Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial

Clifford J Bailey, Jorge L Gross, Anne Pieters, Arnaud Bastien, James F List

Summary

Background Correction of hyperglycaemia and prevention of glucotoxicity are important objectives in the management of type 2 diabetes. Dapagliflozin, a selective sodium-glucose cotransporter-2 inhibitor, reduces renal glucose reabsorption in an insulin-independent manner. We assessed the efficacy and safety of dapagliflozin in patients who have inadequate glycaemic control with metformin.

Methods In this phase 3, multicentre, double-blind, parallel-group, placebo-controlled trial, 546 adults with type 2 diabetes who were receiving daily metformin (≥1500 mg per day) and had inadequate glycaemic control were randomly assigned to receive one of three doses of dapagliflozin (2·5 mg, n=137; 5 mg, n=137; or 10 mg, n=135) or placebo (n=137) orally once daily. Randomisation was computer generated and stratified by site, implemented with a central, telephone-based interactive voice response system. Patients continued to receive their pre-study metformin dosing. The primary outcome was change from baseline in haemoglobin A_{1c} (HbA_{1c}) at 24 weeks. All randomised patients who received at least one dose of double-blind study medication and who had both a baseline and at least one post-baseline measurement (last observation carried forward) were included in the analysis. Data were analysed by use of ANCOVA models. This trial is registered with ClinicalTrials.gov, number NCT00528879.

Findings 534 patients were included in analysis of the primary endpoint (dapagliflozin 2·5 mg, n=135; dapagliflozin 5 mg, n=133; dapagliflozin 10 mg, n=132; placebo, n=134). At week 24, mean HbA_{1c} had decreased by –0·30% (95% CI –0·44 to –0·16) in the placebo group, compared with –0·67% (–0·81 to –0·53, p=0·0002) in the dapagliflozin 2·5 mg group, –0·70% (–0·85 to –0·56, p<0·0001) in the dapagliflozin 5 mg group, and –0·84% (–0·98 to –0·70, p<0·0001) in the dapagliflozin 10 mg group. Symptoms of hypoglycaemia occurred in similar proportions of patients in the dapagliflozin (2–4%) and placebo groups (3%). Signs, symptoms, and other reports suggestive of genital infections were more frequent in the dapagliflozin groups (2·5 mg, 11 patients [8%]; 5 mg, 18 [13%]; 10 mg, 12 [9%]) than in the placebo group (seven [5%]). 17 patients had serious adverse events (four in each of the dapagliflozin groups and five in the placebo group).

Interpretation Addition of dapagliflozin to metformin provides a new therapeutic option for treatment of type 2 diabetes in patients who have inadequate glycaemic control with metformin alone.

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Introduction

From 2000 to 2010, the estimated prevalence of diabetes increased from 121 million to 285 million people, representing 6·4% of the global adult population.[1] Type 2 diabetes, which accounts for more than 90% of all diabetes, is a complex progressive metabolic derangement associated with comorbidities such as obesity, hypertension, and hyperlipidaemia.[2] Strategies for selection of antidiabetic agents aim to balance effectiveness, safety, tolerability, and non-glycaemic effects that can reduce long-term complications, notably microvascular and premature macrovascular disease. Despite efforts to intensify management, many adult patients with type 2 diabetes do not achieve glycaemic control.[3–6]

Pharmacological treatment usually begins with metformin, which together with lifestyle management is a validated first-step approach.[7,8] Although metformin is often initially effective as monotherapy, the progressive nature of diabetes frequently requires additional therapies.[9] As β-cell function deteriorates further, selection of agents and management of their side-effects become increasingly more difficult. For example, sulphonylureas and insulin cause weight gain and hypoglycaemia; thiazolidinediones cause weight gain and are contraindicated in patients with heart failure; and use of α-glucosidase inhibitors is limited by gastrointestinal side-effects. Dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists are not associated with weight gain or hypoglycaemia, but assessment of long-term use is needed. There is also a necessity for additional treatments that avoid side-effects and address some of the broader metabolic issues of diabetes without dependency on β-cell function.[10,11]

As part of the quest for new agents, research has expanded into new targets of glycaemic control that are not directly focused on insulin-dependent mechanisms. Sodium-glucose cotransporter 2 (SGLT2), located mainly in segment S1 of the proximal tubule of the kidney nephron, reabsorbs most glucose filtered by the glomerulus.[12] Dapagliflozin is a stable and highly selective inhibitor of SGLT2.[13,14] Binding of dapagliflozin to SGLT2 inhibits renal glucose reabsorption, promotes urinary glucose excretion, and thereby lowers hyperglycaemia by an insulin-independent mechanism.[15–18] Since the glucotoxicity caused by chronic hyperglycaemia is a major source of microvascular complications and contributes to macrovascular disease, glycaemia per se is a very legitimate therapeutic target for treatment of type 2 diabetes.

This study assessed the efficacy and safety of dapagliflozin when added to metformin in adult patients with type 2 diabetes who are not adequately controlled with metformin alone. We report the results of 24 weeks of treatment.

Methods

Study design and patients

For an **abbreviated version of the protocol for this trial** see http://clinicaltrials.gov/ct2/show/NCT00528879?term=nct00528879&rank=1

This phase 3, randomised, double-blind, parallel-group, placebo-controlled trial was undertaken at 80 sites (30 in the USA, 21 in Canada, 11 in Argentina, ten in Mexico, and eight in Brazil). Patients were accrued from Sept 18, 2007, to April 10, 2008. The study complied with the Declaration of Helsinki and Good Clinical Practice guidelines, and was approved by institutional review boards and independent ethics committees for participating centres. All participants provided written informed consent.

Patients were eligible for inclusion if they were aged 18–77 years, had type 2 diabetes, haemoglobin A_{1c} (HbA_{1c}) 7–10%, C-peptide concentration 0·34 nmol/L or more, body-mass index 45 kg/m² or less, and were taking a stable dose of metformin (≥1500 mg per day) for at least 8 weeks before enrolment. Exclusion criteria included serum creatinine 133 µmol/L or more for men or 124 µmol/L or more for women (consistent with metformin labelling); urine albumin/creatinine ratio more than 203·4 mg/mmol; aspartate aminotransferase or alanine aminotransferase more than three times the upper limit of normal; creatine kinase more than three times the upper limit of normal; symptoms of poorly controlled diabetes (including marked polyuria and polydipsia with >10% weight loss during the 3 months before enrolment); clinically significant renal, hepatic, haematological, oncological, endocrine, psychiatric, or rheumatic disease; recent cardiovascular event (within 6 months) or New York Heart Association class III or IV congestive heart failure; and systolic blood pressure 180 mm Hg or more or diastolic blood pressure 110 mm Hg or more.

No changes were made to the methods after commencement of the trial.

Randomisation and masking

Patients were enrolled at the separate investigation sites. Investigators received substantial training, investigative materials, and study guidelines to ensure quality of trial conduct and measurements. Additionally, investigators had access to the central medical monitor if any questions were to arise. Qualifying participants were assigned a unique sequential patient number by a central interactive voice response system (IVRS). A 2-week, single-blind, lead-in period in which patients received placebo was used to assess compliance with treatment. At the time of entry into the single-blind, placebo lead-in period, the investigation site contacted the IVRS by telephone for assignment and dispensing of single-blind lead-in medication. At all visits when mediation was dispensed, the IVRS randomly assigned each patient a kit number that corresponded to numbers printed on the packages and bottles containing study drug. The IVRS also assigned open-label 500 mg metformin tablets so that patients could continue their pre-study metformin dosing. During lead-in and throughout the duration of the study, patients received diet and exercise counselling consistent with American Diabetes Association recommendations or similar local guidelines.

Patients who successfully completed the lead-in period were randomly assigned (in a 1:1:1:1 ratio) by the IVRS to double-blinded groups of once-daily dapagliflozin 2·5 mg, 5 mg, or 10 mg, or matching placebo given orally before the morning meal for 24 weeks. Randomisation was stratified by investigation site. A site was assigned a block of random patient treatment assignments when calling to randomise the site's first patient. Randomisation schedules were computer-generated by the sponsor and stored in a secure location. The patients, investigators, and sponsor personnel were blinded to treatment allocation and HbA_{1c} and urinary glucose concentrations. The film-coated placebo and active tablets were similar in colour, shape, size, texture, and taste.

Glycaemic measurements were assessed from week 4 to week 24 to determine the need for open-label pioglitazone or acarbose as a rescue medication for fasting plasma glucose concentrations more than 15·0 mmol/L (week 4–8), 13·3 mmol/L (week 8–12), or 11·1 mmol/L (week 12–24). Patients who completed 24 weeks of study were eligible for continuation into a long-term study for a total of 102 weeks.

Endpoints and assessments

All endpoints were predefined. The primary endpoint was change from baseline in HbA_{1c} percentage at week 24, or last observation carried forward if no assessment was available at week 24. Key secondary endpoints were changes in fasting plasma glucose concentration and total bodyweight at week 24, change in fasting plasma glucose concentration at week 1, the proportion of patients achieving a therapeutic glycaemic response (defined as

HbA_{1c} <7% at week 24), and change in HbA_{1c} percentage at week 24 for patients with a baseline HbA_{1c} of 9% or more. Exploratory endpoints (webappendix pp 1–2) included percentage change from baseline in bodyweight, and decreases in bodyweight of 5% or more.

Laboratory tests on fasting plasma and serum were undertaken at bicentral laboratories of Quintiles Laboratories (Marietta, GA, USA, and Buenos Aires, Argentina) by use of conventional standardised techniques. Patients were actively monitored throughout the trial for clinical signs and symptoms suggestive of urinary tract infection and genital infection. These assessments were prospectively defined, were assessed throughout the study by active surveillance of symptoms, and consisted of patient and physician reports that were coded according to preferred terms of the Medical Dictionary for Regulatory Activities (MedDRA, version 11·1). Reports of urinary tract infection were based on 20 preferred terms for upper urinary tract infection events, and 44 preferred terms for non-upper urinary tract infection events. Reports of genital infection were based on 49 preferred terms, including bacterial and mycotic infections. Safety and tolerability measures included changes in blood pressure.

See Online for webappendix

A serious adverse event was defined as an adverse event that was fatal, life threatening, required admission to hospital, prolonged an existing hospital stay, resulted in persistent or significant disability or incapacity, was a cancer or a congenital anomaly, resulted in the development of drug dependency or drug abuse, or was an important medical event that jeopardised the patient or required intervention to prevent a serious outcome.

Planned trial outcomes remained unchanged after commencement of the trial.

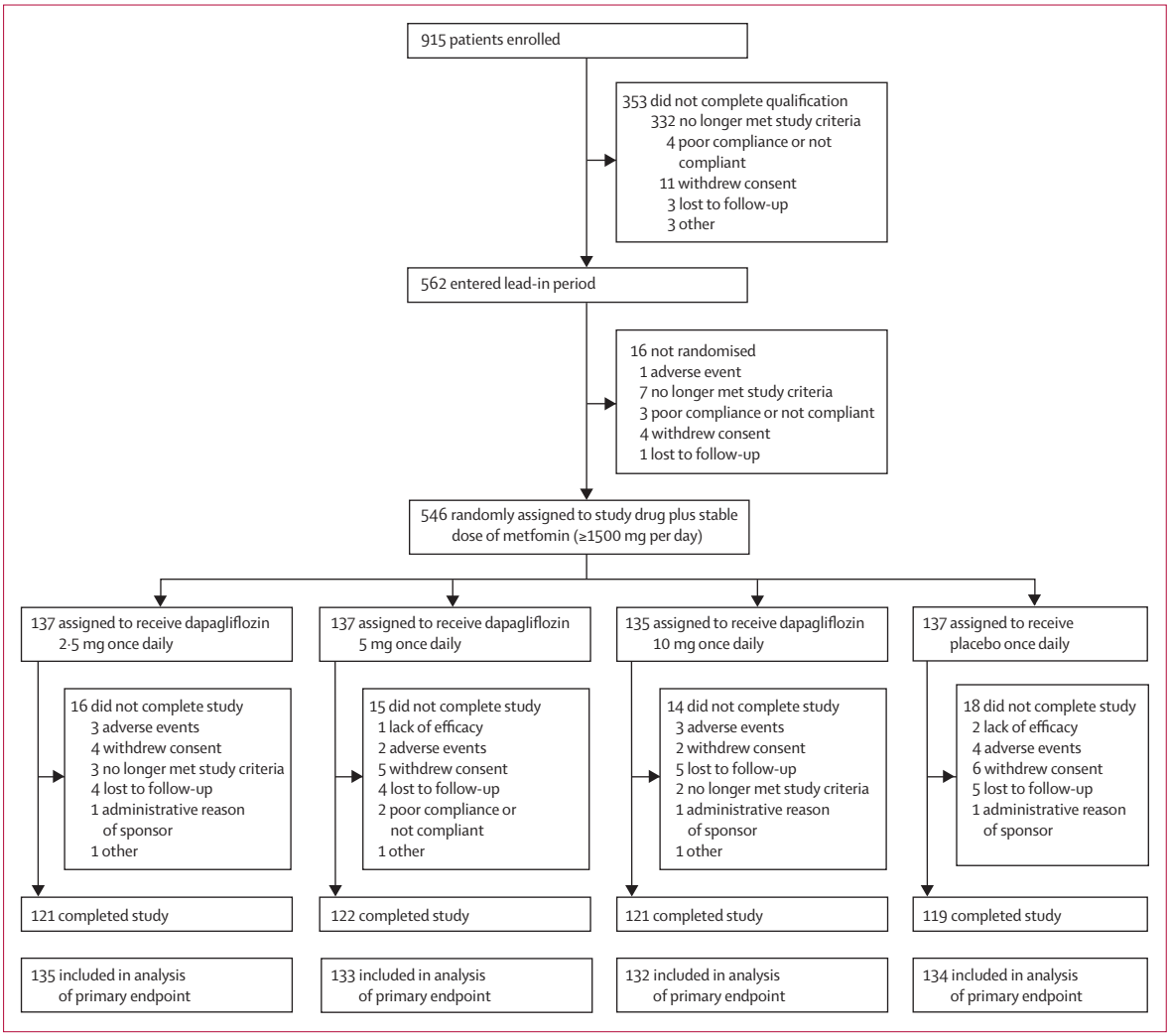

Figure 1: **Trial profile**
The primary efficacy dataset consisted of all randomised patients who received at least one dose of double-blind study medication and who had both a baseline and at least one post-baseline measurement. For rescued patients, measurements obtained after initiation of rescue medication were not included in the efficacy analysis, but were included in the safety analysis.

Statistical analysis

With 129 patients per treatment group with post-baseline measurements, there was 90% power to detect a difference in mean of HbA_{1c} of 0·5% between each dapagliflozin treatment group and the placebo group, on the assumption of an SD of 1·1%.[19] If 5% of patients did not have a post-baseline assessment, 544 patients (136 per group) needed to be randomised.

The primary efficacy dataset consisted of all randomised patients who received at least one dose of double-blind study medication and who had both a baseline and at least one post-baseline measurement. For rescued patients, measurements obtained after initiation of rescue medication were not included in the efficacy analysis, but were included in the safety analysis.

Analyses of continuous outcomes were based on separate ANCOVA models with treatment group as an effect and the baseline value as a covariate, last observation carried forward. As part of the secondary analyses, the comparison of proportions of patients achieving a therapeutic glycaemic response was done with logistic regression based on established methodology, with adjustment for baseline.[20,21] After adjustment for baseline values and differences in mean changes from baseline at week 24, p values for primary and secondary endpoints were calculated to compare the treatment effect of dapagliflozin with that of placebo. For the primary analysis (change from baseline in HbA_{1c} percentage at week 24), comparisons between each dapagliflozin group and placebo group were done at α=0·019 applying Dunnett's adjustment. If the primary endpoint was significant, changes from baseline in secondary endpoints would be tested sequentially at α=0·05 in the following order: fasting plasma glucose concentration at week 24, total bodyweight at week 24, proportion of patients with HbA_{1c} less than 7·0% at week 24, HbA_{1c} percentage at week 24 in patients with baseline HbA_{1c} of 9% or more, total bodyweight at week 24 in patients with baseline body-mass index 27 kg/m² or more (webappendix p 3), HbA_{1c} percentage at week 24 in patients with baseline body-mass index 27 kg/m² or more (webappendix p 3), fasting plasma glucose concentration at week 1, and proportion of patients achieving HbA_{1c} 6·5% or lower at week 24. In accordance with study design, no p values were generated for exploratory endpoints. Only summary statistics were reported for safety. Statistical analyses were done with SAS/STAT version 8.2.

This trial is registered with ClinicalTrials.gov, number NCT00528879.

Role of the funding source

The sponsors of the study were involved in study design, data collection, data review, and data analysis, and were responsible for gathering all data from investigation centres for the clinical database. The report was prepared by the authors, with contributions from the sponsor Bristol-Myers Squibb. All authors had full access to the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. The 24-week data cutoff date was Nov 4, 2008. Table 1 shows demographic and baseline characteristics of study participants. All randomised patients took at least one dose of study medication. 88% of randomised patients completed the trial: the most common reasons for discontinuation during the double-blind period were withdrawal of consent and loss to follow-up (figure 1).

Reductions in HbA_{1c} percentage after 24 weeks were significantly greater in the dapagliflozin groups than in the placebo group (figure 2, table 2). Mean change from baseline at week 24 (last observation carried forward) was –0·30% in the placebo group compared with –0·67% in the dapagliflozin 2·5 mg group (p=0·0002), –0·70% in the dapagliflozin 5 mg group (p<0·0001), and –0·84% in the dapagliflozin 10 mg group (p<0·0001; table 2). More patients in the dapagliflozin groups (33·0–40·6%) achieved a therapeutic response of HbA_{1c} less than 7·0% at week 24 than did patients in

	Placebo group (n=137)	Dapagliflozin 2·5 mg group (n=137)	Dapagliflozin 5 mg group (n=137)	Dapagliflozin 10 mg group (n=135)
Age (years)	53·7 (10·3)	55·0 (9·3)	54·3 (9·4)	52·7 (9·9)
Sex (male)	76 (55%)	70 (51%)	69 (50%)	77 (57%)
Body-mass index (kg/m²)	31·8 (5·3)	31·6 (4·8)	31·4 (5·0)	31·2 (5·1)
Duration of type 2 diabetes (years, mean [SD]; median [IQR])	5·8 (5·1); 5·1 (1·7–8·6)	6·0 (6·2); 4·0 (1·4–9·1)	6·4 (5·8); 5·7 (2·5–8·4)	6·1 (5·4); 4·7 (1·6–9·7)
HbA_{1c} (%)	8·11% (0·96)	7·99% (0·90)	8·17% (0·96)	7·92% (0·82)
Fasting plasma glucose (mmol/L)	9·19 (2·57)	8·96 (2·39)	9·39 (2·72)	8·66 (2·15)
Seated systolic blood pressure (mm Hg)	127·7 (14·6)	126·6 (14·5)	126·9 (14·3)	126·0 (15·9)
Seated diastolic blood pressure (mm Hg)	80·9 (9·0)	79·5 (8·7)	80·8 (8·5)	79·0 (10·2)
Total daily metformin dose during trial (mg, mean [SD]; median [range])	1861 (423); 1500 (1500–3000)	1792 (410); 1500 (0–3000)	1854 (389); 2000 (1500–2500)	1800 (392); 1500 (1500–3000)

Data are mean (SD) or n (%) unless otherwise indicated. HbA_{1c}=haemoglobin A_{1c}.

Table 1: **Demographic and baseline characteristics of study participants**

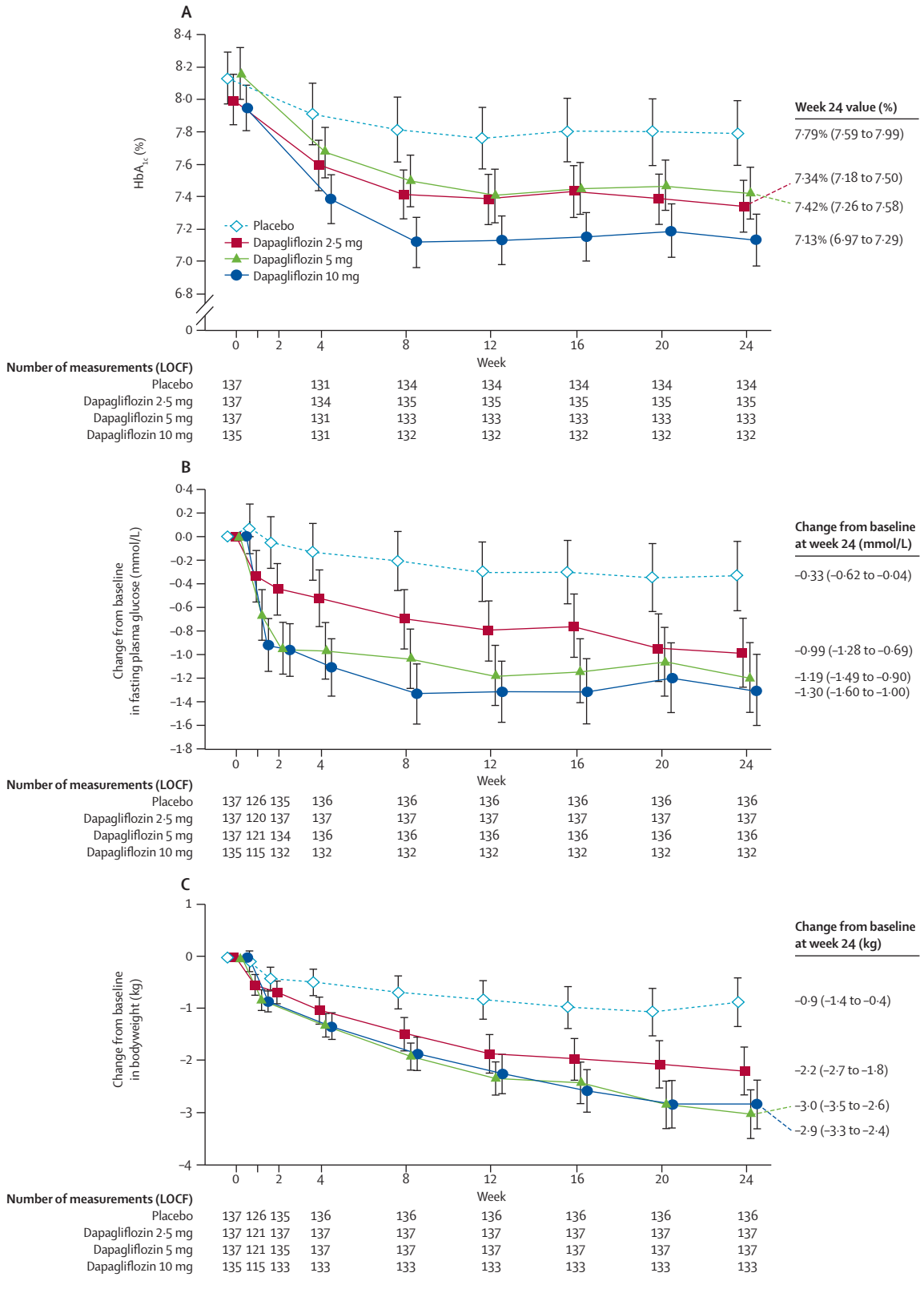

***Figure 2*: Change from baseline in haemoglobin A_{1c} (HbA_{1c}) percentage, fasting plasma glucose concentration, and total bodyweight in dapagliflozin and placebo groups up to week 24**

Data are mean (95% CI). Analyses undertaken are for the numbers of patients randomised to each group (last observation carried forward [LOCF]), excluding data after rescue. (A) Change from baseline in HbA_{1c} percentage. (B) Change from baseline in fasting plasma glucose after adjustment for baseline value. (C) Change from baseline in total bodyweight after adjustment for baseline value.

the placebo group (25·9%); the difference was significant for the dapagliflozin 5 mg and 10 mg groups (table 2). In the dapagliflozin groups, patients with HbA_{1c} of 9·0% or more at baseline had greater mean reductions in HbA_{1c} percentage at week 24 than did patients in the placebo group, with significant placebo-subtracted reductions in the dapagliflozin 5 mg and 10 mg groups (0·84% and 0·78%, respectively).

Decreases in fasting plasma glucose concentration were notable by week 1 in the dapagliflozin groups, with significant differences in the 5 mg and 10 mg groups compared with the placebo group (figure 2, table 2). At week 24, mean changes from baseline in fasting plasma glucose concentration were significant in all dapagliflozin groups (–0·99 to –1·30 mmol/L) compared with placebo (–0·33 mmol/L).

	Placebo group (n=137)	Dapagliflozin 2·5 mg group (n=137)	Dapagliflozin 5 mg group (n=137)	Dapagliflozin 10 mg group (n=135)
HbA_{1c} at week 24 (%)				
n*	134	135	133	132
Baseline	8·11% (0·96)	7·99% (0·90)	8·17% (0·96)	7·92% (0·82)
Week 24	7·79% (1·18)	7·34% (0·93)	7·42% (0·94)	7·13% (0·94)
Change from baseline	–0·30% (–0·44 to –0·16)	–0·67% (–0·81 to –0·53)	–0·70% (–0·85 to –0·56)	–0·84% (–0·98 to –0·70)
p value	..	0·0002†	<0·0001†	<0·0001†
Fasting plasma glucose at week 24 (mmol/L)				
n*	136	137	136	132
Baseline	9·19 (2·57)	8·96 (2·39)	9·39 (2·72)	8·66 (2·15)
Week 24	8·79 (2·48)	8·03 (1·88)	8·03 (2·11)	7·56 (1·88)
Change from baseline	–0·33 (–0·62 to –0·04)	–0·99 (–1·28 to –0·69)	–1·19 (–1·49 to –0·90)	–1·30 (–1·60 to –1·00)
p value	..	0·0019‡	<0·0001‡	<0·0001‡
Total bodyweight at week 24 (kg)				
n*	136	137	137	133
Baseline	87·7 (19·2)	84·9 (17·8)	84·7 (16·3)	86·3 (17·5)
Week 24	86·8 (18·9)	82·7 (17·6)	81·7 (16·1)	83·4 (17·4)
Change from baseline	–0·9 (–1·4 to –0·4)	–2·2 (–2·7 to –1·8)	–3·0 (–3·5 to –2·6)	–2·9 (–3·3 to –2·4)
p value	..	<0·0001‡	<0·0001‡	<0·0001‡
Patients with HbA_{1c} <7·0% at week 24				
n/N§	33/134	46/135	47/133	58/132
Proportion of patients (%)	25·9% (19·1 to 32·6)	33·0% (25·4 to 40·6)	37·5% (30·0 to 45·1)	40·6% (32·9 to 48·3)
p value	..	0·1775	0·0275‡	0·0062‡
HbA_{1c} at week 24 in patients with baseline HbA_{1c} ≥9·0 (%)				
n*	22	17	34	18
Baseline	9·70% (0·57)	9·69% (0·49)	9·50% (0·42)	9·42% (0·31)
Week 24	9·12% (1·26)	8·44% (1·30)	8·16% (1·01)	8·16% (0·96)
Change from baseline	–0·53% (–1·00 to –0·06)	–1·21% (–1·74 to –0·69)	–1·37% (–1·74 to –1·00)	–1·32% (–1·83 to –0·80)
p value	..	NT	0·0068‡	0·0290‡
Fasting plasma glucose at week 1 (mmol/L)				
n*	126	120	121	115
Baseline	9·22 (2·61)	9·00 (2·40)	9·32 (2·76)	8·65 (2·16)
Week 1	9·22 (2·52)	8·69 (1·77)	8·57 (2·12)	7·87 (1·54)
Change from baseline	0·07 (–0·14 to 0·28)	–0·33 (–0·55 to –0·12)	–0·67 (–0·88 to –0·45)	–0·92 (–1·14 to –0·69)
p value	..	NT	<0·0001‡	<0·0001‡
Patients with HbA_{1c} ≤6·5% at week 24				
n/N§	18/134	29/135	18/133	36/132
Proportion of patients (%)	13·8% (8·2 to 19·5)	20·7% (14·1 to 27·3)	14·5% (9·0 to 20·1)	25·2% (18·2 to 32·2)
p value	..	NT	0·8627	0·0149‡

Data are mean (SD) or mean (95% CI). Data after rescue have been excluded (number of rescued patients were 22 of 137, five of 137, five of 137, and five of 135 for the placebo, dapagliflozin 2·5 mg, 5 mg, and 10 mg groups, respectively). Changes reported for week 24 and week 1 are adjusted for baseline values and are based on last observation carried forward (LOCF). HbA_{1c}=haemoglobin A_{1c}. NT=not tested under sequential testing procedure if previously tested endpoint was not statistically significant. *Number of randomised patients with week 24 (LOCF) values. †Significant versus placebo at α=0·019 applying Dunnett's adjustment. ‡Significant after sequential testing procedure at α=0·05. §Number of responders/number of randomised patients with week 24 (LOCF) values.

Table 2: **Primary and secondary efficacy measurements**

	Placebo group (n=137)	Dapagliflozin 2·5 mg group (n=137)	Dapagliflozin 5 mg group (n=137)	Dapagliflozin 10 mg group (n=135)
One or more adverse event	88 (64%)	89 (65%)	95 (69%)	98 (73%)
One or more drug-related adverse event*	22 (16%)	22 (16%)	25 (18%)	31 (23%)
Adverse event leading to discontinuation	5 (4%)	3 (2%)	3 (2%)	4 (3%)
One or more serious adverse event†	5 (4%)	4 (3%)	4 (3%)	4 (3%)
Deaths	0	0	0	0
Adverse events with frequency ≥5% in any group (by preferred term)				
Headache	6 (4%)	4 (3%)	10 (7%)	11 (8%)
Back pain	7 (5%)	5 (4%)	3 (2%)	10 (7%)
Diarrhoea	7 (5%)	3 (2%)	5 (4%)	10 (7%)
Urinary tract infection	7 (5%)	4 (3%)	7 (5%)	9 (7%)
Influenza	10 (7%)	13 (9%)	13 (9%)	8 (6%)
Nasopharyngitis	11 (8%)	12 (9%)	4 (3%)	8 (6%)
Hypertension	6 (4%)	9 (7%)	4 (3%)	5 (4%)
Upper respiratory tract infection	10 (7%)	5 (4%)	4 (3%)	3 (2%)
Cough	7 (5%)	4 (3%)	4 (3%)	1 (<1%)
Special interest categories				
Hypoglycaemia‡§	4 (3%)	3 (2%)	5 (4%)	5 (4%)
Events suggestive of urinary tract infection¶	11 (8%)	6 (4%)	10 (7%)	11 (8%)
Events suggestive of genital infection‡‖	7 (5%)	11 (8%)	18 (13%)	12 (9%)
Hypotension or syncope‡	1 (<1%)	0	2 (1%)	0

Data are number of patients (%), and include data after rescue. *Events with a certain, probable, possible, or unknown relation to study drug were deemed to be drug-related adverse events. †Each patient had only one report of a serious adverse event. ‡None led to discontinuation from study. §None was a major event, defined as a symptomatic episode requiring third party assistance because of severe impairment in consciousness or behaviour, with a capillary or plasma glucose concentration less than 3 mmol/L, and prompt recovery after glucose or glucagon administration. ¶Reports of urinary tract infection (UTI) were based on 20 preferred terms for upper UTI events, and 44 preferred terms for non-upper UTI events. These events included signs, symptoms, and other reports suggestive of UTI, as well as definitive terms for UTI. ‖Reports of genital infection were based on 49 preferred terms, including bacterial and mycotic infections. These events included signs, symptoms, and other reports suggestive of genital infection, as well as definitive terms for genital infection.

Table 3: **Adverse events**

At week 24, significant reductions in bodyweight were noted in all dapagliflozin groups compared with placebo (figure 2, table 2). These reductions began early and continued to progress over the course of the trial. Compared with patients assigned to placebo, 18·1% (95% CI 9·9 to 26·3), 19·5% (11·2 to 27·9), and 22·1% (13·5 to 30·6) more patients assigned to dapagliflozin 2·5 mg, 5 mg, and 10 mg, respectively, had total bodyweight reductions of 5% or more. Waist circumference decreased a mean –1·7 cm (–2·5 to –0·9), –2·7 cm (–3·5 to –1·9), and –2·5 cm (–3·3 to –1·6) in the dapagliflozin 2·5 mg, 5 mg, and 10 mg groups, respectively, compared with –1·3 cm (–2·3 to –0·4) in the placebo group.

Urinary glucose excretion increased in all of the dapagliflozin groups but not in the placebo group. The mean change from baseline at week 24 in the ratio of urinary glucose (g) to urinary creatinine (g) ranged from 10·8 to 32·2 for the dapagliflozin groups versus –0·7 for the placebo group, whereas creatinine remained constant.

Table 3 provides a summary of adverse events. There were no deaths during the study. Adverse events leading to discontinuation were less frequent in the dapagliflozin groups than in the placebo group. Symptoms of hypoglycaemia occurred infrequently, were mild, and occurred in similar proportions of patients in the placebo and dapagliflozin groups. There were no major events of hypoglycaemia, defined as a symptomatic episode requiring third party assistance because of severe impairment in consciousness or behaviour, with a capillary or plasma glucose concentration less than 3 mmol/L, and prompt recovery after glucose or glucagon administration.

Signs, symptoms, and other reports suggestive of urinary tract infections were reported in similar proportions of patients in all groups, including the placebo group. Signs, symptoms, and other reports suggestive of genital infections were more frequent in the dapagliflozin groups (8–13%) than in the placebo group (5%), with the increased rate occurring in both men and women. For most of these patients only a single event was reported, although three events were reported for one patient, and two events were reported for another. All events were of mild or moderate intensity, and either resolved with self-treatment or responded readily to conventional interventions. None led to discontinuation from the study.

There were 17 serious adverse events distributed across the groups (four in the dapagliflozin 2·5 mg group, four

in the dapagliflozin 5 mg group, four in the dapagliflozin 10 mg group, and five in the placebo group). These events were arthralgia (one), rotator cuff syndrome (one), intervertebral disc protrusion (one), chest pain (one), urethral injury (one), thrombocytopenia (one), acute myocardial infarction (two), atrial fibrillation (one), cardiac arrest (one), obstructive inguinal hernia (one), cholecystitis (one), diverticulitis (one), postoperative wound infection (one), urinary tract infection (one), lymphocytic leukaemia (one), and dyspnoea (one), for which there was no association with any particular treatment group.

Mean changes from baseline in laboratory measurements are reported in table 4. No clinically meaningful changes in serum electrolytes occurred in any of the groups. Abnormalities in serum sodium and potassium were rare and transient. Mean change from baseline at week 24 in serum sodium concentration was –0·2 mmol/L (SE 0·2) in the placebo group, compared with 0·1 mmol/L (0·2) in the dapagliflozin 2·5 mg group, 0·3 mmol/L (0·2) in the dapagliflozin 5 mg group, and –0·1 mmol/L (0·2) in the dapagliflozin 10 mg group. Mean change in serum potassium concentration was –0·05 mmol/L (0·05) in the placebo group, compared with –0·04 mmol/L (0·04), –0·09 mmol/L (0·03), and –0·06 mmol/L (0·04) in the dapagliflozin 2·5 mg, 5 mg, and 10 mg groups, respectively.

No alterations of measures of mean renal function, including serum creatinine concentration, were recorded, and no individual abnormalities in these measures led to discontinuation from the study. Small dose-dependent increases in mean blood urea nitrogen and haematocrit were seen in the dapagliflozin groups, consistent with a diuretic action. Isolated abnormalities in blood urea nitrogen occurred in all groups, but no patient had a marked abnormality of haematocrit more than 60%. Dose-related decreases from baseline in serum uric acid were seen in the dapagliflozin groups at week 24 (mean reductions ranged from –30·9 µmol/L to –47·6 µmol/L *vs* –4·2 µmol/L for placebo).

Patients assigned to dapagliflozin showed no apparent changes in fasting lipid profiles, apart from greater mean increases in HDL cholesterol (1·8–4·4% *vs* 0·4%) and decreases in triglycerides (–2·4% to –6·2% *vs* 2·1%) compared with placebo (table 4).

Blood pressure was recorded as a safety assessment. Investigators were allowed to treat patients with raised blood pressure by the usual standard of care with antihypertensive agents, but overall treatment remained stable during the study. Patients assigned to dapagliflozin showed a decrease in mean seated systolic and diastolic blood pressure; however, there was no increase in the proportion of patients with orthostatic hypotension compared with baseline. A post-hoc analysis of patients with a history of hypertension and not meeting the blood pressure goal of less than 130/80 mm Hg at baseline showed that 29·5–37·5% of such patients assigned to dapagliflozin achieved the goal at week 24, compared with 8·8% of patients assigned to placebo (table 5).

	Placebo group	Dapagliflozin 2·5 mg group	Dapagliflozin 5 mg group	Dapagliflozin 10 mg group
Serum creatinine (µmol/L)*				
n	120	119	122	122
Baseline	77·3 (17·9)	78·5 (18·1)	79·3 (19·4)	77·5 (17·7)
Change at week 24	–0·7 (0·7)	0·4 (0·7)	–1·2 (0·9)	–0·1 (0·7)
Cystatin C (µmol/L)*				
n	119	116	116	115
Baseline	0·57 (0·13)	0·58 (0·11)	0·59 (0·17)	0·57 (0·13)
Change at week 24	0·002 (0·006)	0·021 (0·008)	0·006 (0·010)	0·025 (0·008)
Serum uric acid (µmol/L)†				
n	136	137	136	132
Baseline	314·1 (79·0)	322·4 (80·4)	323·0 (88·3)	323·0 (79·9)
Change at week 24	–4·2 (4·2)	–30·9 (4·2)	–36·3 (4·2)	–47·6 (4·3)
Blood urea nitrogen (mmol/L)*				
n	120	119	122	122
Baseline	5·3 (1·6)	5·5 (1·4)	5·6 (1·8)	5·3 (1·4)
Change at week 24	0·2 (0·1)	0·6 (0·1)	0·6 (0·1)	0·7 (0·1)
Haematocrit (%)*				
n	118	118	121	119
Baseline	42·6% (3·9)	42·4% (4·0)	42·1% (3·6)	42·8% (4·0)
Change at week 24	–1·1% (0·2)	1·0% (0·2)	1·3% (0·2)	1·7% (0·2)
Alanine aminotransferase (U/L)*				
n	120	118	122	122
Baseline	33·0 (14·8)	31·4 (16·8)	31·6 (17·1)	32·8 (18·3)
Change at week 24	–3·7 (1·2)	–5·0 (1·4)	–5·1 (1·5)	–6·0 (1·0)
Total bilirubin (µmol/L)*				
n	120	119	122	120
Baseline	8·0 (3·8)	8·0 (4·0)	7·9 (3·8)	7·9 (3·8)
Change at week 24	0·3 (0·3)	–0·2 (0·2)	0·2 (0·3)	1·0 (0·3)
Total cholesterol (mmol/L)‡				
n	123	123	126	121
Baseline	4·7 (1·2)	4·8 (1·0)	4·8 (1·1)	4·8 (1·0)
Percentage change at week 24	2·7% (1·3)	2·9% (1·3)	2·2% (1·3)	4·2% (1·3)
LDL cholesterol (mmol/L)‡				
n	121	123	126	120
Baseline	2·6 (0·9)	2·6 (0·8)	2·7 (0·9)	2·7 (0·9)
Percentage change at week 24	3·5% (2·3)	5·0% (2·3)	3·1% (2·3)	9·5% (2·4)

(Continues on next page)

Discussion

Dapagliflozin offers a novel insulin-independent approach to lowering hyperglycaemia and improving metabolic control of type 2 diabetes: it reduces renal glucose reabsorption by inhibition of SGLT2 transporters in the proximal tubule of the kidney, resulting in urinary glucose excretion. Since SGLT2 inhibition is independent of β-cell function or insulin sensitivity, this treatment approach could have applications throughout the natural history of diabetes.

Patients in this trial did not have adequate glycaemic control with metformin, and the addition of dapagliflozin for 24 weeks resulted in significant reductions in HbA_{1c} percentage and fasting plasma glucose with no increase in risk of hypoglycaemia compared with placebo. As is commonly reported in large trials of type 2 diabetes, there was a modest improvement in glycaemic control in the placebo group. The additional glucose-lowering effect seen in the dapagliflozin groups is consistent with earlier studies in smaller groups of patients who were treatment-naive or concurrently receiving metformin,[16,17] or who had more advanced disease that was poorly controlled with insulin plus oral antidiabetic agents.[18]

The reductions in fasting plasma glucose concentration and bodyweight during the first week of treatment in the dapagliflozin groups continued over the course of 24 weeks. Early weight loss might be partly due to a mild osmotic diuresis caused by dapagliflozin.[17] However, the gradual progressive reduction in bodyweight thereafter, with decreased waist circumference, is consistent with a reduction of fat mass.[22] This reduction is potentially attributable to the loss of excess energy through glucose excretion in the urine, an effect clearly evident at week 24 as supported by the increased urinary glucose/creatinine ratio in patients assigned to dapagliflozin.

Although dapagliflozin was well tolerated, signs, symptoms, and other reports suggestive of genital infections were reported in more patients assigned to the drug than in patients assigned to placebo. Genital infections are not uncommon in patients with diabetes[23,24] and can be appropriately managed with better appreciation of those at highest risk, and a proactive approach to application of standard treatment.[25–27] More detailed information will be provided by long-term studies of dapagliflozin that are currently underway.

At week 24, small dose-dependent increases from baseline in haematocrit were seen in the dapagliflozin groups, consistent with glucose-induced osmotic diuresis. The reductions in blood pressure in patients assigned to dapagliflozin, which were without orthostatic hypotension, might relate in part to diuresis[28] and weight loss.[29] Small increases in blood urea nitrogen and decreases in serum uric acid are not explained at this time. Raised serum uric acid concentration is often associated with diabetes, renal dysfunction, and cardiovascular complications, although causality is unclear.[30,31] The reductions recorded in blood pressure and serum uric acid in the dapagliflozin groups in this and previous trials[17,18] warrant further study as potentially beneficial ancillary effects.

As an initial phase 3 trial of a first-in-class drug, the design of this study needed a broad investigation of efficacy, supported with exploratory endpoints to probe the mechanism of action and extend safety data. Statistical testing of the latter categories was not applicable to this study design, and last observation carried forward analysis was used to accommodate occasional missing data, which were mainly for patients in the placebo group who transferred to rescue therapy.

Every effort was made in the study protocol to keep the opportunity for discrepancy to a minimum. We have

	Placebo group	Dapagliflozin 2·5 mg group	Dapagliflozin 5 mg group	Dapagliflozin 10 mg group
(Continued from previous page)				
HDL cholesterol (mmol/L)‡				
n	123	123	126	121
Baseline	1·1 (0·2)	1·1 (0·3)	1·1 (0·3)	1·1 (0·3)
Percentage change at week 24	0·4% (1·4)	1·8% (1·4)	3·3% (1·4)	4·4% (1·5)
Triglycerides (mmol/L)‡				
n	123	123	126	121
Baseline	2·0 (1·2)	2·4 (1·4)	2·3 (1·2)	2·2 (1·6)
Percentage change at week 24	2·1% (3·6)	–2·4% (3·4)	–6·2% (3·2)	–6·2% (3·3)
Urinary glucose/creatinine ratio (g/g)§				
n	118	115	123	118
Baseline	3·4 (11·6)	1·8 (5·9)	4·2 (21·1)	0·9 (2·8)
Change at week 24	–0·7 (3·4)	10·8 (3·4)	32·2 (3·3)	31·2 (3·4)

n=number of treated patients with week 24 values. *Data are mean baseline (SD) and mean change at week 24 (SE), including data after rescue. †Data are mean baseline (SD) and adjusted mean change at week 24 (SD) based on ANCOVA model with treatment group as an effect and baseline value as a covariate (last observation carried forward; LOCF), excluding data after rescue. ‡Data are mean baseline (SE) and adjusted mean percentage change (SE) at week 24, based on ANCOVA of the logarithms of the post-treatment to baseline ratios with treatment group as an effect and log of baseline value as a covariate (LOCF), excluding data after rescue. §Data are mean baseline (SD) and adjusted mean change from baseline (SE) at week 24 based on ANCOVA model with treatment group as an effect and baseline value as a covariate (LOCF). Measures for urinary glucose/creatinine ratio were derived from a urinary spot-check undertaken in the morning fasting state.

Table 4: **Changes from baseline in laboratory measurements**

	Placebo group	Dapagliflozin 2·5 mg group	Dapagliflozin 5 mg group	Dapagliflozin 10 mg group
Seated blood pressure (mm Hg)				
n*	119	119	122	122
Systolic				
Baseline†	127·7 (14·6)	126·6 (14·5)	126·9 (14·3)	126·0 (15·9)
Mean change at week 24‡	–0·2 (1·2)	–2·1 (1·1)	–4·3 (1·3)	–5·1 (1·3)
Diastolic				
Baseline†	80·9 (9·0)	79·5 (8·7)	80·8 (8·5)	79·0 (10·2)
Mean change at week 24‡	–0·1 (0·7)	–1·8 (0·9)	–2·5 (0·8)	–1·8 (0·8)
Patients with history of hypertension and not at blood pressure goal§ at baseline, who achieved goal at week 24				
n/N¶	5/57	18/61	18/59	18/48
Proportion of patients (%)	8·8%	29·5%	30·5%	37·5%
Difference versus placebo (%)‖	..	20·7% (6·7–34·8)	21·7% (7·3–36·1)	28·7% (12·7–44·3)

Investigators were allowed to treat blood pressure by usual standard of care. *Number of treated patients with week 24 values (last observation carried forward), including data after rescue. †Data are mean (SD). ‡Data are mean (SE). §Goal blood pressure of less than 130/80 mm Hg. ¶Number of patients achieving blood pressure goal at week 24/number of patients with history of hypertension and not at blood pressure goal at baseline. ‖Data are percentage difference versus placebo (95% CI), based on a post-hoc analysis.

Table 5: **Changes from baseline in seated blood pressure and proportion of patients with hypertension who achieved blood pressure goal at week 24**

controlled for recognised variables and confounding factors, but some effects might still be unaccounted for. Although the study population was heterogeneous and included patients of different ethnic origins, recruitment occurred only in North and South America, and patients were mainly white. The number of elderly patients was also low. These factors could affect extrapolation of data to population subsets. Use of intention-to-treat analysis could bias the primary endpoint results against statistical significance, but this is the accepted approach for this type of trial, and the number of missing values represented only a very small proportion of the total patients randomised.

This trial shows that dapagliflozin can improve glycaemic control in patients who have inadequate control with metformin. The drug acts independently of insulin, lowers weight, and is not associated with risk of hypoglycaemia. Safety and tolerability of the drug were also confirmed. Therefore, addition of dapagliflozin to metformin provides a new therapeutic option for treatment of type 2 diabetes.

Contributors

CJB, JLG, AP, AB, and JFL participated in the analysis and interpretation of data. AB and JFL participated in study concept and design. AB participated in acquisition of data. AP participated in the statistical verification of data. JLG, AB, and JFL participated in study supervision. CJB, JLG, AP, AB, and JFL contributed to writing and revising the report. All authors saw and approved the final version of this report.

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Conflicts of interest

AP, AB, and JFL are employees of Bristol-Myers Squibb and hold stock interests in the company. CJB has attended advisory board meetings of Bristol-Myers Squibb and AstraZeneca; undertaken ad-hoc consultancy for Bristol-Myers Squibb, AstraZeneca, Merck Sharp & Dohme, Novo Nordisk, GlaxoSmithKline, and Takeda; received research grants from AstraZeneca and Sanofi-Aventis; delivered continuing medical educational programmes sponsored by Bristol-Myers Squibb, AstraZeneca, GlaxoSmithKline, Merck Serono, and Merck Sharp & Dohme; and received travel or accommodation reimbursement from GlaxoSmithKline and Bristol-Myers Squibb. JLG, a trialist for this study, has attended advisory board meetings, received research support, and undertaken clinical trials sponsored by Bristol-Myers Squibb.

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