Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial

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Summary

Background Sodium–glucose cotransporter 2 (SGLT2) inhibitors improve glycaemia in patients with type 2 diabetes by enhancing urinary glucose excretion. We compared the efficacy and safety of canagliflozin, an SGLT2 inhibitor, with glimepiride in patients with type 2 diabetes inadequately controlled with metformin.

Methods We undertook this 52 week, randomised, double-blind, active-controlled, phase 3 non-inferiority trial at 157 centres in 19 countries between Aug 28, 2009, and Dec 21, 2011. Patients aged 18–80 years with type 2 diabetes and glycated haemoglobin A_{1c} (HbA_{1c}) of 7·0–9·5% on stable metformin were randomly assigned (1:1:1) by computer-generated random sequence via an interactive voice or web response system to receive canagliflozin 100 mg or 300 mg, or glimepiride (up-titrated to 6 mg or 8 mg per day) orally once daily. Patients, study investigators, and local sponsor personnel were masked to treatment. The primary endpoint was change in HbA_{1c} from baseline to week 52, with a non-inferiority margin of 0·3% for the comparison of each canagliflozin dose with glimepiride. If non-inferiority was shown, we assessed superiority on the basis of an upper bound of the 95% CI for the difference of each canagliflozin dose versus glimepiride of less than 0·0%. Analysis was done in a modified intention-to-treat population, including all randomised patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, number NCT00968812.

Findings 1450 of 1452 randomised patients received at least one dose of glimepiride (n=482), canagliflozin 100 mg (n=483), or canagliflozin 300 mg (n=485). For lowering of HbA_{1c} at 52 weeks, canagliflozin 100 mg was non-inferior to glimepiride (least-squares mean difference –0·01% [95% CI –0·11 to 0·09]), and canagliflozin 300 mg was superior to glimepiride (–0·12% [–0·22 to –0·02]). 39 (8%) patients had serious adverse events in the glimepiride group versus 24 (5%) in the canagliflozin 100 mg group and 26 (5%) in the 300 mg group. In the canagliflozin 100 mg and 300 mg groups versus the glimepiride group, we recorded a greater number of genital mycotic infections (women: 26 [11%] and 34 [14%] *vs* five [2%]; men: 17 [7%] and 20 [8%] *vs* three [1%]), urinary tract infections (31 [6%] for both canagliflozin doses *vs* 22 [5%]), and osmotic diuresis-related events (pollakiuria: 12 [3%] for both doses *vs* one [<1%]; polyuria: four [<1%] for both doses *vs* two [<1%]).

Interpretation Canagliflozin provides greater HbA_{1c} reduction than does glimepiride, and is well tolerated in patients with type 2 diabetes receiving metformin. These findings support the use of canagliflozin as a viable treatment option for patients who do not achieve sufficient glycaemic control with metformin therapy.

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Introduction

Type 2 diabetes is well known as a progressive disease, and to adequately manage hyperglycaemia after an initial period of lifestyle management and monotherapy, patients often need combination treatments to maintain glycaemic control.[1–3] Metformin is the standard and preferred first-line pharmacological drug for type 2 diabetes.[2] After metformin failure, various drugs are available as add-on therapy, such as sulphonylureas, insulin, thiazolidinediones, and incretins. However, many of these drugs not only reduce glucose concentrations, but also cause weight gain and increase the risk of hypoglycaemia.[2] Thus, drugs are needed that can provide glycaemic control while having beneficial effects on weight and hypoglycaemia. In this regard, pharmacological inhibition of the sodium–glucose cotransporter 2 (SGLT2) is an appealing alternative. Specifically, SGLT2 inhibitors lower the renal threshold for glucose, leading to increased urinary glucose excretion, decreased plasma glucose, a mild osmotic diuresis, and a net loss of calories.[4] Therefore, these inhibitors have an insulin-independent mechanism for the correction of hyperglycaemia through decreased renal glucose reabsorption.

Canagliflozin is an SGLT2 inhibitor developed for the treatment of type 2 diabetes.[5–9] In patients with type 2 diabetes inadequately controlled with metformin, canagliflozin has been associated with significant reductions in glycated haemoglobin A_{1c} (HbA_{1c}), fasting plasma

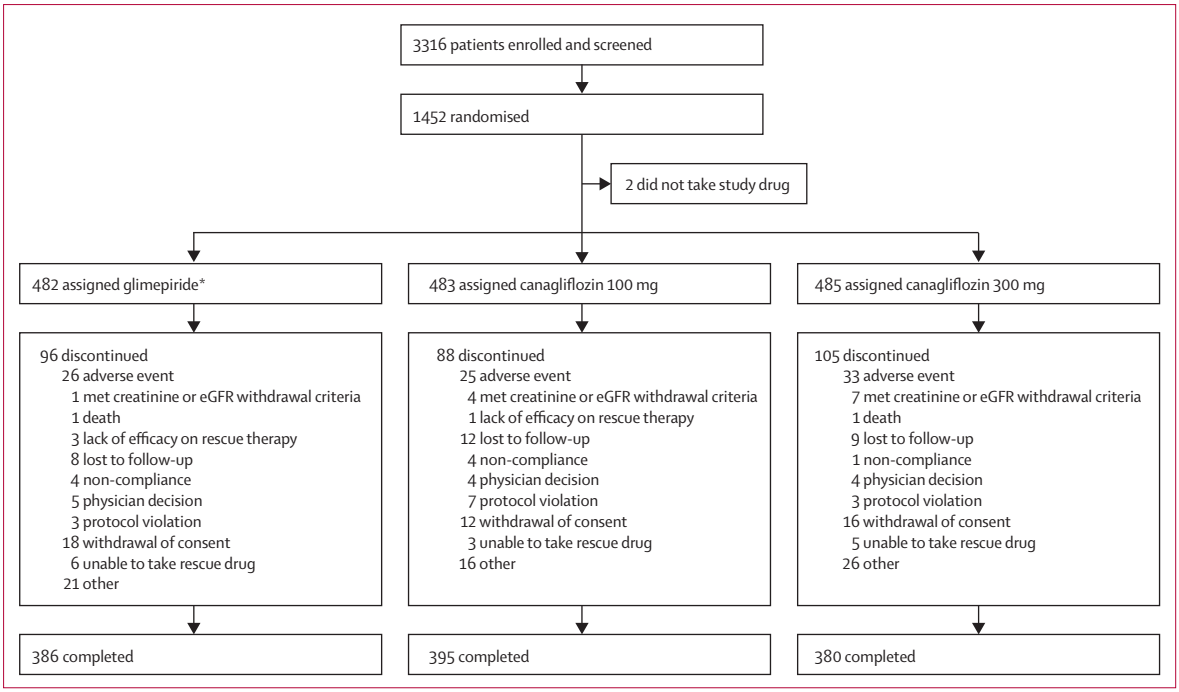

Figure 1: **Trial profile**
eGFR=estimated glomerular filtration rate. *484 patients randomly assigned.

	Glimepiride (n=482)	Canagliflozin 100 mg (n=483)	Canagliflozin 300 mg (n=485)	Total (N=1450)
Sex				
Male	263 (55%)	252 (52%)	241 (50%)	756 (52%)
Female	219 (45%)	231 (48%)	244 (50%)	694 (48%)
Age (years)	56·3 (9·0)	56·4 (9·5)	55·8 (9·2)	56·2 (9·2)
Race*				
White	322 (67%)	323 (67%)	333 (69%)	978 (67%)
Black or African American	22 (5%)	20 (4%)	19 (4%)	61 (4%)
Asian	93 (19%)	99 (21%)	92 (19%)	284 (20%)
Other†	45 (9%)	41 (9%)	41 (9%)	127 (9%)
HbA_{1c} (%)	7·8 (0·8)	7·8 (0·8)	7·8 (0·8)	7·8 (0·8)
FPG (mmol/L)	9·2 (2·1)	9·2 (2·1)	9·1 (2·0)	9·2 (2·1)
Bodyweight (kg)	86·5 (19·8)	86·9 (20·1)	86·6 (19·5)	86·6 (19·8)
Body-mass index (kg/m²)	30·9 (5·5)	31·0 (5·3)	31·2 (5·4)	31·0 (5·4)
Duration of type 2 diabetes (years)	6·6 (5·0)	6·5 (5·5)	6·7 (5·5)	6·6 (5·3)
Median (range)	5·1 (0·0–30·0)	5·0 (0·2–37·0)	5·0 (0·0–32·0)	5·0 (0·0–37·0)
Entered antihyperglycaemic drug adjustment period				
Yes	171 (36%)	173 (36%)	178 (37%)	522 (36%)
No	311 (65%)	310 (64%)	307 (63%)	928 (64%)

Data are n (%) or mean (SD), unless otherwise indicated. HbA_{1c}=glycated haemoglobin A_{1c}. FPG=fasting plasma glucose. *Percentages might not total 100% because of rounding. †Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple origin, and other.

Table 1: **Baseline demographics and disease characteristics**

glucose, and bodyweight at 12 weeks, with a low frequency of hypoglycaemia.[8] In view of these potential beneficial effects, we assessed the efficacy and safety of canagliflozin compared with glimepiride as add-on therapy in patients with type 2 diabetes inadequately controlled with metformin.

Methods

Study design and participants

We report findings from our CANagliflozin Treatment And Trial Analysis versus SUlphonylurea (CANTATA-SU) study. We undertook this randomised, double-blind, active-controlled, phase 3 non-inferiority trial at 157 centres in 19 countries. 54 centres were in North America, 39 in Europe, and nine in Central or South America; the other 55 were spread around the rest of the world. The study consisted of a 2 week, single-blind, placebo run-in period and a 52 week, double-blind, core treatment period, which took place between Aug 28, 2009, and Dec 21, 2011 (reported here), followed by a 52 week, double-blind, extension period.

Eligible participants were aged 18–80 years, had type 2 diabetes and HbA_{1c} of 7·0–9·5%, and were receiving stable metformin therapy (≥2000 mg per day or ≥1500 mg per day if unable to tolerate a higher dose) for at least 10 weeks. Participants who were receiving metformin in combination with one other oral non-thiazolidinedione antihyperglycaemic drug at screening discontinued the second antihyperglycaemic drug and, if needed, had their metformin dose increased. Patients who were receiving metformin at doses lower than specified in the protocol had their metformin dose increased before entering an up to 12 week metformin dose-stable run-in period before the 2 week placebo run-in period. Key

exclusion criteria included a history of more than one severe hypoglycaemic episode (within 6 months); repeated measurements of fasting plasma glucose or fasting self-monitored blood glucose, or both, of 15·0 mmol/L or more during the pretreatment phase; an estimated glomerular filtration rate (GFR) of less than 55 mL/min/1·73 m² (or <60 mL/min/1·73 m² if based on restriction of metformin use in local label) or serum creatinine concentrations of 124 µmol/L or more for men and 115 µmol/L or more for women; or were given thiazolidinedione within 16 weeks before screening. We selected a subset of patients for participation in a body composition substudy on the basis of site capabilities (ability to undertake imaging for body composition) and expected sufficient enrolment within a country. During the double-blind treatment period, glycaemic rescue therapy with pioglitazone was started in patients who were at the maximum level of study drug titration and met specific criteria (appendix).

The study protocol and amendments were approved by institutional review boards or independent ethics committees at participating institutions. The study was done in accordance with guidelines of Good Clinical Practice and the Declaration of Helsinki, and with applicable regulatory requirements. All participants provided written informed consent before participation.

Randomisation and masking

Single-blind placebo capsules matching study drug were given to all participants once daily during the placebo run-in period. Participants were then randomly assigned, in a 1:1:1 ratio, by an interactive voice or web response system to be given canagliflozin 100 mg or 300 mg or glimepiride. The sponsor prepared the computer-generated randomisation schedule before the study. Randomisation was balanced with the use of permuted blocks of three patients per block and stratified by whether the patient was taking a stable, protocol-specified dose of metformin before screening versus whether they had either undergone metformin dose adjustment or discontinued use of a second anti-hyperglycaemic drug, or both, and by country.

After randomisation, HbA_{1c} and fasting plasma glucose values were masked to staff at the study centres unless values met glycaemic rescue criteria (and were subsequently provided unmasked). Patients, study investigators, and local sponsor personnel were masked to treatment assignment until final database lock. To maintain masked treatment, study drug was supplied in levels (levels one to five) to allow for masked increases and decreases of glimepiride throughout the double-blind treatment period.

Procedures

We chose the doses of canagliflozin on the basis of previously published findings from a dose-ranging, phase 2 study showing significant reductions in HbA_{1c} with canagliflozin 100 mg and an additional improvement in glycaemic control with canagliflozin 300 mg in patients with type 2 diabetes.[8] Titration of glimepiride ranged from a starting dose of 1 mg to a maximum dose of 6 mg or 8 mg (on the basis of maximum approved dose in the country of the investigational site) after 2 or more weeks at the current dose if patients met protocol-specified glycaemic criteria (ie, ≥50% of fasting self-monitored blood glucose readings >6·0 mmol/L, with no hypoglycaemic events during the 2 weeks preceding clinic visit or telephone contact). Patients assigned to the canagliflozin groups were mock up-titrated.

The prespecified primary efficacy endpoint was the change in HbA_{1c} from baseline to week 52. Prespecified secondary efficacy endpoints were percentage change from baseline in bodyweight, and proportion of patients with documented hypoglycaemic episodes, including

See Online for appendix

	Glimepiride (n=473)	Canagliflozin 100 mg (n=478)	Canagliflozin 300 mg (n=474)
Mean (SD) baseline (%)	7·8 (0·8)	7·8 (0·8)	7·8 (0·8)
LS mean (SE) change	−0·81 (0·04)	−0·82 (0·04)	−0·93 (0·04)
Difference (95% CI) *vs* glimepiride	..	−0·01 (−0·11 to 0·09)	−0·12 (−0·22 to −0·02)

Last observation carried forward analysis. LS=least squares.

Table 2: **Changes from baseline in glycated haemoglobin A_{1c} at week 52**

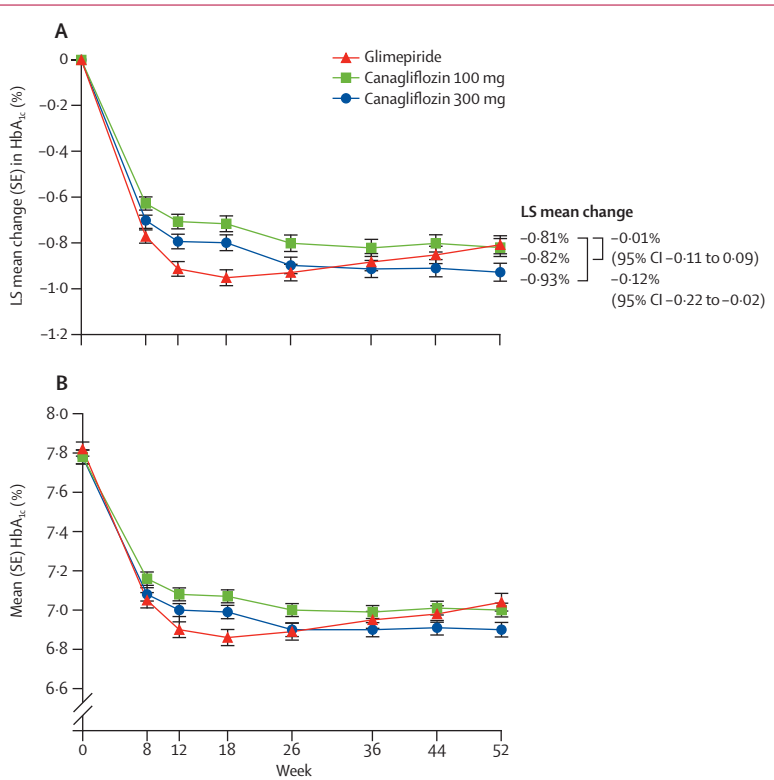

Figure 2: **Change in HbA_{1c} (A), and mean HbA_{1c} over time (B)**
Last observation carried forward analyses. Mean baseline HbA_{1c} of 7·8% for each treatment group. LS=least squares. HbA_{1c}=glycated haemoglobin A_{1c}.

biochemically documented episodes (concurrent finger-stick glucose or plasma glucose ≤3·9 mmol/L with or without symptoms) and severe episodes (those needing assistance of another individual or resulting in seizure or loss of consciousness). Additional endpoints included the proportion of patients achieving HbA_{1c} less than either 7·0% or 6·5%; change in fasting plasma glucose and systolic and diastolic blood pressure; and percentage change in fasting plasma lipids, including HDL cholesterol, triglycerides, LDL cholesterol, non-HDL cholesterol, and ratio of LDL cholesterol to HDL cholesterol.

We assessed body composition endpoints for a subset of patients at week 52. Changes from baseline in total fat mass, total lean mass, and percentage of total fat (total fat measurement as a percentage of the sum of total fat measurement, total lean measurement, and bone mineral content) were assessed with dual-energy X-ray absorptiometry scans and analysed by a single vendor (BioClinica, Newtown, PA, USA). Percentage changes in subcutaneous adipose tissue and visceral adipose tissue, and the change in the ratio of subcutaneous to visceral adipose tissue, were determined with CT scans (appendix). We assessed safety with adverse event reports, laboratory tests, vital sign measurements, physical examinations, self-monitored blood glucose, and 12-lead electrocardiograms. Additional data collection was prespecified for adverse events of genital mycotic infections and urinary tract infections; these events were diagnosed on the basis of clinical assessment by the investigator of associated signs and symptoms and, in some cases, laboratory tests including culture results.

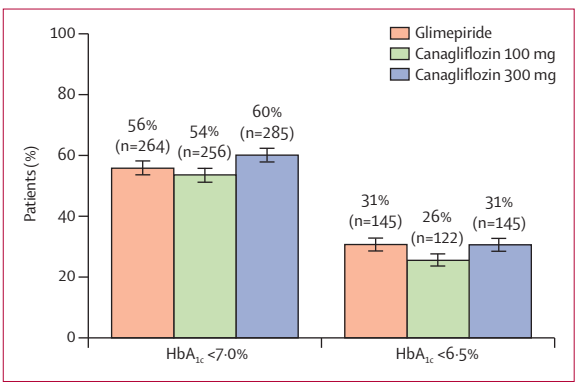

Figure 3: **Proportion of patients achieving HbA_{1c} goals**
Last observation carried forward analysis. Statistical comparison for canagliflozin 100 mg and 300 mg versus glimepiride not undertaken (not prespecified). Error bars show SE. HbA_{1c}=glycated haemoglobin A_{1c}.

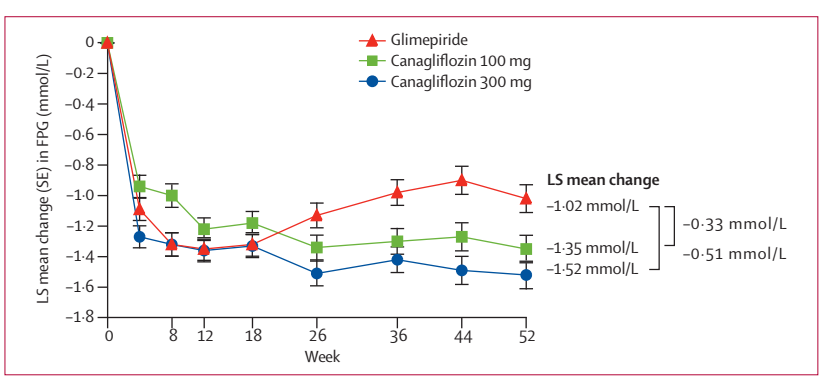

Figure 4: **Change in FPG**
Last observation carried forward analysis. Statistical comparison for canagliflozin 100 mg and 300 mg versus glimepiride not undertaken (not prespecified). Mean baseline FPG of 9·2 mmol/L, 9·1 mmol/L, and 9·2 mmol/L for canagliflozin 100 and 300 mg and glimepiride, respectively. FPG=fasting plasma glucose. LS=least squares.

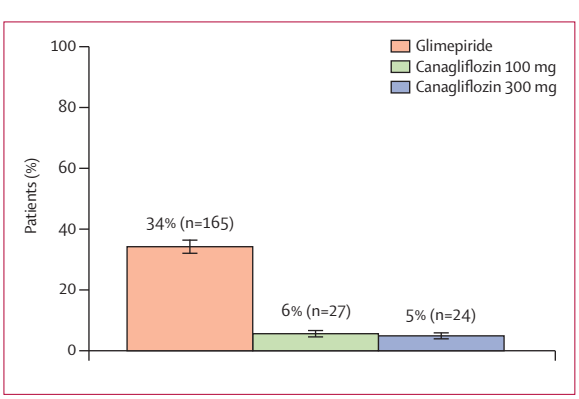

Figure 5: **Proportion of patients with documented hypoglycaemia episodes**
Modified intention-to-treat population. p<0·0001 for both canagliflozin groups *vs* glimepiride. Error bars show SE.

Statistical analyses

The primary hypothesis of this study was the non-inferiority of canagliflozin 100 mg or 300 mg, or both, to glimepiride for HbA_{1c} reduction at week 52. The primary analysis was based on a last observation carried forward (LOCF) approach in the modified intention-to-treat population (all randomised patients receiving at least one dose of study drug). To support this analysis, a secondary per-protocol analysis (all patients who completed the 52 week study, did not need glycaemic rescue drug, and had no prespecified protocol violations that could affect efficacy analyses) was done. Sample size was calculated on the basis of the per-protocol analysis; an estimated 277 patients per group would be needed to provide approximately 90% power to show non-inferiority of canagliflozin to glimepiride for HbA_{1c} lowering, with an assumed difference of 0·0% between canagliflozin and glimepiride and an assumed common SD of 1·0%. We assumed that 35% of patients would discontinue the study before week 52; therefore, about 427 patients were planned for inclusion in each group. For the body composition substudy, 46 or more patients per group would provide 90% power for the comparisons between groups in percentage of total fat and visceral adipose tissue; to assure collection of imaging at both baseline and week 52, approximately 70 patients per group were planned for inclusion.

We did primary efficacy analyses in the modified intention-to-treat population, according to randomised treatment assignment. We did safety analyses in the same population according to the predominant treatment received (no patients received treatment other than that

to which they were randomly assigned, so the modified intention-to-treat and safety analysis populations were identical). Missing data were imputed with the LOCF approach; in patients given glycaemic rescue drug, the last observation before rescue initiation was used. We used an ANCOVA model with treatment and stratification factors as fixed effects and the corresponding baseline value as a covariate to assess primary and continuous secondary endpoints. We estimated least squares mean differences between groups (each canagliflozin dose *vs* glimepiride) and two-sided 95% CIs. We analysed the incidence of documented hypoglycaemia with a logistic regression model with terms for treatment, stratification factors, and baseline HbA_{1c} to derive the two-sided 95% CI and corresponding p value for each comparison. All statistical tests were interpreted at a two-sided significance level of 5%, and all CIs at a two-sided confidence level of 95%.

Assessment of non-inferiority of canagliflozin to glimepiride was based on a prespecified non-inferiority margin of 0·3%. If non-inferiority was shown, the protocol specified a step-down assessment of superiority, on the basis of an upper bound of the 95% CI for the difference of each canagliflozin dose versus glimepiride of less than 0·0%. We implemented a prespecified hierarchical testing sequence to strongly control for overall type I error; p values are reported only for prespecified comparisons. For body composition endpoints, descriptive statistics and 95% CIs for changes from baseline were provided; we assessed comparisons between each canagliflozin dose and glimepiride at week 52 with a similar ANCOVA model as that used for the primary endpoint.

This study is registered with ClinicalTrials.gov, number NCT00968812.

Role of the funding source

The sponsor of the study had a role in study design and conduct; data collection, analysis, and interpretation; and writing of the Article. The authors prepared the report with editorial assistance funded by the sponsor. All authors had full access to all study data, were responsible for the integrity of the data and the accuracy of the data analysis, and reviewed, edited, and approved the report for publication.

Results

Figure 1 shows the trial profile. 1450 of 1452 randomised patients received at least one dose of glimepiride (n=482), canagliflozin 100 mg (n=483), or canagliflozin 300 mg (n=485), and thus comprised the modified intention-to-treat group. 1161 (80%) patients completed 52 weeks of treatment, with similar rates of discontinuation between groups (figure 1). Demographic and baseline characteristics were similar between groups (table 1). For patients assigned glimepiride, the mean maximum dose achieved was 5·6 (SD 2·3) mg per day, with 395 (82%) patients

	Glimepiride	Canagliflozin 100 mg	Canagliflozin 300 mg
Overall population			
Bodyweight (n)	478	479	480
Mean (SD) baseline (kg)	86·6 (19·8)	86·8 (20·0)	86·6 (19·3)
LS mean (SE) change	0·7 (0·2)	−3·7 (0·2)	−4·0 (0·2)
Difference (95% CI) *vs* glimepiride	..	−4·4 (−4·8 to −3·9)	−4·7 (−5·2 to −4·3)
LS mean (SE) percentage change	1·0% (0·2)	−4·2% (0·2)	−4·7% (0·2)
Difference (95% CI) *vs* glimepiride	..	−5·2 (−5·7 to −4·7)*	−5·7 (−6·2 to −5·1)*
Body composition subsets†			
Bodyweight (n)	96	111	102
Mean (SD) baseline (kg)	83·8 (20·2)	84·4 (22·0)	85·9 (21·4)
LS mean (SE) change	0·8 (0·7)	−4·4 (0·6)	−4·2 (0·7)
Difference (95% CI) *vs* glimepiride	..	−5·3 (−6·3 to −4·2)	−5·0 (−6·0 to −4·0)
LS mean (SE) percentage change	1·4% (0·8)	−5·0% (0·7)	−4·9% (0·7)
Difference (95% CI) *vs* glimepiride	..	−6·4 (−7·5 to −5·2)	−6·2 (−7·4 to −5·1)
DXA measurements (n)	68	71	69
Total fat mass measurement			
Mean (SD) baseline (kg)	26·3 (10·2)	28·2 (11·5)	29·3 (9·5)
LS mean (SE) percentage change	1·0% (0·5)	−2·9% (0·5)	−2·5% (0·5)
Difference (95% CI) *vs* glimepiride	..	−3·9 (−4·8 to −3·0)	−3·5 (−4·4 to −2·7)
Total lean mass measurement			
Mean (SD) baseline (kg)	46·6 (10·8)	47·7 (12·2)	44·6 (10·3)
LS mean (SE) change	1·1 (0·3)	−0·9 (0·3)	−1·1 (0·3)
Difference (95% CI) *vs* glimepiride	..	−2·0 (−2·6 to −1·4)	−2·2 (−2·8 to −1·6)
Percentage total fat			
Mean (SD) baseline (%)	34·4 (8·4)	35·5 (8·8)	38·3 (9·2)
LS mean (SE) change	0·7 (0·4)	−1·9 (0·4)	−1·5 (0·5)
Difference (95% CI) *vs* glimepiride	..	−2·6 (−3·3 to −1·8)	−2·2 (−3·0 to −1·4)
CT measurements (n)	72	70	75
SAT			
Mean (SD) baseline (pixels)	29 830 (13 982)	31 208 (14 401)	32 877 (14 500)
LS mean (SE) percentage change	1·8% (3·1)	−5·4% (3·3)	−5·6% (3·0)
Difference (95% CI) *vs* glimepiride	..	−7·2 (−15·2 to 0·9)	−7·4 (−15·3 to 0·5)
VAT			
Mean (SD) baseline (pixels)	26 269 (10 499)	25 506 (9038)	25 090 (9085)
LS mean (SE) percentage change	0·1% (3·2)	−7·3% (3·4)	−8·1% (3·1)
Difference (95% CI) *vs* glimepiride	..	−7·4 (−15·7 to 0·8)	−8·3 (−16·3 to −0·2)
SAT to VAT ratio			
Mean (SD) baseline	1·3 (0·8)	1·4 (0·7)	1·5 (0·9)
LS mean (SE) change	0·01 (0·03)	0·04 (0·03)	0·05 (0·03)
Difference (95% CI) *vs* glimepiride	..	0·03 (−0·05 to 0·10)	0·04 (−0·04 to 0·12)

Last observation carried forward analyses. LS=least squares. DXA=dual-energy x-ray absorptiometry. SAT=subcutaneous adipose tissue. VAT=visceral adipose tissue. *p<0·0001 *vs* glimepiride. †Statistical comparisons for canagliflozin 100 mg and 300 mg *vs* glimepiride not undertaken (not prespecified) in the body composition subsets.

Table 3: **Changes from baseline in bodyweight and body composition parameters at week 52**

	Glimepiride	Canagliflozin 100 mg	Canagliflozin 300 mg
Systolic blood pressure (n)	480	479	480
Mean (SD) baseline (mm Hg)	129·5 (13·5)	130·0 (12·4)	130·0 (13·8)
LS mean (SE) change	0·2 (0·6)	−3·3 (0·6)	−4·6 (0·6)
Difference (95% CI) *vs* glimepiride	..	−3·5 (−4·9 to −2·1)	−4·8 (−6·2 to −3·4)
Diastolic blood pressure (n)	480	479	480
Mean (SD) baseline (mm Hg)	79·0 (8·4)	78·7 (8·0)	79·2 (8·4)
LS mean (SE) change	−0·1 (0·4)	−1·8 (0·4)	−2·5 (0·4)
Difference (95% CI) *vs* glimepiride		−1·7 (−2·6 to −0·8)	−2·4 (−3·3 to −1·5)
Pulse rate (n)	346	365	357
Mean baseline (beats per min)	73·5	74·2	74·6
Mean (SD) change	0·5 (8·3)	−1·1 (8·5)	−1·2 (8·7)
Triglycerides (n)	466	465	461
Mean (SD) baseline (mmol/L)	1·9 (1·2)	2·1 (1·5)	2·1 (2·1)
LS mean (SE) change	−0·01 (0·05)	−0·22 (0·06)	−0·10 (0·05)
Median (IQR) percentage change	2·6% (−17·9 to 29·3)	−10·2% (−29·5 to 13·3)	−7·7% (−27·7 to 19·6)
LS mean (SE) percentage change	9·5% (2·5)	−3·7% (2·5)	2·3% (2·5)
Difference (95% CI) *vs* glimepiride	..	−13·2 (−19·4 to −7·0)	−7·2 (−13·4 to −1·0)
LDL cholesterol (n)	460	463	456
Mean (SD) baseline (mol/mol)	2·7 (0·9)	2·6 (0·9)	2·8 (0·9)
LS mean (SE) change	0·05 (0·04)	0·12 (0·04)	0·25 (0·04)
Median (IQR) percentage change	−1·0% (−12·1 to 14·2)	5·7% (−7·9 to 20·4)	6·7% (−6·7 to 21·8)
LS mean (SE) percentage change	5·0% (1·9)	9·6% (1·9)	14·1% (1·9)
Difference (95% CI) *vs* glimepiride	..	4·5 (0·0 to 9·1)	9·0 (4·4 to 13·7)
HDL cholesterol (n)	465	465	460
Mean (SD) baseline (mmol/L)	1·2 (0·3)	1·2 (0·3)	1·2 (0·3)
LS mean (SE) change	−0·01 (0·01)	0·08 (0·01)	0·10 (0·01)
Median (IQR) percentage change	−0·8% (−9·5 to 7·6)	5·0% (−3·8 to 17·0)	6·3% (−2·5 to 18·4)
LS mean (SE) percentage change	0·3% (0·8)	7·9% (0·8)	9·0% (0·8)
Difference (95% CI) *vs* glimepiride	..	7·5 (5·6 to 9·5)	8·6 (6·7 to 10·6)
LDL cholesterol to HDL cholesterol ratio (n)	460	463	456
Mean (SD) baseline (mol/mol)	2·3 (0·9)	2·3 (0·9)	2·4 (0·9)
LS mean (SE) change	0·05 (0·03)	−0·05 (0·03)	0·02 (0·03)
Median (IQR) percentage change	−0·6% (−13·3 to 17·4)	−0·3% (−13·8 to 16·5)	0·0% (−14·2 to 17·0)
LS mean (SE) percentage change	6·2% (2·0)	3·4% (2·0)	5·7% (2·0)
Difference (95% CI) *vs* glimepiride	..	−2·7 (−7·6 to 2·1)	−0·5 (−5·3 to 4·4)
Non-HDL cholesterol (n)	464	465	457
Mean (SD) baseline (mmol/L)	3·5 (1·0)	3·5 (1·0)	3·7 (1·1)
LS mean (SE) change	0·06 (0·04)	0·03 (0·04)	0·22 (0·04)

(Continues on next page)

reaching a dose of 4 mg per day or greater. More patients were given glycaemic rescue drug in the glimepiride group (51 [11%]) than in the canagliflozin 100 mg (32 [7%]) and 300 mg (24 [5%]) groups.

All treatments reduced HbA_{1c} from baseline to week 52 (table 2, figure 2). In the primary LOCF analysis in the modified intention-to-treat population, both canagliflozin doses were non-inferior to glimepiride for lowering of HbA_{1c}, and canagliflozin 300 mg was superior to glimepiride for HbA_{1c} reduction (table 2, figure 2). The magnitude of HbA_{1c} changes at week 52 was greater in the per-protocol analysis than in the primary LOCF analysis for all groups, with differences between groups showing consistent results (appendix). Proportions of patients achieving HbA_{1c} less than 7·0% or less than 6·5% at week 52 were similar between groups (figure 3).

Patients given canagliflozin 100 mg and 300 mg had numerically greater reductions in fasting plasma glucose from baseline to week 52 than did those who were given glimepiride (figure 4). Compared with glimepiride, differences in least squares mean changes were –0·33 mmol/L (95% CI –0·6 to –0·1) for canagliflozin 100 mg, and –0·51 mmol/L (–0·7 to –0·3) for canagliflozin 300 mg. Both canagliflozin doses provided sustained reduction in fasting plasma glucose over 52 weeks; we noted an increase after week 18 with glimepiride (figure 4). The proportion of patients with documented hypoglycaemic episodes was significantly lower with canagliflozin 100 mg and 300 mg than with glimepiride ($p<0·0001$ for both; figure 5). The frequency of severe hypoglycaemia was also lower with canagliflozin 100 mg (two [<1%] patients) and 300 mg (three [<1%]) than with glimepiride (15 [3%]).

Both canagliflozin doses significantly reduced bodyweight at week 52, whereas we noted a slight increase with glimepiride ($p<0·0001$ for both canagliflozin doses *vs* glimepiride; table 3). In the body composition substudy, patients had baseline characteristics and weight changes over 52 weeks that were generally similar to those reported in the main study (table 3). In the canagliflozin groups, roughly two-thirds of the reduction in bodyweight was from fat mass and a third from lean body mass; the increase in bodyweight with glimepiride included both fat and lean body mass (table 3). Analysis of abdominal fat in the canagliflozin groups with CT imaging showed a slightly greater reduction in visceral adipose tissue than in subcutaneous adipose tissue (table 3). Canagliflozin modestly reduced systolic and diastolic blood pressure compared with glimepiride (table 4). Canagliflozin was associated with increases in HDL cholesterol and decreases in triglycerides compared with glimepiride (table 4). We noted a dose-related increase in LDL cholesterol with canagliflozin compared with glimepiride, with smaller increases in non-HDL cholesterol; we recorded similar small increases from baseline in the ratio of LDL cholesterol to HDL cholesterol across groups (table 4). Decreases in fasting plasma

insulin were noted with both canagliflozin doses compared with glimepiride (table 4).

Overall frequency of adverse events and study discontinuations attributable to adverse events was similar between groups (table 5). Glimepiride was associated with a slightly higher frequency of serious adverse events than was either canagliflozin dose (table 5). Canagliflozin 100 mg and 300 mg were associated with higher incidences of genital mycotic infections in men and women than was glimepiride (table 5). Genital mycotic infections were generally mild or moderate in intensity and were treated with topical or oral antifungal drugs that were self-initiated or given at the discretion of the treating physician. Rates of urinary tract infections were slightly higher with canagliflozin than with glimepiride in a non-dose-dependent manner (table 5). Adverse events indicative of osmotic diuresis (ie, pollakiuria [increased urinary frequency], polyuria [increased urinary volume]) were more common with canagliflozin than glimepiride; frequencies of these adverse events were low (table 5), were assessed by investigators as mild or moderate in severity, and led to few discontinuations (data not shown). Similarly, adverse events that might be attributable to reduced intravascular volume due to the diuretic effect (ie, orthostatic hypotension, postural dizziness) were low in frequency and did not notably differ between groups (table 5).

We recorded only small differences in laboratory parameters (table 6). Decreases in alanine aminotransferase, gamma-glutamyltransferase, and serum urate, and increases in haemoglobin, bilirubin, and blood urea nitrogen were noted with canagliflozin compared with glimepiride (table 6). Increases in bilirubin were not associated with increases in other liver function tests (eg, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase). We recorded no notable differences in serum electrolytes, sodium and potassium, with canagliflozin compared with glimepiride (data not shown). With both canagliflozin doses, initial decreases in estimated GFR, noted at week 4, were generally stable from week 12 to week 52; we recorded a progressive decrease in estimated GFR with glimepiride from baseline to week 44 (figure 6).

	Glimepiride	Canagliflozin 100 mg	Canagliflozin 300 mg
(Continued from previous page)			
Median (IQR) percentage change	0·7% (–9·3 to 11·0)	1·5% (–8·5 to 13·1)	3·5% (–7·5 to 16·7)
LS mean (SE) percentage change	4·4% (1·2)	2·6% (1·2)	8·3% (1·2)
Difference (95% CI) *vs* glimepiride	..	–1·8 (–4·8 to 1·3)	3·9 (0·8 to 7·0)
Insulin (n)	461	458	454
Mean (SD) baseline (pmol/L)	71·1 (71·7)	69·2 (50·4)	64·4 (43·5)
LS mean (SE) change	10·3 (2·1)	–11·8 (2·1)	–11·5 (2·1)
Difference (95% CI) *vs* glimepiride	..	–22·1 (–27·2 to –17·0)	–21·7 (–26·9 to –16·6)

Last observation carried forward analyses. Statistical comparison for canagliflozin 100 mg and 300 mg versus glimepiride not undertaken (not prespecified). LS=least squares.

***Table 4*: Changes from baseline in blood pressure, pulse rate, fasting plasma lipids, and fasting insulin at week 52**

	Glimepiride (n=482)	Canagliflozin 100 mg (n=483)	Canagliflozin 300 mg (n=485)
Any adverse event	330 (69%)	311 (64%)	332 (69%)
Adverse events leading to discontinuation	28 (6%)	25 (5%)	32 (7%)
Adverse events related to study drug*	113 (23%)	118 (24%)	145 (30%)
Serious adverse events	39 (8%)	24 (5%)	26 (5%)
Deaths	2 (<1%)	0	2 (<1%)
Genital mycotic infection			
Male†	3 (1%)	17 (7%)	20 (8%)
Female‡	5 (2%)	26 (11%)	34 (14%)
Urinary tract infection§	22 (5%)	31 (6%)	31 (6%)
Osmotic diuresis-related adverse events			
Pollakiuria¶	1 (<1%)	12 (3%)	12 (3%)
Polyuria‖	2 (<1%)	4 (<1%)	4 (<1%)
Volume-related adverse events			
Postural dizziness	3 (<1%)	3 (<1%)	2 (<1%)
Orthostatic hypotension	0	1 (<1%)	1 (<1%)

All adverse events are reported irrespective of rescue drug, except for osmotic diuresis-related and volume-related events, which are reported for before the start of rescue therapy. *Possibly, probably, or very likely related to study drug, as assessed by investigators. †Glimepiride n=263, canagliflozin 100 mg n=252, canagliflozin 300 mg n=241; including balanitis, balanitis candida, balanoposthitis, genital candidiasis, and genital infection fungal. ‡Glimepiride n=219, canagliflozin 100 mg n=231, canagliflozin 300 mg n=244; including vaginal infection, vulvitis, vulvovaginal candidiasis, vulvovaginal mycotic infection, and vulvovaginitis. §Including cystitis, pyelonephritis chronic, and urinary tract infection. ¶Increased urine frequency. ‖Increased urine volume.

***Table 5*: Overall safety and selected adverse events**

Discussion

At 52 weeks, both canagliflozin doses were non-inferior to glimepiride for reduction of HbA_{1c} on the background of metformin therapy. Furthermore, canagliflozin 300 mg was associated with a modest, but statistically superior reduction in HbA_{1c} versus glimepiride. As with all sulphonylureas, gradual up-titration of glimepiride is recommended to minimise the risk of hypoglycaemia. We up-titrated glimepiride over the entire treatment period to achieve aggressive glucose targets, with the maximum dose allowed based on the labelled dose in the country of the investigational site. Thus, the mean maximum dose of 5·6 mg and the frequent occurrence of hypoglycaemia suggest that titration was appropriately aggressive. It is therefore noteworthy that the efficacy of glimepiride in our study is similar to that in previous reports taking into account differences in baseline glycaemic control, which is also consistent with appropriate titration of glimepiride.[10,11] The beneficial effects of canagliflozin compared with glimepiride were also evident with reductions in fasting plasma glucose. Notably, the effects of canagliflozin in lowering of HbA_{1c} and fasting plasma glucose were sustained over 52 weeks,

	Glimepiride	Canagliflozin 100 mg	Canagliflozin 300 mg
ALT (n)	344	362	350
Mean (SD) baseline (U/L)	29·2 (17·1)	29·8 (16·1)	28·9 (16·7)
Mean (SD) percentage change	9·1% (47·5)	−10·0% (34·5)	−12·2% (37·7)
Alkaline phosphatase (n)	345	364	352
Mean (SD) baseline (U/L)	73·2 (21·6)	73·6 (21·2)	72·6 (20·5)
Mean (SD) percentage change	−2·8% (15·8)	−2·8% (15·5)	−4·6% (13·2)
AST (n)	344	360	348
Mean (SD) baseline (U/L)	23·7 (10·9)	24·3 (11·0)	23·5 (10·8)
Mean (SD) percentage change	7·6% (33·9)	−3·8% (33·0)	−3·1% (39·2)
Bilirubin (n)	345	362	353
Mean (SD) baseline (μmol/L)	8·8 (4·4)	9·1 (4·3)	8·6 (3·6)
Mean (SD) percentage change	−2·4% (37·1)	7·8% (36·9)	8·2% (39·3)
BUN (n)	345	364	353
Mean (SD) baseline (mmol/L)	5·3 (1·6)	5·3 (1·6)	5·0 (1·5)
Mean (SD) percentage change	6·5% (26·4)	15·3% (29·1)	22·0% (30·8)
GGT (n)	345	364	352
Mean (SD) baseline (U/L)	37·8 (36·3)	41·9 (59·7)	37·0 (30·4)
Mean (SD) percentage change	4·5% (32·5)	−12·5% (37·3)	−15·8% (38·3)
Urate (n)	345	364	353
Mean (SD) baseline (μmol/L)	327·0 (74·9)	330·0 (80·6)	314·5 (83·4)
Mean (SD) percentage change	8·0% (19·6)	−9·9% (19·0)	−10·3% (18·8)
Haemoglobin (n)	337	357	349
Mean (SD) baseline (g/L)	140·4 (14·1)	140·2 (15·6)	140·2 (14·8)
Mean (SD) percentage change	−0·7% (6·5)	4·6% (8·1)	4·8% (7·5)
Urine albumin/creatinine	332	352	344
Mean (SD) baseline (g/mol)	3·7 (22·3)	2·4 (4·6)	3·8 (11·6)
Mean (SD) change	0·7 (15·3)	−0·1 (4·7)	−0·9 (6·7)
Median (IQR) change	0·02 (−0·29 to 0·61)	−0·01 (−0·40 to 0·36)	−0·05 (−0·64 to 0·28)

Statistical comparison for canagliflozin 100 mg and 300 mg versus glimepiride not undertaken (not prespecified). ALT=alanine aminotransferase. AST=aspartate aminotransferase. BUN=blood urea nitrogen. GGT=gamma-glutamyltransferase.

***Table 6*: Summary of laboratory parameters at baseline and week 52**

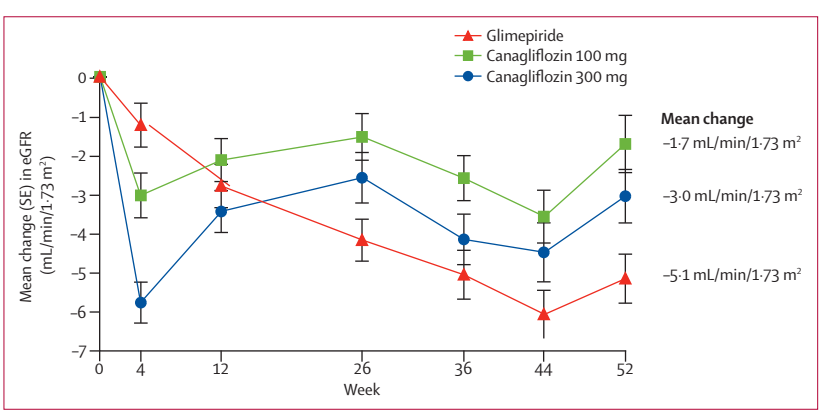

***Figure 6*: Change in eGFR over time**
Statistical comparison for canagliflozin 100 mg and 300 mg versus glimepiride not undertaken (not prespecified). eGFR=estimated glomerular filtration rate.

whereas we noted increases in both parameters with glimepiride after 18 weeks, which is consistent with previous findings (panel).[11,15]

Findings from previous studies have shown an increased risk of hypoglycaemia with sulphonylureas,[16] and the increase in frequency of hypoglycaemia with glimepiride in this study was expected on the basis of the mechanism of action of sulphonylureas. However, because the usual threshold for hypoglycaemia is 3·9 mmol/L (below the mean renal threshold for glucose with canagliflozin—ie, canagliflozin 100 mg and 300 mg reduce the mean renal threshold for glucose to roughly 4·4–5·0 mmol/L[5,8]), we anticipated the low frequency of hypoglycaemia with canagliflozin. However, without a placebo group, whether the hypoglycaemia rate with canagliflozin is greater than a background rate is unknown. In addition to hypoglycaemia, another concern with sulphonylureas is weight gain. In this regard, and when compared with the small increase noted with sulphonylurea, canagliflozin provided sustained reductions in bodyweight over 52 weeks.

An obvious contribution to the weight loss associated with canagliflozin is the glucosuria, which has been reported to be on average 80–120 g per day in previous studies of canagliflozin in patients with type 2 diabetes.[17,18] Reductions in bodyweight with canagliflozin seemed to plateau after week 26, similar to findings noted with other weight-loss interventions.[19] Sustained rates of urinary glucose excretion have been previously shown with canagliflozin in studies of up to 12 weeks.[5,8,9] This finding suggests that there could be a compensatory mechanism restricting further weight reduction; however, we noted no evidence of subsequent weight regain over 52 weeks. In addition to assessment of general adiposity, body composition results from assessment of dual-energy X-ray absorptiometry suggest that the weight loss recorded with canagliflozin is mainly due to loss of fat mass rather than lean mass. Furthermore, the proportion of fat and lean body mass lost with canagliflozin in our study is consistent with changes in body composition noted in previous studies of drugs associated with weight reduction.[20,21] Obesity is a common comorbidity in patients with type 2 diabetes that contributes to hyperglycaemia by inducing insulin resistance. With the reduction in weight and the resulting increase in insulin sensitivity, the weight loss recorded with canagliflozin is proposed to contribute to improvement in glycaemic control. Of drugs that are recommended for use when metformin as monotherapy does not provide sufficient glycaemic control, only subcutaneously administered glucagon-like peptide-1 agonists provide a weight reduction benefit as reported for canagliflozin and other SGLT2 inhibitors.[20,21] Sulphonylureas, insulin, and peroxisome proliferator-activated receptor agonists increase weight, whereas dipeptidyl peptidase-4 inhibitors are thought to have a neutral effect on weight.

Overall, canagliflozin treatment showed favourable effects on cardiovascular risk, along with improvements in systolic blood pressure and glycaemic control. Specifically, in addition to the improved glycaemia, both canagliflozin

doses reduced blood pressure with no increase in heart rate, and with a low frequency of adverse events related to reduced intravascular volume (ie, orthostatic hypotension, postural dizziness), which is consistent with other reports of canagliflozin.[14,22,23] In addition to an increase in HDL cholesterol and a decrease in triglycerides, an increase in LDL cholesterol was noted with canagliflozin, which could show downstream metabolic effects of SGLT2 inhibition and urinary caloric loss (eg, increased lipoprotein lipase activity leading to increased cholesterol content of LDL cholesterol[24]), and modest haemoconcentration resulting from an osmotic diuretic effect due to glucosuria (similar to what has been reported with other agents with diuretic action[25]). However, because the specific mechanism is not precisely known, further investigation is needed to ascertain the mechanism by which SGLT2 inhibition leads to increases in LDL cholesterol. Thus, the effect on LDL cholesterol will be better understood with additional planned analyses of fasting lipids, and the ongoing CANagliflozin cardioVascular Assessment Study (CANVAS; NCT01032629) will provide additional data for the effects of canagliflozin on cardiovascular outcomes.

As required of any new drug, a comprehensive assessment of safety is warranted. In this study, canagliflozin was generally well tolerated, consistent with previous reports.[5,8] The rate of completion for this study was comparable with similar 52 week studies comparing other antihyperglycaemic drugs with sulphonylureas.[13,26,27] As has been consistently reported with previous studies of canagliflozin and other SGLT2 inhibitors,[8,13,28–30] we recorded increases in the frequency of genital mycotic infections, urinary tract infections, and osmotic diuresis-related adverse events with canagliflozin compared with glimepiride. We noted a small decrease in estimated GFR at week 6 that attenuated, consistent with a modest decrease in intravascular volume, and only a minimum reduction in estimated GFR was recorded at week 52, which was smaller with canagliflozin than with glimepiride. We recorded small to moderate decreases in alanine aminotransferase and gamma-glutamyltransferase with canagliflozin—a finding that has been consistently reported with this drug.[14,22,23] The mechanism is not known, but could be related to low insulin concentrations and a shift of metabolism towards fat, lowering hepatic fat deposition; however, only a study that directly measures hepatic fat content can confirm this hypothesis. The changes in haemoglobin, bilirubin, and blood urea nitrogen might be related to water loss associated with canagliflozin.

This study had several potential limitations. First, the patient population included a range of HbA_{1c} (7·0–9·5%), so no conclusions can be made about the comparison of these drugs in patients with more severe hyperglycaemia. Second, the 52 week primary timepoint is reasonably long, but a longer duration of observation is needed to understand the comparative benefits and risks of these drugs and the durability of response, and whether the favourable effects on cardiovascular risk factors will translate into cardiovascular benefits. Third, although the study population was reasonably broad, it did not include a high proportion of black or African-American or Hispanic patients, which restricts conclusions about the comparative profile in specific ethnic groups with high prevalence of type 2 diabetes. Fourth, this study was very specific and compared canagliflozin with glimepiride. Studies with other active comparators that are recommended for use after metformin failure will help to assess canagliflozin relative to other antihyperglycaemic drug classes used for this purpose. Finally, we did not assess the change in postprandial glucose. However, in a separate phase 3 study of canagliflozin monotherapy, which included a frequently sampled mixed-meal tolerance test, canagliflozin 100 mg and 300 mg lowered postprandial glucose compared with placebo in patients with type 2 diabetes.[14]

Panel: Research in context

Systematic review

A systematic review[12] published in October, 2012, assessed the clinical efficacy and safety of sodium–glucose cotransporter 2 (SGLT2) inhibitors in patients with type 2 diabetes in the context of dual or triple therapy. Seven published, randomised controlled trials of dapagliflozin and one of canagliflozin were included in the analysis. Of these trials, only one directly compared an SGLT2 inhibitor (dapagliflozin) with a sulphonylurea drug (glipizide).[13] An additional search for randomised controlled trials of canagliflozin published since October, 2012, identified only the placebo-controlled study of canagliflozin as monotherapy.[14] Therefore, this study reports the only direct comparison of the efficacy and safety of canagliflozin with those of a sulphonylurea drug in patients with type 2 diabetes.

Interpretation

Treatment with canagliflozin 100 mg and 300 mg improved glycaemic control over 52 weeks in patients with type 2 diabetes receiving background metformin. Canagliflozin treatment was associated with significant weight loss and a lower risk of hypoglycaemia than was treatment with glimepiride, and was generally well tolerated. These findings could inform discussions about treatment options for patients with type 2 diabetes who do not achieve sufficient glycaemic control with metformin therapy.

Contributors

WTC, LAL, K-HY, PA, LN, DAB, WC, and GM contributed to the design and conduct of the study and the acquisition, analysis, and interpretation of data. JX contributed to the design of the study and the analysis and interpretation of data. All authors reviewed and approved the manuscript.

Conflicts of interest

WTC has served as a consultant for Lexicon Pharmaceuticals, Johnson & Johnson, AstraZeneca, Bristol-Myers Squibb, Sanofi-Aventis, Halozyme Therapeutics, and Intarcia Therapeutics, and has served as principal investigator on research studies with funding awarded to his institution from Eli Lilly, AstraZeneca, Bristol-Myers Squibb, Johnson & Johnson, MannKind Corporation, GlaxoSmithKline, and Lexicon Pharmaceuticals. LAL has received research funding from, has provided continuing medical education on behalf of, or has served as a consultant to, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Merck, Novartis, Novo Nordisk, Roche, Sanofi-Aventis, Servier, and Takeda. K-HY has served on advisory boards for AstraZeneca, Eli Lilly, Merck, and Pfizer; has received research support from Merck, AstraZeneca, and Bayer; and has received speaker fees from Eli Lilly, Novo Nordisk, Boehringer Ingelheim, Merck, and Novartis. PA has served on advisory boards for AstraZeneca,

Bristol-Myers Squibb, GlaxoSmithKline, Janssen-Cilag, and Novartis; has received speaker fees from AstraZeneca, Bayer, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Johnson & Johnson, Novartis, and Servier; and has received honoraria for conducting clinical research studies from AstraZeneca, Bayer, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Johnson & Johnson, Mannkind Corporation, Novartis, Novo Nordisk, Sanofi-Aventis, and Servier. LN has received funding for the institution from Janssen-Cilag, Novo Nordisk, Sanofi-Aventis, Boehringer Ingelheim, and Bristol-Myers Squibb for conducting clinical research studies; has received speaker fees from Amgen, Eli Lilly, Novo Nordisk, Boehringer Ingelheim, Servier, and Sanofi-Aventis; and has served on advisory boards for Amgen, Novo Nordisk, and Boehringer Ingelheim. JX, DAB, WC, and GM are full-time employees of Janssen Research & Development, LLC.

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