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ORIGINAL ARTICLE

Efficacy and safety of canagliflozin when used in conjunction with incretin-mimetic therapy in patients with type 2 diabetes

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Aims: To assess the efficacy and safety of canagliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, in patients with type 2 diabetes enrolled in the CANagliflozin cardioVascular Assessment Study (CANVAS) who were on an incretin mimetic [dipeptidyl peptidase-4 (DPP-4) inhibitor or glucagon-like peptide-1 (GLP-1) receptor agonist].

Methods: CANVAS is a double-blind, placebo-controlled study that randomized participants to canagliflozin 100 or 300 mg or placebo added to routine therapy. The present *post hoc* analysis assessed the efficacy and safety of canagliflozin 100 and 300 mg compared with placebo in subsets of patients from CANVAS who were taking background DPP-4 inhibitors or GLP-1 receptor agonists with or without other antihyperglycaemic agents at week 18.

Results: Of the 4330 patients in CANVAS, 316 were taking DPP-4 inhibitors and 95 were taking GLP-1 receptor agonists. At 18 weeks, canagliflozin 100 and 300 mg provided larger placebo-subtracted reductions in glycated haemoglobin (HbA1c) in patients taking DPP-4 inhibitors [−0.56% (95% confidence interval [CI]: −0.77, −0.35), and −0.75% (95% CI: −0.95, −0.54), respectively] and GLP-1 receptor agonists [−1.00% (95% CI: −1.35, −0.65), and −1.06% (95% CI: −1.43, −0.69), respectively]. Body weight and blood pressure (BP) reductions were seen with canagliflozin versus placebo in both subsets. Higher incidences of genital mycotic infections and osmotic diuresis–related adverse events (AEs) were seen with canagliflozin compared with placebo. The incidence of hypoglycaemia was numerically higher with canagliflozin versus placebo; nearly all events occurred in patients on background insulin or insulin secretagogues.

Conclusions: In patients on background incretin mimetics, canagliflozin improved HbA1c, body weight and BP, with an increased incidence of AEs related to SGLT2 inhibition.

Keywords: canagliflozin, type 2 diabetes

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Introduction

The progressive nature of type 2 diabetes means that combination therapy with multiple antihyperglycaemic agents (AHAs) is usually needed to achieve and maintain glycaemic control [1,2]. Although metformin together with a sulphonylurea has been a standard early pharmacological approach, the possible adverse effects of sulphonylureas, such as hypoglycaemia and weight gain [2], have led to a decrease in the use of this class of agents and an increase in the prescription of newer AHAs, such as incretin mimetics [e.g. dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists], which minimize these reactions [3].

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Canagliflozin is a sodium glucose co-transporter 2 (SGLT2) inhibitor developed for the treatment of adults with type 2 diabetes [4–18]. Canagliflozin lowers the renal threshold for glucose, which results in urinary glucose loss; this translates to beneficial effects on glycaemic control, as well as body weight and blood pressure (BP) reductions [5–18]. In general, canagliflozin is also well tolerated, with increased incidence of adverse events (AEs) related to the mechanism of SGLT2 inhibition (e.g. genital mycotic infections, AEs related to osmotic diuresis and volume depletion) [5–18]. As the risk of hypoglycaemia is low when used in isolation, canagliflozin could be an attractive option for combination therapy with other agents, such as incretin mimetics. The use of multiple agents that lower glucose without substantially increasing the risk of hypoglycaemia could be a significant advantage for patients with type 2 diabetes.

This *post hoc* analysis describes the short-term effects of canagliflozin on indicators of glycaemia, safety and tolerability compared with placebo using interim data from subsets of patients with type 2 diabetes enrolled in the CANagliflozin cardioVascular Assessment Study (CANVAS) who were on background therapy with either DPP-4 inhibitors or GLP-1 receptor agonists, alone or in combination with other AHAs.

Materials and Methods

Overall Design of CANVAS

CANVAS is an ongoing, randomized, double-blind, placebo-controlled, parallel-group, multicentre trial that has randomized 4330 individuals with type 2 diabetes and a history or high risk of cardiovascular disease to canagliflozin 100 or 300 mg or placebo once daily added to a stable AHA regimen (ClinicalTrials.gov Identifier, NCT01032629). Interim analyses of efficacy and safety data from CANVAS were planned to evaluate the short-term effects of canagliflozin in these patients. The CANVAS trial continues in a blinded fashion to investigators and patients for the purposes of collecting additional safety data, including cardiovascular endpoints, which will be reported upon study completion. Patients included in this *post hoc* analysis were to remain on a stable dose of DPP-4 inhibitor or GLP-1 receptor agonist through week 18, unless criteria for rescue therapy were met. Randomization was not stratified by baseline use of DPP-4 inhibitors or GLP-1 receptor agonists. Details of the study design and recruitment strategy have been previously published [19].

The study is being conducted in accordance with the Declaration of Helsinki and is consistent with Good Clinical Practice. Regulatory approval for the conduct of the trial was obtained in each country and ethics approval was received at every site before initiation. All participants in CANVAS were required to provide written informed consent.

Participant Inclusion and Exclusion Criteria

Inclusion and exclusion criteria and screening and randomization procedures for CANVAS have been published [19]. To ensure the recruitment of a broad population, there were minimal restrictions on the use of background therapies. The subset of patients in this analysis included participants who were taking DPP-4 inhibitors or GLP-1 receptor agonists alone or in combination with other AHAs at study entry.

Study Endpoints

This *post hoc* (and thus not prespecified) analysis assessed the efficacy and safety of canagliflozin compared with placebo in subsets of patients enrolled in CANVAS who were on an incretin mimetic (DPP-4 inhibitor or GLP-1 receptor agonist) with or without other AHAs. Efficacy endpoints evaluated at week 18 in the present analysis included: change from baseline in glycated haemoglobin (HbA1c), fasting plasma glucose (FPG) and systolic BP; percent change from baseline in body weight and fasting plasma lipids; and the proportion of patients reaching HbA1c <7.0%. Overall safety and tolerability were assessed by AE reports.

AEs of specific interest included those likely related to the mechanism of SGLT2 inhibition [i.e. genital mycotic infections, urinary tract infections (UTIs) and AEs related to osmotic diuresis and reduced intravascular volume]. Hypoglycaemic episodes, defined as biochemically documented [≤3.9 mmol/l (70 mg/dl)] and severe episodes (i.e. requiring the assistance of another individual or resulting in seizure or loss of consciousness), were also reported. Glycaemic rescue therapy was initiated in patients meeting prespecified FPG criteria and was selected to be complementary to the patient's background therapies, as previously described [19].

Statistical Analyses

Efficacy and safety analyses were performed using the modified intent-to-treat (mITT) population (i.e. all randomized patients who received ≥1 dose of study drug). Missing efficacy data were imputed using the last observation carried forward (LOCF) approach. Primary and continuous secondary endpoints were assessed using an analysis of covariance (ANCOVA) model including treatment as a fixed effect and corresponding baseline value as a covariate. Least squares (LS) means and two-sided 95% confidence intervals (CIs) were estimated for the comparison of each canagliflozin dose versus placebo. The categorical secondary efficacy endpoint (i.e. proportion of patients reaching HbA1c <7.0%) was analysed using a logistic regression model with treatment as a factor and baseline HbA1c as a covariate. Statistical testing of canagliflozin versus placebo was not prespecified for this *post hoc* analysis; however, 95% CIs are reported for descriptive purposes. For patients who received rescue therapy, the last post-baseline value before the initiation of rescue therapy was used for analysis. Data for other outcomes remain blinded to investigators and patients, and are monitored by an Independent Data Monitoring Committee.

Results

Patients

During a recruitment period of 15 months, 7691 individuals were screened and 4330 were randomized. Of the 4330 CANVAS participants who were randomized, 411 met the inclusion criteria for the present analysis (316 were taking DPP-4 inhibitors and 95 were taking GLP-1 receptor agonists). Among patients in the DPP-4 inhibitor subset, 75.6% (239/316), 22.5% (71/316) and 2.2% (7/316) were taking sitagliptin, vildagliptin and saxagliptin, respectively, and one patient was taking both sitagliptin and vildagliptin. Among patients in the GLP-1 receptor agonist subset, 73.7% (70/95) were taking exenatide and 26.3% (25/95) were taking liraglutide. The majority of patients were receiving the recommended doses of DPP-4 inhibitor or GLP-1 receptor agonist. In the DPP-4 inhibitor subset, 102 patients were assigned to placebo, 103 to canagliflozin 100 mg, and 111 to canagliflozin 300 mg. In the GLP-1 receptor agonist subset, 30 patients were assigned to placebo, 35 to canagliflozin 100 mg, and 30 to canagliflozin 300 mg. Of the 316 patients in the DPP-4 inhibitor subset who were randomized and dosed, 294 (93.0%) completed the 18-week treatment period (i.e. did not discontinue from

Table 1. Baseline demographic and disease characteristics.*

Characteristic	DPP-4 inhibitor subset			GLP-1 receptor agonist subset		
	CANA 100 mg (n = 103)	CANA 300 mg (n = 111)	PBO (n = 102)	CANA 100 mg (n = 35)	CANA 300 mg (n = 30)	PBO (n = 30)
Sex, n (%)						
Male	66 (64)	81 (73)	60 (59)	28 (80)	19 (63)	19 (63)
Female	37 (36)	30 (27)	42 (41)	7 (20)	11 (37)	11 (37)
Age, years	62.4 (7.3)	62.7 (7.7)	63.9 (8.3)	60.7 (9.3)	61.5 (7.4)	60.9 (7.3)
Race, n (%)†						
White	84 (82)	91 (82)	80 (78)	31 (89)	21 (70)	25 (83)
Black or African-American	1 (1)	2 (2)	4 (4)	2 (6)	4 (13)	2 (7)
Asian	15 (15)	14 (13)	9 (9)	2 (6)	0	0
Other‡	3 (3)	4 (4)	9 (9)	0	5 (17)	3 (10)
HbA1c, %	8.1 (0.9)	8.0 (0.8)	8.1 (1.0)	8.2 (0.8)	8.3 (1.1)	8.0 (0.9)
BMI, kg/m^2	32.3 (5.8)	32.3 (5.9)	32.3 (5.8)	37.2 (6.1)	37.7 (7.7)	37.3 (7.6)
eGFR, ml/min/1.73 m^2	76.8 (17.5)	74.7 (20.2)	77.2 (19.9)	79.0 (17.8)	77.2 (21.3)	75.8 (21.7)
Duration of type 2 diabetes, years	12.3 (6.2)	13.2 (7.1)	12.5 (5.4)	14.6 (5.8)	15.3 (9.0)	14.7 (8.0)

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; CANA, canagliflozin; PBO, placebo; HbA1c, glycated haemoglobin; BMI, body mass index; eGFR, estimated glomerular filtration rate; s.d., standard deviation.
*Data are mean (s.d.) unless otherwise noted.
†Percentages may not total 100% because of rounding.
‡Including multiple and other.

the study for any reason); of the 95 patients in the GLP-1 receptor agonist subset who were randomized and dosed, 89 (93.7%) completed the 18-week treatment period (Table S1). The percentage of patients requiring rescue therapy in each of the subsets is presented in Table S1.

Baseline demographic and disease characteristics were generally similar across treatment groups within each subset, except for a higher number of male patients in the canagliflozin 100 mg group in the GLP-1 receptor agonist subset (Table 1). At baseline, the mean age was 63.0 and 61.0 years in patients on DPP-4 inhibitors and GLP-1 receptor agonists, respectively. The mean HbA1c was 8.1% in both subsets. The mean body mass index was 32.3 and 37.4 kg/m^2 in the DPP-4 inhibitor and GLP-1 receptor agonist subsets, respectively; the mean duration of type 2 diabetes was 12.7 and 14.9 years, respectively. In addition to DPP-4 inhibitors, the most frequently used background AHAs in the DPP-4 inhibitor subset were biguanides (80.1%), sulphonylureas (53.8%) and insulin (30.4%). Similarly, biguanides (72.6%), insulin (54.7%) and sulphonylureas (53.7%) were the most frequently used additional background AHAs in the GLP-1 receptor agonist subset (Table S2). Patients were not randomized by baseline use of DPP-4 inhibitors or GLP-1 receptor agonists, which resulted in some variation in background AHA use across groups in both subsets.

Effects of Canagliflozin on Efficacy Outcomes

In the DPP-4 inhibitor and GLP-1 receptor agonist subsets, both doses of canagliflozin lowered HbA1c relative to placebo at week 18 (Figure 1A, B and Table S3). At 18 weeks, placebo-subtracted changes in HbA1c with canagliflozin 100 and 300 mg were −0.56% (95% CI: −0.77, −0.35) and −0.75% (95% CI: −0.95, −0.54), respectively, in patients taking DPP-4 inhibitors. Placebo-subtracted changes in HbA1c with canagliflozin 100 and 300 mg were −1.00% (95% CI: −1.35, −0.65) and −1.06% (95% CI: −1.43, −0.69), respectively, in patients taking GLP-1 receptor agonists. Consequently, a higher proportion of patients treated with canagliflozin 100 and 300 mg achieved HbA1c <7.0% compared with placebo in the DPP-4 inhibitor subset (21.8, 34.3 and 14.6%, respectively) and in the GLP-1 receptor agonist subset (29.4, 34.5 and 6.9%, respectively). FPG was also lowered with both doses of canagliflozin compared with placebo in both subsets (Table S3).

Canagliflozin 100 and 300 mg provided body weight reductions compared with placebo in both subsets (Figure 1C, D and Table S3). At 18 weeks, placebo-subtracted changes in body weight with canagliflozin 100 and 300 mg were −2.3% (95% CI: −3.1, −1.5) and −3.0% (95% CI: −3.8, −2.2), respectively, in the DPP-4 inhibitor subset; and −2.5% (95% CI: −3.7, −1.4) and −3.2% (95% CI: −4.5, −2.0), respectively, in the GLP-1 receptor agonist subset. Reductions in systolic BP were observed with both doses of canagliflozin in combination with either DPP-4 inhibitors or GLP-1 receptor agonists; modest changes in diastolic BP were also observed (Figure 2A, B and Table S3). Changes in pulse rate were −3.1, 0.4 and −0.6 beats/min, respectively, in the DPP-4 inhibitor subset, and 0.0, 0.7 and 0.2 beats/min, respectively, in the GLP-1 receptor agonist subset, with canagliflozin 100 and 300 mg or placebo. Clear effects on blood lipids were not apparent, with large uncertainty intervals about most estimates (Figure 2C, D and Table S3).

Effects of Canagliflozin on Safety and Tolerability Outcomes

In the DPP-4 inhibitor subset, AEs were reported for 64.1, 63.1 and 58.8% of participants treated with canagliflozin 100 mg, canagliflozin 300 mg and placebo, respectively (Table 2). The corresponding figures for serious AEs were 2.9% (n = 3), 4.5% (n = 5) and 2.0% (n = 2), respectively. Genital mycotic infections were more common with canagliflozin compared with placebo for women and men. The incidence of UTIs

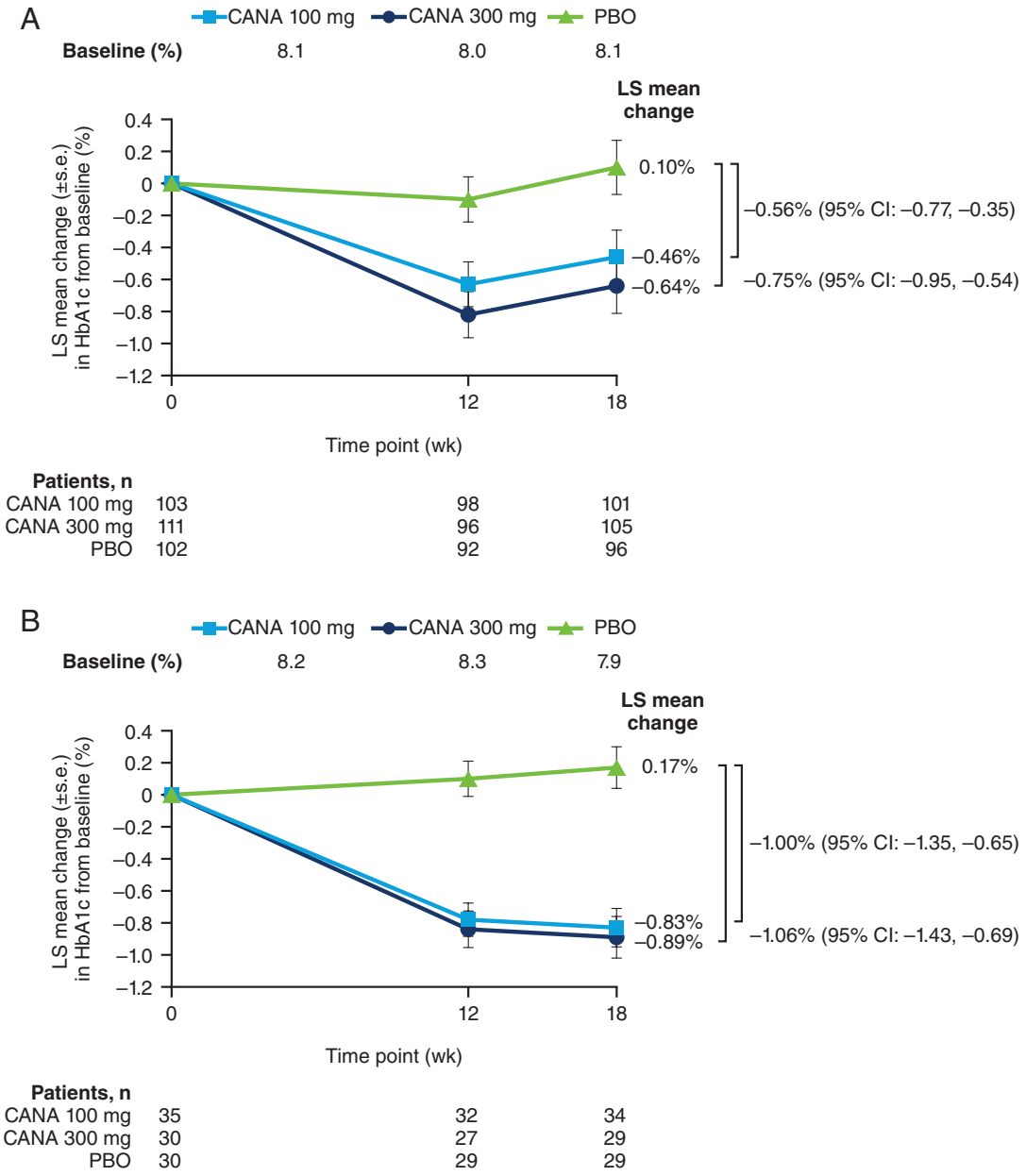

Figure 1. Change in glycated haemoglobin (HbA1c) and body weight in the dipeptidyl peptidase-4 (DPP-4) inhibitor (A, C) and glucagon-like peptide-1 (GLP-1) receptor agonist (B, D) subsets over 18 weeks (last observation carried forward [LOCF]). CANA, canagliflozin; PBO, placebo; LS, least squares; s.e., standard error; CI, confidence interval.

was 6.8, 4.5 and 1.0% with canagliflozin 100 mg, canagliflozin 300 mg and placebo, respectively. AEs attributable to volume depletion, such as postural hypotension and dizziness, were more common with canagliflozin 300 mg than placebo; none were reported with canagliflozin 100 mg. Rates of documented hypoglycaemia were 24.3, 33.3 and 16.2% with canagliflozin 100 mg, canagliflozin 300 mg and placebo, respectively, in patients who were taking background insulin or insulin secretagogues (i.e. sulphonylurea, meglitinide); there was one severe hypoglycaemia episode in the canagliflozin 300 mg group in a patient whose background AHA therapy consisted of vildagliptin 50 mg and glimepiride 4 mg (Table 2). Among those who were not taking background insulin or insulin secretagogues, only one patient (4.2%) in the canagliflozin 300 mg group reported documented hypoglycaemia (no severe episodes).

In the GLP-1 receptor agonist subset, the overall incidence of AEs was 62.9, 73.3 and 76.7% with canagliflozin 100 mg, canagliflozin 300 mg and placebo, respectively (Table 2); serious AEs were more frequent with canagliflozin 300 mg (n = 5; 16.7%) compared with canagliflozin 100 mg (n = 2; 5.7%) and placebo (n = 1; 3.3%). The incidence of genital mycotic infections, UTIs and volume depletion–related AEs was higher with canagliflozin 300 mg compared with canagliflozin 100 mg and

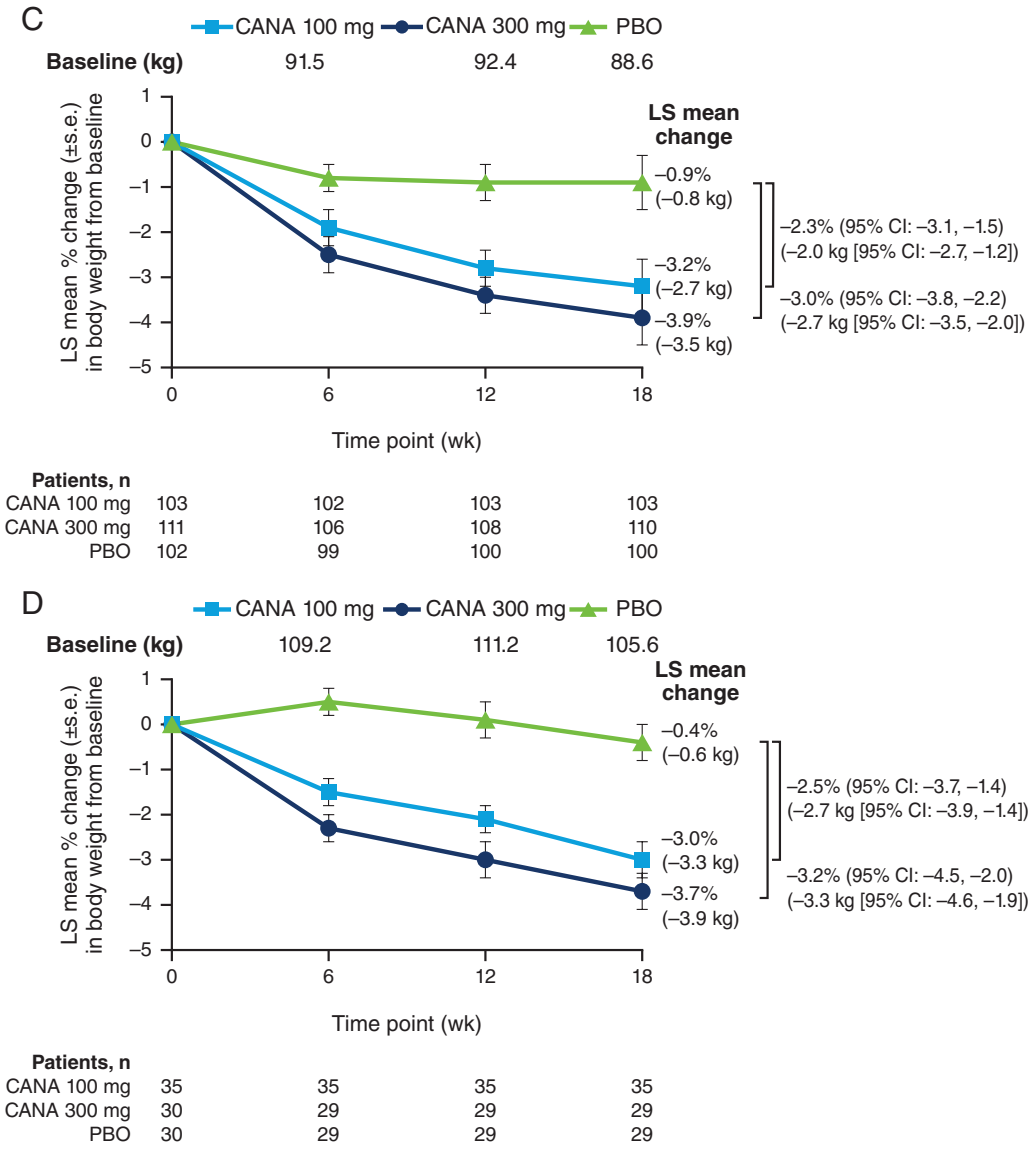

Figure 1. Continued.

placebo. Both doses of canagliflozin were associated with an increased incidence of osmotic diuresis–related AEs compared with placebo. Rates of AEs in the gastrointestinal disorders system organ class were 28.6, 30.0 and 23.3% with canagliflozin 100 mg, canagliflozin 300 mg and placebo, respectively. Rates of documented hypoglycaemia were 37.9, 50.0 and 15.4% with canagliflozin 100 mg, canagliflozin 300 mg and placebo, respectively, among patients who were taking background insulin or insulin secretagogues; there was one severe hypoglycaemia episode in the canagliflozin 300 mg group in a patient whose background AHA therapy consisted of exenatide 20 µg, metformin 2000 mg and insulin glargine 26 IU (Table 2). Among those who were not taking background insulin or insulin secretagogues, one patient (12.5%) in the canagliflozin 300 mg group reported documented hypoglycaemia (no severe episodes).

Changes in laboratory safety parameters are summarized in Table S4. In the DPP-4 inhibitor subset, reductions in estimated glomerular filtration rate (eGFR) of −6.0, −7.3 and −3.5% were observed with canagliflozin 100 mg, canagliflozin 300 mg and placebo, respectively; in the GLP-1 receptor agonist subset, reductions in eGFR were −1.7, −4.9 and −3.3%, respectively. These reductions in eGFR were associated with commensurate increases in serum creatinine. Changes in blood urea nitrogen were 18.1, 18.4 and 4.5% with canagliflozin 100 mg, canagliflozin 300 mg and placebo, respectively, in the DPP-4 inhibitor subset; and 14.2, 4.6 and 8.4%, respectively, in the GLP-1 receptor agonist subset. In both subsets, reductions in serum urate and increases in haemoglobin were observed with canagliflozin 100 and 300 mg compared with placebo.

Discussion

Findings from this *post hoc* analysis in a small subset of patients with type 2 diabetes show that canagliflozin added to

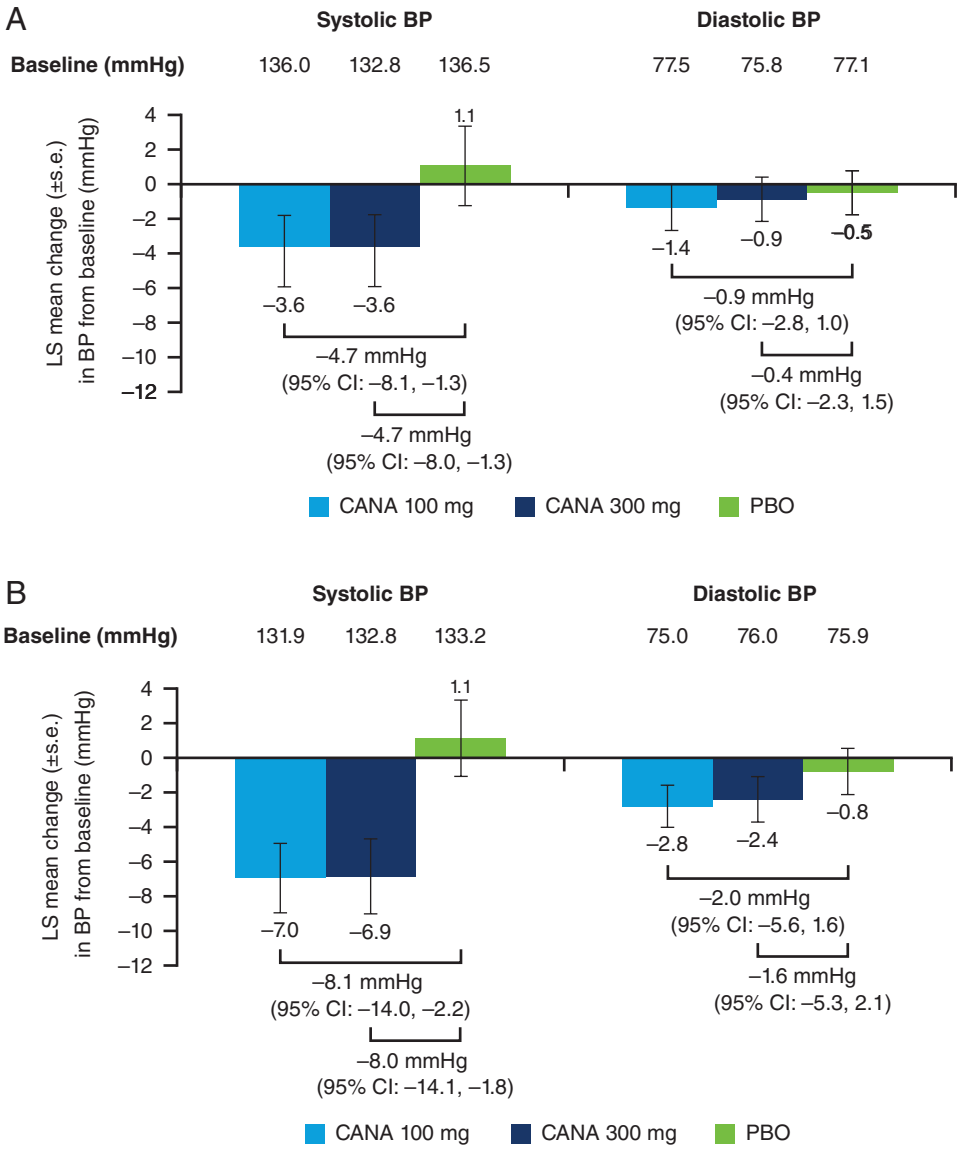

Figure 2. Change in blood pressure (BP) and fasting plasma lipids at week 18 in the dipeptidyl peptidase-4 (DPP-4) inhibitor (A, C) and glucagon-like peptide-1 (GLP-1) receptor agonist (B, D) subsets (last observation carried forward [LOCF]). LS, least squares; s.e., standard error; CI, confidence interval; CANA, canagliflozin; PBO, placebo; LDL-C, low-density lipoprotein cholesterol; HDL-C; high-density lipoprotein cholesterol.

a stable background treatment regimen consisting of a DPP-4 inhibitor or GLP-1 receptor agonist with or without other AHAs improves efficacy outcomes, including HbA1c, body weight and BP, over 18 weeks. Canagliflozin was generally well tolerated in both subsets, with an increased incidence of AEs related to the SGLT2 mechanism.

Efficacy and safety findings from this *post hoc* analysis in patients on background DPP-4 inhibitors or GLP-1 receptor agonists were generally consistent with those seen in previous phase III studies of canagliflozin [5–18]. Compared with the two prespecified substudies of the CANVAS trial in patients on background insulin and sulphonylurea, HbA1c reductions at week 18 were slightly smaller in the DPP-4 inhibitor subset and slightly larger in the GLP-1 receptor agonist subset [9,20]. Body weight and systolic BP reductions with canagliflozin versus placebo in both subsets were larger compared with those seen in the add-on to insulin and add-on to sulphonylurea substudies [9,20]. In particular, the changes in weight were consistent with the class effects of these agents; DPP-4 inhibitors are weight-neutral and GLP-1 receptor agonists are associated with weight loss, while insulin and sulphonylurea are associated with weight gain [2]. Changes in lipids were variable and associated with large uncertainty in the present analysis, and therefore cannot be compared with data from previous studies of canagliflozin. Inconsistent effects on lipid variables were also observed in the previous substudies of CANVAS [9,20].

A key benefit of canagliflozin compared with some other AHA classes is that its action is independent of β-cell function [2], suggesting that it may be useful in patients with more advanced type 2 diabetes (i.e. greater impairment of β-cell

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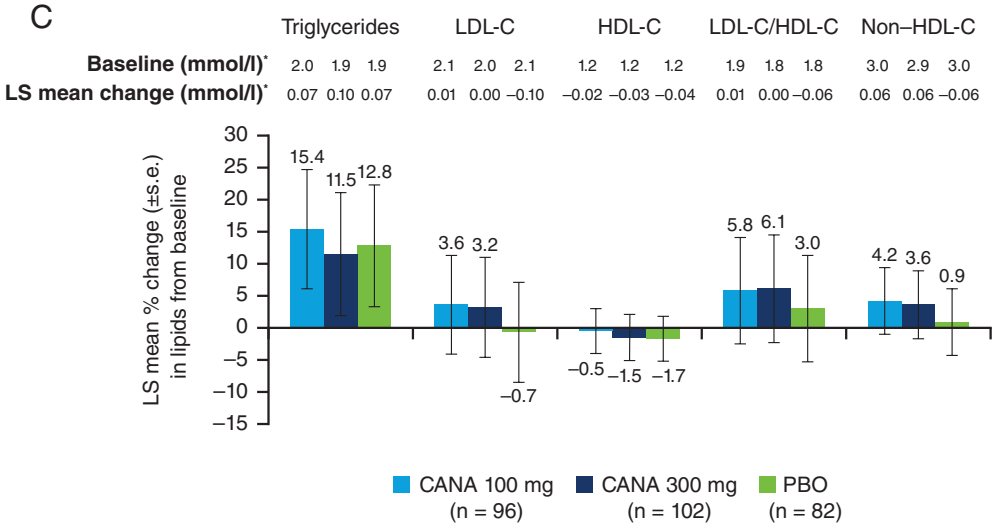
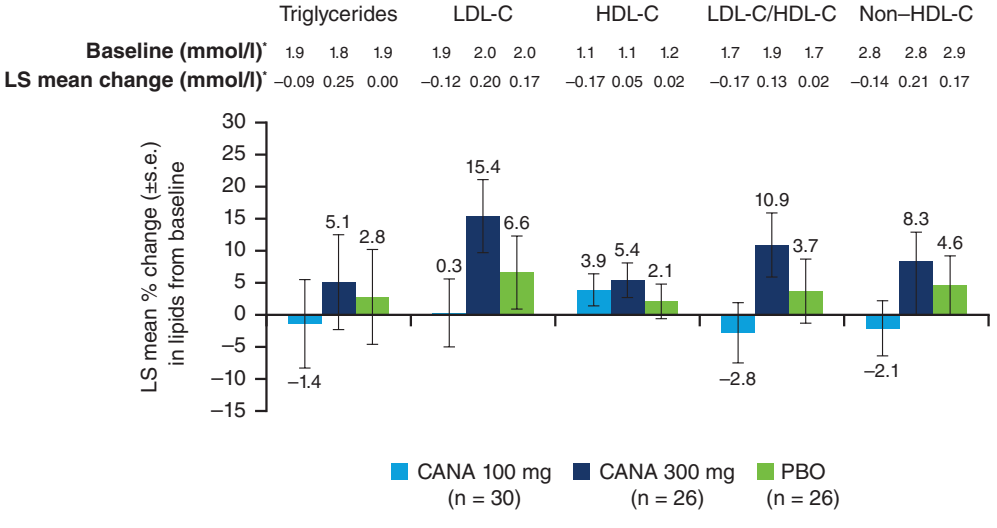


Parameter	Differences vs PBO (95% CI) CANA 100 mg	CANA 300 mg
Triglycerides	2.6% (–9.2, 14.5)	–1.3% (–12.9, 10.3)
LDL-C	4.3% (–5.4, 14.0)	4.0% (–5.6, 13.5)
HDL-C	1.2% (–3.2, 5.6)	0.2% (–4.1, 4.6)
LDL-C/HDL-C	2.8% (–7.7, 13.2)	3.1% (–7.2, 13.4)
Non–HDL-C	3.3% (–3.3, 9.8)	2.6% (–3.8, 9.1)

D



Parameter	Differences vs PBO (95% CI) CANA 100 mg	CANA 300 mg
Triglycerides	–4.2% (–24.4, 16.0)	2.3% (–18.6, 23.2)
LDL-C	–6.3% (–21.7, 9.2)	8.9% (–7.1, 24.8)
HDL-C	1.8% (–5.6, 9.3)	3.3% (–4.5, 11.1)
LDL-C/HDL-C	–6.5% (–20.1, 7.1)	7.2% (–7.0, 21.4)
Non–HDL-C	–6.7% (–19.2, 5.8)	3.7% (–9.2, 16.5)

Figure 2. Continued. *Units of mol/mol for LDL-C/HDL-C.

function). In this analysis, which included older patients with long disease duration and high cardiovascular disease risk, canagliflozin 100 and 300 mg provided reductions in HbA1c compared with placebo in patients whose background therapy included DPP-4 inhibitors and GLP-1 receptor agonists; these glycaemic improvements resulted in a higher proportion of patients achieving HbA1c <7.0% with canagliflozin 100 and 300 mg compared with placebo in both patient subsets.

The safety and tolerability of canagliflozin in this analysis was generally consistent with previous phase III studies,

Table 2. Overall safety and selected adverse events.*

Patients, n (%)	DPP-4 inhibitor subset			GLP-1 receptor agonist subset		
	CANA 100 mg (n = 103)	CANA 300 mg (n = 111)	PBO (n = 102)	CANA 100 mg (n = 35)	CANA 300 mg (n = 30)	PBO (n = 30)
Any AE	66 (64.1)	70 (63.1)	60 (58.8)	22 (62.9)	22 (73.3)	23 (76.7)
AEs leading to discontinuation	1 (1.0)	6 (5.4)	1 (1.0)	2 (5.7)	3 (10.0)	0
AEs related to study drug†	21 (20.4)	29 (26.1)	14 (13.7)	10 (28.6)	11 (36.7)	7 (23.3)
Serious AEs	3 (2.9)	5 (4.5)	2 (2.0)	2 (5.7)	5 (16.7)	1 (3.3)
Deaths	0	0	2 (2.0)	0	0	0
AEs of special interest						
Genital mycotic infections						
Male‡,§	3 (4.5)	5 (6.2)	1 (1.7)	1 (3.6)	2 (10.5)	1 (5.3)
Female¶,**	5 (13.5)	5 (16.7)	1 (2.4)	0	5 (45.5)	0
UTIs	7 (6.8)	5 (4.5)	1 (1.0)	2 (5.7)	4 (13.3)	2 (6.7)
Osmotic diuresis–related AEs††	6 (5.8)	9 (8.1)	1 (1.0)	5 (14.3)	4 (13.3)	1 (3.3)
Volume depletion–related AEs‡‡	0	4 (3.6)	0	0	3 (10.0)	1 (3.3)
Hypoglycaemia episodes						
Patients on insulin, SU or meglitinide, n	70	87	74	29	22	26
Documented hypoglycaemia§§	17 (24.3)	29 (33.3)	12 (16.2)	11 (37.9)	11 (50.0)	4 (15.4)
Severe hypoglycaemia	0	1 (1.1)	0	0	1 (4.5)	0
Patients not on insulin, SU or meglitinide, n	33	24	28	6	8	4
Documented hypoglycaemia§§	1 (3.0)	1 (4.2)	0	0	1 (12.5)	0
Severe hypoglycaemia	0	0	0	0	0	0

DPP-4, dipeptidyl peptidase-4; GLP-1 glucagon-like peptide-1; CANA, canagliflozin; PBO, placebo; AE, adverse event; UTI, urinary tract infection; SU, sulphonylurea.

*All AEs are reported regardless of rescue medication; hypoglycaemia episodes are reported prior to rescue medication.

†Possibly, probably or very likely related to study drug as assessed by investigators.

‡DPP-4 inhibitors: CANA 100 mg, n = 66; CANA 300 mg, n = 81; PBO, n = 60; GLP-1 receptor agonists: CANA 100 mg, n = 28; CANA 300 mg, n = 19; PBO, n = 19.

§DPP-4 inhibitors: including balanitis, balanoposthitis, genital infection fungal and penile infection; GLP-1 receptor agonists: including balanitis, balanitis candida and genital infection fungal.

¶DPP-4 inhibitors: CANA 100 mg, n = 37; CANA 300 mg, n = 30; PBO, n = 42; GLP-1 receptor agonists: CANA 100 mg, n = 7; CANA 300 mg, n = 11; PBO, n = 11.

**DPP-4 inhibitors: including genital infection fungal, vaginal infection, vulvitis, vulvovaginal candidiasis and vulvovaginal mycotic infection; GLP-1 receptor agonists: including genital candidiasis, vulvovaginal candidiasis and vulvovaginal mycotic infection.

††DPP-4 inhibitors: including dry mouth, thirst, micturition urgency, nocturia, pollakiuria and polyuria; GLP-1 receptor agonists: including urine output increased, micturition urgency, pollakiuria and polyuria.

‡‡DPP-4 inhibitors: including blood pressure decreased, dizziness postural and hypotension; GLP-1 receptor agonists: including dehydration, dizziness postural, syncope and hypotension.

§§Including biochemically documented episodes [≤3.9 mmol/l (70 mg/dl)] with or without symptoms and severe episodes (i.e. requiring the assistance of another individual or resulting in seizure or loss of consciousness).

including the two prespecified substudies of CANVAS [5–18,20]; as expected, incidences of AEs related to SGLT2 inhibition were generally higher with canagliflozin versus placebo. In the DPP-4 inhibitor subset, both canagliflozin doses were associated with higher incidences of male and female genital mycotic infections, UTIs and osmotic diuresis–related AEs compared with placebo. In the GLP-1 receptor agonist subset, incidences of these AEs were generally higher with canagliflozin 300 mg compared with canagliflozin 100 mg and placebo. In both subsets, volume depletion–related AEs were reported with canagliflozin 300 mg, but not with canagliflozin 100 mg. Documented hypoglycaemia episodes were reported infrequently in patients who were not taking AHAs associated with hypoglycaemia. Among those on insulin or insulin secretagogues, the incidence of documented hypoglycaemia was numerically higher with canagliflozin compared with placebo, consistent with the CANVAS add-on to insulin and add-on to sulphonylurea substudies [9,20]; severe episodes were rare in the present analysis and in both of the previous CANVAS substudies [9,20]. Changes in laboratory variables were consistent with those seen in other studies of canagliflozin [5–18,20].

As patients included in this subset analysis were not randomized on the basis of background incretin usage, the lack of randomized comparisons is a limitation of this analysis. Related to this, another limitation was the relatively small number of patients enrolled in CANVAS who were taking DPP-4 inhibitors or GLP-1 receptor agonists. In addition, although the use of background AHA therapies was randomized to be balanced across treatment groups in the overall study, balance was not assured in these *post hoc* subgroups defined by baseline DPP-4 inhibitor or GLP-1 receptor agonist use. This analysis was also limited by its *post hoc* nature. Finally, this analysis only reports data over 18 weeks. Prespecified studies of canagliflozin added to DPP-4 inhibitors or GLP-1 receptor agonists in larger populations and over longer durations would be beneficial.

In summary, canagliflozin provided consistent glycaemic benefits, weight loss and BP reductions in patients with type 2 diabetes who were on a background AHA regimen including DPP-4 inhibitors or GLP-1 receptor agonists over 18 weeks and was generally well tolerated, with a similar safety profile to that reported in previous phase III studies of canagliflozin.

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Conflict of Interest

G. F. has served on advisory boards for Johnson & Johnson and as a consultant to Janssen. D. R. M. has served on advisory boards or as a consultant for Novo Nordisk, GlaxoSmithKline, Novartis, Eli Lilly, Sanofi-Aventis, Janssen and Servier; receives current research support from Janssen and UK National Institute for Health Research (NIHR); and has given lectures for Novo Nordisk, Servier, Sanofi-Aventis, Eli Lilly, Novartis, Janssen and Aché Laboratories. V. P. is supported by a Senior Research Fellowship from the Australian National Health and Medical Research Council; has served on advisory boards and/or spoken at scientific meetings sponsored by Janssen, Baxter, AbbVie, Astellas, Boehringer Ingelheim, AstraZeneca, Eli Lilly, Merck and GlaxoSmithKline; and has a policy of honoraria going to his employer. D. d. Z. serves as a consultant for AbbVie, Astellas, Chemocentryx, Eli Lilly, Fresenius, Janssen and Merck Darmstadt; all consultancy honoraria are paid to his institution. K. W. M. has provided continuing medical education on behalf of and/or has served as a consultant to the American College of Cardiology, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cubist, Eli Lilly, Elsevier, Forest, GlaxoSmithKline, Johnson & Johnson, Medtronic, Merck, Omthera, Portola Pharma, Spring Publishing, The Medicines Company and WebMD, and has received research support from Medtronic and St. Jude. C. M. has served on the advisory panel for Novo Nordisk, Sanofi-Aventis, Merck Sharp and Dohme Ltd, Eli Lilly and Company, Novartis, Bristol-Myers Squibb, AstraZeneca LP, Pfizer, Johnson & Johnson, Boehringer Ingelheim and Mannkind; has served on the speakers bureau for Novo Nordisk, Sanofi-Aventis, Merck Sharp and Dohme Ltd, Eli Lilly and Company and Novartis; and her institution has received research support from Novo Nordisk, Sanofi-Aventis, Merck Sharp and Dohme Ltd., Eli Lilly and Company and Novartis. V. W. has been a speaker, served on advisory boards and participated in clinical trials for Janssen, Merck, Boehringer Ingelheim, AstraZeneca, Bristol-Myers Squibb, Novo Nordisk, Lilly and Sanofi. C. W. has served as a consultant for and her institution has received research support from Janssen. B. N. is supported by a National Health and Medical Research Council Senior Research Fellowship; holds a research grant for this study from Janssen and for other large-scale cardiovascular outcome trials from Roche, Servier and Merck Schering-Plough; and has received honoraria or travel support for contributions to the continuing medical education programmes of Abbott, Novartis, Pfizer, Roche and Servier. G. C., M. D., W. S., F. V. and G. M. are full-time employees of Janssen Research & Development, LLC. G. C., F. V. and G. M. are shareholders of Johnson & Johnson.

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Supporting Information

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

Table S1. Participant disposition.

Table S2. Baseline use of AHAs.

Table S3. Summary of efficacy endpoints at week 18 (mITT, LOCF).

Table S4. Summary of laboratory safety parameters at week 18.

Appendix S1. CANVAS collaborating sites.

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