6.9±5.3

Data are mean ± SD unless otherwise indicated

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

CANA, canagliflozin; PBO, placebo; SITA, sitagliptin

sitagliptin (Fig. 3, Table 2), with differences in LS mean per cent changes vs sitagliptin of −2.4% (−2.1 kg) and −2.9% (−2.5 kg), respectively ($p<0.001$ for both). Weight loss occurred most rapidly with canagliflozin up to week 6, with a continuing, slower decrease followed by an apparent plateau after week 34. A small, gradual decrease from baseline was observed with sitagliptin, which also plateaued after week 34.

Canagliflozin 100 mg and 300 mg significantly decreased systolic BP relative to sitagliptin at 52 weeks (difference in

LS mean changes of −2.9 and −4.0 mmHg, respectively; $p<0.001$ for both; Table 2). The change in diastolic BP from baseline was −1.8 mmHg with both canagliflozin doses and −0.3 mmHg with sitagliptin. No notable differences were observed across groups in changes in pulse rate (−1.3, −1.9 and −1.4 beats/min with canagliflozin 100 mg, canagliflozin 300 mg and sitagliptin, respectively).

At week 52, increases in triacylglycerol from baseline were seen with both canagliflozin doses, whereas a decrease was observed with sitagliptin; the difference between canagliflozin

Fig. 2 Changes in glycaemic variables (LOCF). (**a**) Change in HbA$_{1c}$ at week 26, (**b**) change in HbA$_{1c}$ at week 52, (**c**) mean HbA$_{1c}$ over time and (**d**) change in FPG at week 52. CANA, canagliflozin; PBO, placebo; SITA, sitagliptin. Light-grey triangles, PBO; white diamonds, SITA 100 mg; dark-grey squares, CANA 100 mg; black circles, CANA 300 mg. Error bars show SE. 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/
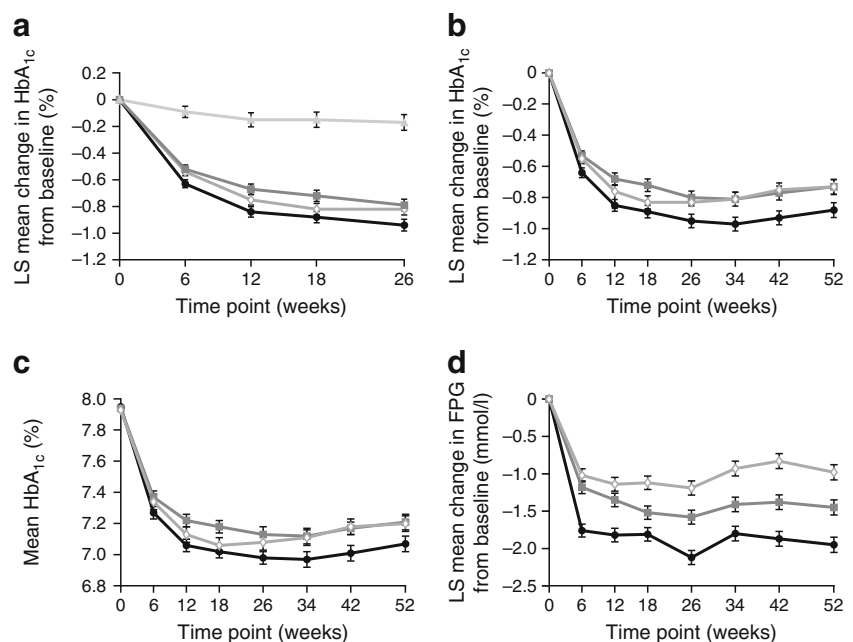
Table 2 Summary of efficacy findings at week 52 (LOCF)

Variable	SITA 100 mg ($n=366$)	CANA 100 mg ($n=368$)	CANA 300 mg ($n=367$)
HbA$_{1c}$, n	354	365	360
Mean ± SD baseline, % (mmol/mol)	7.9±0.9 (63±9.8)	7.9±0.9 (63±9.8)	8.0±0.9 (64±9.8)
LS mean ± SE change, % (mmol/mol)	−0.73±0.05 (−8.0±0.5)	−0.73±0.05 (−8.0±0.5)	−0.88±0.05 (−9.6±0.5)
Difference vs SITA (95% CI), %		0.00 (−0.12, 0.12)	−0.15 (−0.27, −0.03)
Difference vs SITA (95% CI), mmol/mol		0.0 (−1.3, 1.3)	−1.6 (−3.0, −0.3)
FPG, n	354	365	360
Mean ± SD baseline, mmol/l	9.4±2.3	9.4±2.3	9.6±2.5
LS mean ± SE change	−1.0±0.1	−1.5±0.1	−2.0±0.1
Difference vs SITA (95% CI)		−0.5 (−0.7, −0.2)[a]	−1.0 (−1.2, −0.7)[a]
Body weight, n	355	365	360
Mean ± SD baseline, kg	87.6±20.9	88.7±22.3	85.4±20.7
LS mean ± SE change, kg	−1.2±0.2	−3.3±0.2	−3.7±0.2
LS mean ± SE per cent change	−1.3±0.2	−3.8±0.2	−4.2±0.2
Difference vs SITA (95% CI)		−2.4 (−3.0, −1.8)[a]	−2.9 (−3.4, −2.3)[a]
Systolic BP, n	355	365	360
Mean ± SD baseline, mmHg	128.0±13.5	128.0±12.7	128.7±13.0
LS mean ± SE change	−0.7±0.6	−3.5±0.6	−4.7±0.6
Difference vs SITA (95% CI)		−2.9 (−4.5, −1.3)[a]	−4.0 (−5.6, −2.4)[a]
Diastolic BP, n	355	365	360
Mean ± SD baseline, mmHg	77.5±8.0	77.7±8.4	77.9±8.3
LS mean ± SE change	−0.3±0.4	−1.8±0.4	−1.8±0.4
Difference vs SITA (95% CI)		−1.4 (−2.4, −0.5)[b]	−1.5 (−2.5, −0.5)[b]
Triacylglycerol, n	339	359	343
Mean ± SD baseline, mmol/l	2.0±1.1	2.2±1.6	2.1±1.5
LS mean ± SE change	−0.15±0.05	−0.12±0.05	−0.19±0.05
Median (IQR) per cent change	−3.3 (−22.8, 16.7)	−2.7 (−28.4, 22.5)	−8.7 (−29.1, 23.3)
LS mean ± SE per cent change	−0.4±2.5	1.9±2.4	2.8±2.4
Difference vs SITA (95% CI)		2.3 (−3.9, 8.5)[c]	3.2 (−3.1, 9.5)[c]
LDL-cholesterol, n	338	358	343
Mean ± SD baseline, mmol/l	2.8±0.9	2.8±0.8	2.8±0.9
LS mean ± SE change	0.08±0.04	0.11±0.04	0.11±0.04
Median (IQR) per cent change	0.9 (−9.6, 16.8)	6.0 (−9.9, 21.8)	5.3 (−8.8, 22.6)
LS mean ± SE per cent change	6.0±1.8	7.7±1.7	8.8±1.8
Difference vs SITA (95% CI)		1.7 (−2.8, 6.2)[b]	2.8 (−1.8, 7.4)[b]
HDL-cholesterol, n	338	359	343
Mean ± SD baseline, mmol/l	1.2±0.3	1.2±0.3	1.2±0.3
LS mean ± SE change	0.06±0.01	0.12±0.01	0.14±0.01
Median (IQR) per cent change	4.4 (−4.0, 14.8)	8.0 (0.0, 19.8)	11.1 (0.0, 22.8)
LS mean ± SE per cent change	6.0±1.1	11.2±1.0	13.2±1.1
Difference vs SITA (95% CI)		5.2 (2.5, 7.9)[d]	7.2 (4.4, 10.0)[d]
LDL-cholesterol/HDL-cholesterol, n	338	358	343
Mean ± SD baseline, mol/mol	2.6±1.0	2.5±0.9	2.4±0.9
LS mean ± SE change	−0.04±0.04	−0.13±0.04	−0.15±0.04
Median (IQR) per cent change	−1.7 (−14.1, 14.6)	−5.3 (−19.3, 11.7)	−4.3 (−18.1, 13.2)
LS mean ± SE per cent change	1.6±1.8	−0.8±1.8	−1.3±1.8
Difference vs SITA (95% CI)		−2.4 (−7.1, 2.2)[b]	−2.9 (−7.6, 1.8)[b]
Non-HDL-cholesterol, n	337	357	340
Mean ± SD baseline, mmol/l	3.7±1.0	3.8±1.1	3.7±1.0
LS mean ± SE change	0.03±0.05	0.04±0.05	0.05±0.05

Table 2 (continued)

Variable	SITA 100 mg ($n = 366$)	CANA 100 mg ($n = 368$)	CANA 300 mg ($n = 367$)
Median (IQR) per cent change	1.9 (−9.7, 13.7)	2.4 (−8.8, 14.8)	2.8 (−8.3, 18.8)
LS mean ± SE per cent change	2.8±1.4	3.8±1.3	4.0±1.4
Difference vs SITA (95% CI)		0.9 (−2.6, 4.4)[b]	1.1 (−2.4, 4.7)[b]

[a] $p < 0.001$ vs SITA

[b] Statistical comparison vs SITA not performed (not pre-specified)

[c] $p = $ NS vs SITA

[d] Statistical comparison vs SITA not performed due to multiplicity control

CANA, canagliflozin; IQR, interquartile range; SITA, sitagliptin

and sitagliptin did not reach statistical significance (Table 2). Median per cent decreases in triacylglycerol were observed across all groups. Both canagliflozin doses increased HDL-cholesterol, but statistical comparison of canagliflozin vs sitagliptin was not performed due to the hierarchical statistical testing sequence. Statistical testing was not performed (not pre-specified) for other lipid variables, but 95% CIs for between-group comparisons in these variables are reported in Table 2. The 100 mg and 300 mg dosages of canagliflozin were associated with increases from baseline in LDL-cholesterol and increases in non-HDL-cholesterol that were smaller than those in LDL-cholesterol. Decreases from baseline in the LDL-cholesterol/HDL-cholesterol ratio were observed with both canagliflozin doses, whereas an increase was seen with sitagliptin.

Safety and tolerability

Overall incidences of AEs and AE-related discontinuations were generally comparable across groups over 52 weeks, with slightly higher incidences in the group receiving canagliflozin 100 mg (Table 3). The higher incidence of AE-related discontinuations with canagliflozin 100 mg was not due to an increase in any specific AE. The incidence of AEs related to the study drug was higher with canagliflozin and sitagliptin than with placebo/sitagliptin; the incidence of serious AEs was low and similar across groups. The overall incidence of AEs that occurred in period II was similar across groups; the incidence of AEs related to study drug in period II was higher with canagliflozin and sitagliptin than with placebo/sitagliptin (ESM Table 2). During period II, the incidence of AEs leading to discontinuation was higher in the sitagliptin group than in the other groups, as was the incidence of serious AEs.

Over 52 weeks, canagliflozin was associated with a higher incidence of genital mycotic infections in men and women. These were generally mild or moderate in intensity and led to few discontinuations; most (~80%) were reported during the first 26 weeks. The incidence of UTIs was similar across groups over 52 weeks. A higher incidence of AEs related to osmotic diuresis (i.e. pollakiuria [increased urine frequency], polyuria [increased urine volume]) was seen with canagliflozin vs sitagliptin and placebo/sitagliptin; most were mild in severity and infrequently led to discontinuation. The incidence of AEs related to reduced intravascular volume (i.e. postural dizziness, orthostatic hypotension) was low across groups; events with canagliflozin were mild to moderate in severity and none led to discontinuation.

The proportion of participants with documented episodes of hypoglycaemia over 52 weeks was 6.8% with both canagliflozin doses, 4.1% with sitagliptin and 2.7% with placebo/sitagliptin. One participant each receiving canagliflozin 100 mg and sitagliptin experienced a severe hypoglycaemic event. During weeks 26–52 (period II), the incidence of documented hypoglycaemia was similar with canagliflozin 100 mg and 300 mg and sitagliptin (4.2%, 5.0% and 4.7%, respectively) and was higher than with placebo/sitagliptin (1.6%).

Over 52 weeks, decreases in alanine aminotransferase were observed with canagliflozin, whereas increases were seen with sitagliptin and placebo/sitagliptin (Table 4). Canagliflozin was associated with increased bilirubin, whereas decreases were seen with sitagliptin and placebo/sitagliptin. Increases in serum creatinine were observed across groups, being of a lower
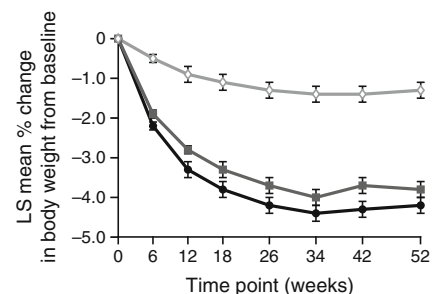

Fig. 3 Per cent change in body weight (LOCF). CANA, canagliflozin; SITA, sitagliptin. White diamonds, SITA 100 mg; dark-grey squares, CANA 100 mg; black circles, CANA 300 mg. Error bars show SE

Table 3 Summary of overall safety and selected AEs over 52 weeks

AE	No. (%) of participants			
	PBO/SITA ($n=183$)	SITA 100 mg ($n=366$)	CANA 100 mg ($n=368$)	CANA 300 mg ($n=367$)
Any AE	122 (66.7)	236 (64.5)	266 (72.3)	230 (62.7)
AEs leading to discontinuation	8 (4.4)	16 (4.4)	19 (5.2)	12 (3.3)
AEs related to study drug[a]	23 (12.6)	72 (19.7)	97 (26.4)	73 (19.9)
Serious AEs	7 (3.8)	18 (4.9)	15 (4.1)	12 (3.3)
Deaths	1 (0.5)	1 (0.3)	0	1 (0.3)
Selected AEs				
UTI	12 (6.6)	23 (6.3)	29 (7.9)	18 (4.9)
Genital mycotic infection				
Men[b,c]	1 (1.1)	2 (1.2)	9 (5.2)	4 (2.4)
Women[d,e]	1 (1.1)	5 (2.6)	22 (11.3)	20 (9.9)
Osmotic diuresis-related AEs				
Pollakiuria[f]	1 (0.5)	2 (0.5)	21 (5.7)	11 (3.0)
Polyuria[g]	0	0	2 (0.5)	2 (0.5)
Volume-related AEs				
Postural dizziness	1 (0.5)	1 (0.3)	2 (0.5)	2 (0.5)
Orthostatic hypotension	0	0	0	1 (0.3)

All AEs are reported, regardless of rescue medication

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

[b] PBO/SITA, $n=94$; SITA 100 mg, $n=172$; CANA 100 mg, $n=174$; CANA 300 mg, $n=165$

[c] Including balanitis, balanoposthitis and fungal genital infection

[d] PBO/SITA, $n=89$; SITA 100 mg, $n=194$; CANA 100 mg, $n=194$; CANA 300 mg, $n=202$

[e] Including vaginal infection, vaginal inflammation, vulvitis, vulvovaginal candidiasis, vulvovaginal mycotic infection and vulvovaginitis

[f] Increased urine frequency

[g] Increased urine volume

CANA, canagliflozin; PBO, placebo; SITA, sitagliptin

magnitude with canagliflozin than with sitagliptin or placebo/sitagliptin. All groups showed a reduction in eGFR. This reduction was observed by week 6 with canagliflozin and trended back toward baseline over time; eGFR progressively decreased with sitagliptin through week 18, followed by a small improvement. An increase in blood urea nitrogen was seen with canagliflozin vs sitagliptin and placebo/sitagliptin. Canagliflozin was associated with a decrease in serum urate, whereas an increase was seen with sitagliptin and placebo/sitagliptin. An increase in haemoglobin was seen with canagliflozin, whereas sitagliptin and placebo/sitagliptin were associated with decreased haemoglobin.

Discussion

Patients with type 2 diabetes often require combination therapies to achieve and/or maintain effective glycaemic control [1, 2]. In this study of patients with type 2 diabetes on background metformin, canagliflozin 100 mg and 300 mg significantly reduced HbA$_{1c}$ from baseline compared with placebo at week 26 and demonstrated non-inferiority to sitagliptin 100 mg in HbA$_{1c}$-lowering effect at week 52; canagliflozin 300 mg also showed statistical superiority to sitagliptin in HbA$_{1c}$-lowering effect. Significant decreases in FPG, body weight and systolic BP were seen with canagliflozin 100 mg and 300 mg vs placebo at week 26 and sitagliptin at week 52, with a sustained effect over 52 weeks. The 100 mg and 300 mg dosages of canagliflozin were associated with significant increases in HDL-cholesterol vs placebo at week 26, with increases from baseline also observed at week 52.

Increases from baseline in LDL-cholesterol were observed with canagliflozin and sitagliptin, with similar per cent changes at weeks 26 and 52. The mechanism of LDL-cholesterol increase with canagliflozin is unknown, but may reflect downstream metabolic effects of UGE and modest haemoconcentration resulting from an osmotic diuretic effect [17]. Increases from baseline in non-HDL-cholesterol, which were smaller than those in LDL-cholesterol, were seen with canagliflozin and sitagliptin at weeks 26 and 52.

The safety and tolerability profile of canagliflozin was consistent with findings from previous Phase 3 studies [6, 8, 9]. Canagliflozin was generally well tolerated, with a pattern of specific AEs (e.g. genital mycotic infections, osmotic diuresis-related AEs) that were generally mild or moderate in severity, occurred at a low incidence and infrequently led to discontinuation. The incidence of documented hypoglycaemia was low but was slightly higher with canagliflozin than with sitagliptin or placebo/sitagliptin. While the incidence of UTIs was similar with canagliflozin 100 mg and 300 mg and the control groups (i.e. sitagliptin and placebo/sitagliptin) in the current study, a small increase in the incidence of UTIs was observed with canagliflozin 100 mg (5.9%) compared with canagliflozin 300 mg and placebo (4.3% and 4.0%, respectively) in a pooled analysis across four placebo-controlled Phase 3 studies [18]. The slight imbalance in overall AE incidence with canagliflozin 100 mg vs 300 mg was primarily driven by early events during period I; AE rates were more balanced during period II. In all groups except canagliflozin 300 mg, the incidence of AEs leading to discontinuation increased from week 26 to week 52; incidences were generally lower during period II relative to the entire 52 week period.

The results of the current study complement and support findings from a similar 52 week, Phase 3 study comparing canagliflozin 300 mg with sitagliptin 100 mg in patients with type 2 diabetes inadequately controlled with metformin plus sulfonylurea [8]. In that study, canagliflozin 300 mg

Table 4 Summary of clinical laboratory variables at baseline and week 52

Variable	PBO/SITA	SITA 100 mg	CANA 100 mg	CANA 300 mg
ALT, n	137	282	294	293
Mean baseline, μkat/l	0.5	0.5	0.5	0.5
Mean ± SD per cent change	7.1±40.7	5.1±41.6	−2.2±39.9	−10.2±39.6
AST, n	137	281	292	293
Mean baseline, μkat/l	0.4	0.4	0.4	0.4
Mean ± SD per cent change	9.8±31.8	7.1±36.8	2.6±32.6	−2.4±28.9
Bilirubin, n	138	282	296	293
Mean baseline, μmol/l	9.1	8.7	9.0	8.5
Mean ± SD per cent change	−3.9±31.4	−1.3±33.4	11.6±45.6	14.3±41.1
BUN, n	139	282	296	295
Mean baseline, mmol/l	5.4	5.5	5.1	5.2
Mean ± SD per cent change	5.9±33.8	3.5±26.6	14.8±26.7	16.1±33.4
Creatinine, n	139	282	296	295
Mean baseline, μmol/l	73.9	72.0	71.4	70.2
Mean ± SD per cent change	3.3±18.0	3.4±13.6	2.3±11.4	2.5±12.4
eGFR, n	139	282	296	295
Mean baseline, ml min^{-1} (1.73 m^2)$^{-1}$	87.7	89.1	89.7	90.2
Mean ± SD per cent change	−1.4±18.2	−2.4±12.8	−1.4±12.8	−1.5±12.9
Urate, n	139	282	296	295
Mean baseline, μmol/l	333.4	328.8	316.6	311.2
Mean ± SD per cent change	5.0±17.4	3.9±18.4	−10.5±18.3	−11.0±18.8
Haemoglobin, n	134	277	292	285
Mean baseline, g/l	141.3	141.0	140.5	140.0
Mean ± SD per cent change	−1.6±6.0	−1.6±6.2	4.0±7.2	3.7±7.1

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CANA, canagliflozin; PBO, placebo; SITA, sitagliptin

demonstrated non-inferiority and statistical superiority to sitagliptin in HbA$_{1c}$-lowering effect at 52 weeks (difference in LS mean changes of −0.37% [−4.0 mmol/mol]). Greater reduction in body weight was observed with canagliflozin relative to sitagliptin (difference of −2.8% [−2.4 kg]); reductions in FPG and systolic BP were also seen with canagliflozin vs sitagliptin. Overall AE incidence was similar with canagliflozin and sitagliptin but the incidence of genital mycotic infection and osmotic diuresis-related AEs was higher with canagliflozin. The incidence of hypoglycaemia was similar with canagliflozin and sitagliptin but was higher than that observed in the current study, which is likely related to the additional sulfonylurea treatment in the previous study. Together with these previous results, the current findings provide additional evidence supporting the non-inferiority of canagliflozin 100 mg and 300 mg, and statistical superiority of canagliflozin 300 mg, to sitagliptin in HbA$_{1c}$-lowering effect in patients with inadequate glycaemic control with their ongoing AHA therapy. Improvements in glycaemic control have also been observed with other SGLT2 inhibitors, and safety findings with canagliflozin in the current study were generally consistent with those seen with other SGLT2 inhibitors [11–14].

The current study is strengthened by its placebo- and active-controlled design, allowing for comparison of canagliflozin with placebo (week 26) and sitagliptin (week 52). The study population reflects a typical profile of patients with type 2 diabetes (e.g. broad age range, mostly overweight/obese, wide range of racial/ethnic groups); thus, study results should be generalisable to a broad type 2 diabetes population. This study has several potential limitations. It was designed with pre-specified comparisons between canagliflozin and sitagliptin only at week 52, consistent with the assessment time point commonly used in other active-controlled studies [8, 19, 20]; therefore, statistical comparisons of canagliflozin with sitagliptin at week 26 are not reported. Because type 2 diabetes is a chronic disorder, study durations beyond 52 weeks may better define the long-term efficacy and safety of canagliflozin. Studies comparing canagliflozin with other AHAs would also be useful for determining the relative efficacy/safety of canagliflozin as add-on therapy.

In summary, treatment with canagliflozin improved glycaemic control and reduced body weight compared with placebo over 26 weeks and with sitagliptin over 52 weeks and was generally well tolerated in patients whose type 2 diabetes was inadequately controlled with metformin monotherapy.

These findings support the clinical usefulness of canagliflozin as add-on therapy in patients with type 2 diabetes.

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