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ORIGINAL ARTICLE

Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial

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Aims: Progressive deterioration of glycaemic control in type 2 diabetes mellitus (T2DM) often requires treatment intensification. Dapagliflozin increases urinary glucose excretion by selective inhibition of renal sodium-glucose cotransporter 2 (SGLT2). We assessed the efficacy, safety and tolerability of dapagliflozin added to glimepiride in patients with uncontrolled T2DM.

Methods: This 24-week, randomized, double-blind, placebo-controlled, parallel-group, international, multicentre trial (ClinicalTrials.gov NCT00680745) enrolled patients with uncontrolled T2DM [haemoglobin A1c (HbA1c) 7–10%] receiving sulphonylurea monotherapy. Adult patients (n = 597) were randomly assigned to placebo or dapagliflozin (2.5, 5 or 10 mg/day) added to open-label glimepiride 4 mg/day for 24 weeks. Primary endpoint was HbA1c mean change from baseline at 24 weeks. Secondary endpoints included change in body weight and other glycaemic parameters.

Results: At 24 weeks, HbA1c adjusted mean changes from baseline for placebo versus dapagliflozin 2.5/5/10 mg groups were −0.13 versus −0.58, −0.63, −0.82%, respectively (all $p < 0.0001$ vs. placebo by Dunnett's procedure). Corresponding body weight and fasting plasma glucose values were −0.72, −1.18, −1.56, −2.26 kg and −0.11, −0.93, −1.18, −1.58 mmol/l, respectively. In placebo versus dapagliflozin groups, serious adverse events were 4.8 versus 6.0–7.1%; hypoglycaemic events 4.8 versus 7.1–7.9%; events suggestive of genital infection 0.7 versus 3.9–6.6%; and events suggestive of urinary tract infection 6.2 versus 3.9–6.9%. No kidney infections were reported.

Conclusions: Dapagliflozin added to glimepiride in patients with T2DM uncontrolled on sulphonylurea monotherapy significantly improved HbA1c, reduced weight and was generally well tolerated, although events suggestive of genital infections were reported more often in patients receiving dapagliflozin.

Keywords: SGLT2 inhibitor, sulphonylureas, type 2 diabetes, glycaemic control, randomized trial, renal glucose handling

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Introduction

Although intensive glycaemic control with sulphonylurea treatment can reduce the risk of long-term microvascular complications [1,2], this is achieved at the expense of weight gain and increased risk of hypoglycaemia [1,3]. In addition, the natural history of progressive loss of β-cell function during the course of T2DM reduces sulphonylurea long-term effectiveness [4]. Thus, patients not achieving glycaemic control on sulphonylurea therapy may benefit from combination treatment [5].

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New therapies affecting insulin-independent mechanisms of glucose homeostasis may be beneficial in the long-term management of patients with T2DM, particularly when used in combination with insulin-dependent therapies. One such mechanism targets the sodium-glucose cotransporter 2 (SGLT2), located principally in the proximal tubule of the kidney nephron, which reabsorbs the majority of glucose filtered by the glomerulus [6]. Dapagliflozin, a stable and highly selective competitive inhibitor of SGLT2 [7], inhibits renal glucose reabsorption, promotes urinary glucose excretion and thus reduces hyperglycaemia while also providing weight control and weight loss benefits [8–11]. Given that increased renal glucose reabsorption is one of the multiple pathophysiological mechanisms contributing to T2DM [12], this novel insulin-independent mechanism of action of

dapagliflozin is a potentially useful treatment option for patients with T2DM.

A recent study has shown the efficacy and safety of dapagliflozin as add-on therapy in patients with inadequate glycaemic control receiving metformin alone [13]. Here we report the efficacy, safety and tolerability of 24 weeks of dapagliflozin treatment as add-on therapy to the sulphonylurea glimepiride in patients with inadequately controlled T2DM who had been treated with sulphonylurea monotherapy.

Materials and Methods

Study Design

This was a 24-week randomized, double-blind, parallel-group, placebo-controlled, phase III trial with a 24-week double-blind extension period conducted from April 2008 to November 2009 at 84 sites in the Czech Republic (11 centres), Hungary (16), Republic of Korea (12), Philippines (5), Poland (29), Thailand (3) and Ukraine (8). The study complied with the Declaration of Helsinki and the International Conference on Harmonization/Good Clinical Practice Guidelines (July 1996). It was approved by institutional review boards and independent ethics committees for participating centres and is registered with ClinicalTrials.gov (NCT00680745). All participants provided informed consent. Results from the first 24-week double-blind treatment period are presented here.

Patients

Eligible patients were men and women aged ≥18 years with inadequately controlled T2DM, defined as haemoglobin A1c (HbA1c) ≥7 and ≤10%, who were receiving a stable dose of sulphonylurea monotherapy that was at a dose level of at least half the maximum recommended for at least 8 weeks prior to enrolment. In addition, patients had to have a fasting plasma glucose (FPG) ≤15 mmol/l and fasting C-peptide ≥0.33 nmol/l. For detailed exclusion criteria, see Appendix S1 (Supporting information).

Study Medications and Treatments

Eligible patients either continued with, or were switched to, open-label glimepiride 4 mg/day during the 8-week lead-in period. During a 1-week qualification period all inclusion/exclusion criteria were reviewed in those patients switched to glimepiride 4 mg/day. Those patients still meeting eligibility criteria were then randomized to receive double-blind dapagliflozin 2.5, 5 or 10 mg or placebo taken orally once per day before the first meal of the day and added to continuing open-label glimepiride 4 mg/day. Open-label glimepiride could be down-titrated to 2 mg or discontinued to mitigate hypoglycaemic events at the discretion of the investigator. However, no up-titration was allowed.

Patients with inadequate glycaemic control during the treatment period remained in the trial, but received open-label rescue therapy as metformin or pioglitazone (in patients intolerant to metformin or if serum creatinine was >124 μmol/l in women and >133 μmol/l in men) or rosiglitazone (if pioglitazone was unavailable). The progressively stricter criteria defining inadequate glycaemic control and eligibility for rescue therapy were a central laboratory FPG (confirmed on a second measurement within 3–5 days) >15 mmol/l (weeks 4–8); an FPG >13.2 mmol/l (weeks 8–12); or an FPG >11.1 mmol/l (weeks 12–24). Patients with an HbA1c > 8% for a continuous 12-week period, despite maximum dose of rescue therapy, discontinued the trial.

All patients received dietary and lifestyle counselling, and in addition, patients whose body mass index (BMI) was ≥27 kg/m^2 received advice concerning reducing caloric intake and increasing physical activity.

A computer-generated randomization schedule was provided by AstraZeneca using blocks to balance the treatment groups in a 1 : 1 : 1 : 1 ratio. Patients were randomized strictly sequentially at each centre. Blinding of dapagliflozin tablets was achieved by double-blind allocation and use of a double-dummy technique because the dapagliflozin 10 mg tablet size was slightly larger than that for the 2.5 and 5 mg doses. Glimepiride and rescue therapy were administered as open-label treatments.

Outcome Measures

All endpoints were predefined. The primary endpoint was change in central laboratory HbA1c percentage from baseline to week 24, measured using Bio-Rad Laboratories High-Performance Liquid Chromatography calibrated to the Diabetes Control and Complications Trial standard [14]. Secondary endpoints were: (i) change in total body weight (TBW) from baseline to week 24; (ii) change from baseline to week 24 in 2-h postchallenge plasma glucose (PPG) rise in response to an oral glucose-tolerance test (OGTT) using 75 g of glucose; (iii) proportion of patients achieving a therapeutic glycaemic response, defined as HbA1c < 7% at week 24; (iv) change in TBW from baseline to week 24 in patients with baseline BMI ≥ 27 kg/m^2; and (v) change in FPG from baseline to week 24. See Appendix S2 for details of OGTT administration.

A number of exploratory endpoints were assessed, which included proportions of patients receiving rescue therapy for failing to reach prespecified glycaemic targets or discontinuing for lack of efficacy, seated systolic and diastolic blood pressure and lipid parameters.

Safety and tolerability were assessed by collating data on adverse events using the Medical Dictionary for Regulatory Activities (MedDRA version 12.1), hypoglycaemic events, laboratory tests, electrocardiographic and physical examinations and vital signs (including orthostatic hypotension). A prespecified list of MedDRA preferred terms identified signs, symptoms and other reports suggestive of urinary tract infection (UTI) and of genital infection in the database. This list included terms for nonspecific signs and symptoms suggestive of genital infection (e.g. genital pruritus, vulvovaginal pruritus) as well as terms for clinical infection (e.g. vaginal infection), but did not include terms for sexually transmitted diseases. Patients reported these events both spontaneously and in response to questions proactively posed by the investigator during study

visits. Both spontaneous and solicited responses were coded using the prespecified list of MedDRA preferred terms.

Statistical Analysis

A hierarchical closed testing procedure was used to control the type I error rate across the primary and secondary endpoints at the 0.05 level. The primary endpoint was tested using Dunnett's method at 0.019 level for each pair-wise group comparison of dapagliflozin dose versus placebo (overall level 0.05). The statistical testing of the primary and secondary endpoints proceeded in a sequential manner. Only those dapagliflozin groups significantly superior to placebo for the primary endpoint had statistical inference tested versus placebo for the first secondary endpoint (0.05 level) and, if significant, followed by the second secondary endpoint and so forth.

The primary and continuous secondary and exploratory endpoints were evaluated using analysis of covariance (ANCOVA) with treatment group as fixed effect and baseline value as covariate. The proportion of patients achieving HbA1c $< 7\%$ at week 24 and proportion of patients receiving rescue therapy for failing to reach prespecified glycaemic targets or discontinuing for lack of efficacy were analysed by logistic regression using the methodology of Zhang et al. [15] with adjustment for baseline HbA1c.

For graphical presentation of HbA1c, TBW and FPG at weeks 4, 8, 12, 16, 20 and 24, the change from baseline [last observation carried forward (LOCF)] was analysed at each time point using ANCOVA with treatment group as fixed effect and baseline value as covariate.

Two analysis sets were defined: the safety analysis set consisting of all patients who received ≥ 1 dose of study medication and the full analysis set consisting of all randomized patients who received ≥ 1 dose of study medication and who had a non-missing baseline and ≥ 1 postbaseline efficacy value for ≥ 1 efficacy variable.

Primary, secondary and exploratory endpoints were analysed with the full analysis set. Observations after initiation of rescue therapy were excluded, and these and other missing values were replaced using the LOCF method, as recommended by the US Food and Drug Administration [16]. Safety data were summarized with the safety analysis set using descriptive statistics.

Sample size calculations were conducted on the basis of anticipated differences for the primary endpoint. In order to detect a difference of 0.5% between dapagliflozin versus placebo for changes from baseline to week 24 in HbA1c, assuming a standard deviation of 1.1% and at a significance level of 0.019, 129 patients per group were needed to provide 90% power. Assuming that 5% of patients would not be evaluable in the full analysis set, 136 patients per group (544 in total) were planned for randomization.

Results

Patients

Demographic and baseline characteristics were balanced across treatment groups, with 30.6% of patients recruited from the Asia/Pacific region (Table 1). The majority of randomized patients completed the study (91.5%), with the commonest

Table 1. Demographic and baseline characteristics of patients in the full analysis set.

	Placebo + glimepiride	Dapagliflozin 2.5 mg + glimepiride	Dapagliflozin 5 mg + glimepiride	Dapagliflozin 10 mg + glimepiride
Number of patients	145	154	142	151
Age, years				
Mean ± s.d.	60.3 ± 10.16	59.9 ± 10.14	60.2 ± 9.73	58.9 ± 8.32
Gender, n (%)				
Male	71 (49.0)	77 (50.0)	71 (50.0)	66 (43.7)
Female	74 (51.0)	77 (50.0)	71 (50.0)	85 (56.3)
Geographical region, n (%)				
Europe	101 (69.7)	108 (70.1)	96 (67.6)	106 (70.2)
Asia/Pacific	44 (30.3)	46 (29.9)	46 (32.4)	45 (29.8)
BMI categorization, n (%)				
≥ 25 kg/m^2	125 (86.2)	130 (84.4)	114 (80.3)	120 (79.5)
≥ 30 kg/m^2	66 (45.5)	74 (48.1)	73 (51.4)	68 (45.0)
Prior history of CVD*, n (%)	55 (37.9)	56 (36.4)	55 (38.7)	46 (30.5)
Hypertension, n (%)	116 (80.0)	108 (70.1)	100 (70.4)	113 (74.8)
Duration of T2DM, years				
Mean ± s.d.	7.4 ± 5.7	7.7 ± 6.0	7.4 ± 5.7	7.2 ± 5.5
HbA1c, %				
Mean ± s.d.	8.15 ± 0.74	8.11 ± 0.75	8.12 ± 0.78	8.07 ± 0.79
FPG, mmol/l				
Mean ± s.d.	9.58 ± 2.07	9.56 ± 2.13	9.68 ± 2.12	9.55 ± 2.04

BMI, body mass index; CVD, cardiovascular disease; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; s.d., standard deviation; T2DM, type 2 diabetes mellitus.

*Does not include patients with a cardiovascular history of hypertension only.

reasons for discontinuation being withdrawal of consent (2.9 and 5.5% in the dapagliflozin and placebo groups, respectively) and adverse events (3.1 and 2.1% in the dapagliflozin and placebo groups, respectively) (figure 1). For further details of patients receiving rescue therapy for failing to reach prespecified glycaemic targets or discontinuing for lack of efficacy, see Tables S1 and S2.

Primary Endpoint

Dapagliflozin 2.5, 5 and 10 mg as add-on therapy to glimepiride compared with placebo plus glimepiride met the primary endpoint at week 24 (figure 2). Statistically significant mean reductions in HbA1c percentage were observed for all dapagliflozin groups compared with placebo. Differences compared with placebo in adjusted mean reductions from baseline were >0.5% in the dapagliflozin 10 mg group and the effect of dapagliflozin on HbA1c appeared to be dose-related. ANCOVA assumption assessment, including distributional assumptions, treatment-by-baseline interaction and outlier detection, supported the validity of the primary model.

Secondary Endpoints

Dapagliflozin 5 and 10 mg produced sustained mean reductions in total body weight from baseline in all patients (figure 3) and in patients with baseline BMI $\geq$ 27 kg/m^2. Dapagliflozin 2.5 mg as add-on therapy to glimepiride did not meet the first secondary endpoint, reduction in total body weight at week 24 compared with placebo plus glimepiride. Therefore, because of the hierarchical testing procedure, statistical inferences for subsequent secondary endpoints for this dose were not further evaluated.

The proportion of patients achieving an HbA1c < 7.0% at week 24 was significantly increased with dapagliflozin 5 mg (30.3%, p = 0.0001) and 10 mg (31.7%, p < 0.0001) compared with placebo (13.0%). Reduction from baseline in mean 2-h PPG rise in response to an OGTT was significantly greater with dapagliflozin 5 mg (−1.78 mmol/l, p = 0.0002) and 10 mg (−1.94 mmol/l, p < 0.0001) compared with placebo (−0.33 mmol/l). Reduction from baseline in mean FPG was significantly greater with dapagliflozin 5 mg (−1.18 mmol/l, p < 0.0001) and 10 mg (−1.58 mmol/l, p < 0.0001) compared with placebo (−0.11 mmol/l). For further detail on these secondary endpoints see figure S1. In addition, reduction in HbA1c with dapagliflozin was observed at all levels of baseline HbA1c, was similar in patients with baseline BMI < 25 kg/m^2 versus BMI $\geq$ 25 kg/m^2 and was similar in patients from Europe versus those from the Asia/Pacific region (figure 4).

Exploratory Endpoints

All doses of dapagliflozin were associated with modest reductions in seated systolic blood pressure (Table S3). For a description of other exploratory endpoints, see Tables S1–S3.

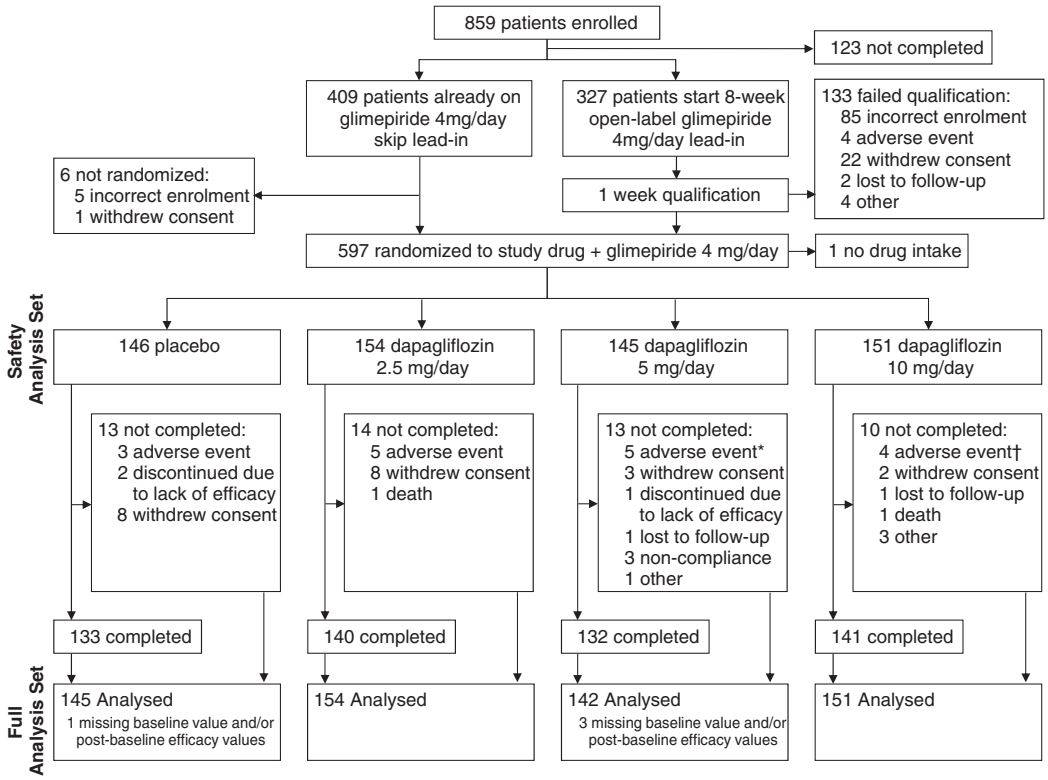
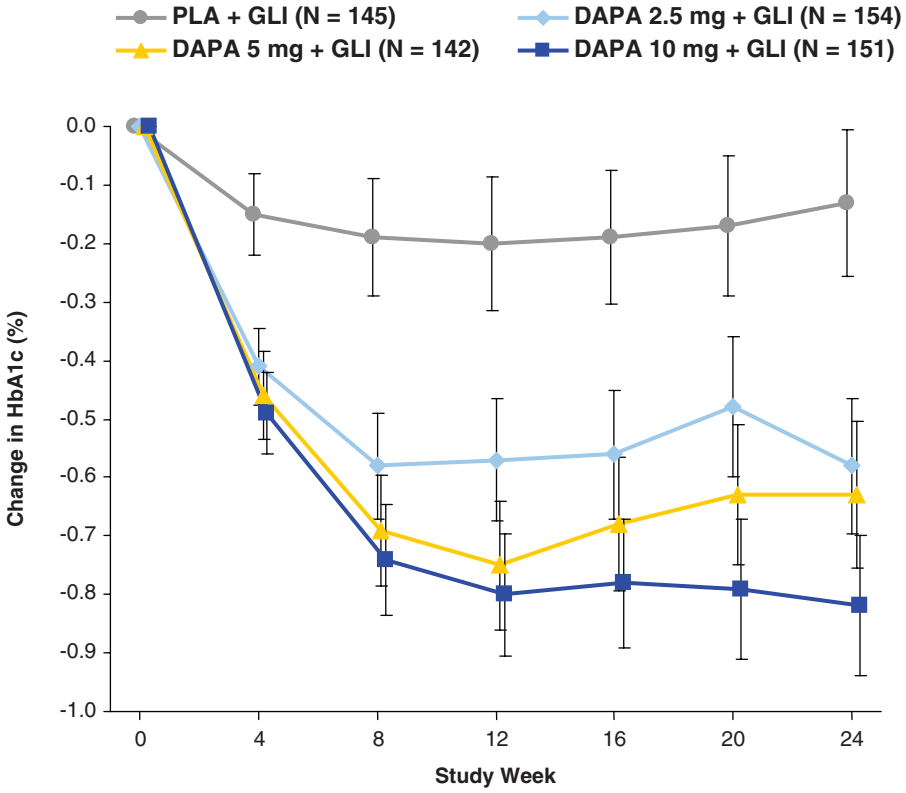


Figure 1. Trial profile. The term 'incorrect enrolment' was defined as patients not meeting inclusion criteria or meeting exclusion criteria during the enrolment process. *Includes one patient who was also classified as having discontinued because of lack of efficacy. †Includes one patient who discontinued secondary to a serious adverse event and who subsequently died.

(a) over study period



(b) week 24 primary endpoint

	PLA + GLI (n = 143)	DAPA 2.5 mg + GLI (n = 154)	DAPA 5 mg + GLI (n = 142)	DAPA 10 mg + GLI (n = 150)
Baseline HbA1c (%)	8.15	8.11	8.12	8.07
Change from baseline	−0.13	−0.58	−0.63	−0.82
Difference vs PLA		−0.44	−0.49	−0.68
95% CI of difference		−0.61 to −0.27	−0.67 to −0.32	−0.86 to −0.51
P of difference		<0.0001*	<0.0001*	<0.0001*

Figure 2. Change in haemoglobin A1c with treatment: (a) over study period and (b) at week 24 primary endpoint. Data are adjusted mean change from baseline ± 95% confidence intervals derived from ANCOVA and exclude data after rescue therapy. N is the number of patients in the full analysis set; n is the number of patients in the full analysis set with non-missing baseline and week 24 (last observation carried forward) values. *Significant versus placebo at $\alpha = 0.019$ applying Dunnett's adjustment. DAPA, dapagliflozin; GLI, glimepiride; PLA, placebo.

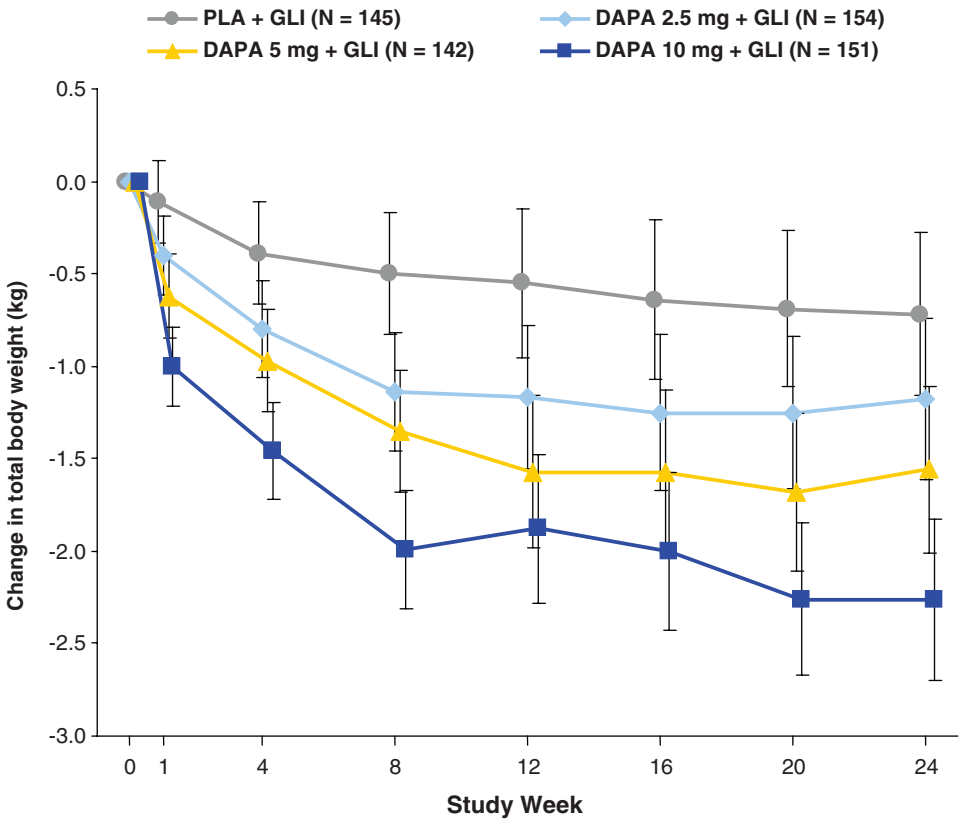
Safety and Tolerability

Overall dapagliflozin was safe and well tolerated. Adverse events (AEs) and AEs leading to study discontinuation were balanced across treatment groups (Table 2a, b). The frequency of serious adverse events (SAEs) was higher in the dapagliflozin groups compared with the placebo group (Table 2a).

SAEs leading to study discontinuation were observed in seven patients; two in the placebo group (pulmonary oedema and multiple stenosis of the coronary arteries), three in the dapagliflozin 2.5 mg group (neutropenic fever, chronic lymphatic leukaemia and gastroduodenitis), one in the dapagliflozin 5 mg group (decompensation of diabetes mellitus) and one in the dapagliflozin 10 mg group (stroke). Two deaths were reported, one in the dapagliflozin 2.5 mg group (cardiopulmonary arrest) and one in the dapagliflozin 10 mg group (pulmonary embolism after ischaemic stroke in a patient with a history of aortic valve replacement). The latter patient's haematocrit was 38% at baseline, 42% on day 112 and 45% (reference range 40–52%) on day 125, one day after the onset of the ischaemic stroke.

Regarding the prespecified safety analyses, hypoglycaemic events were reported more frequently in the dapagliflozin groups (6.9–7.9%) compared with the placebo group (4.8%).

(a) over study period



(b) week 24 secondary endpoint

	PLA + GLI (n = 145)	DAPA 2.5 mg + GLI (n = 154)	DAPA 5 mg + GLI (n = 142)	DAPA 10 mg + GLI (n = 151)
Baseline weight (kg)	80.94	81.89	81.00	80.56
Change from baseline	−0.72	−1.18	−1.56	−2.26
Difference vs PLA		−0.46	−0.84	−1.54
95% CI of difference		−1.08 to 0.15	−1.47 to −0.21	−2.17 to −0.92
P of difference		0.1410	0.0091*	<.0001*

Figure 3. Change in total body weight adjusted with treatment: (a) over study period and (b) at week 24 secondary endpoint. Data are adjusted mean change from baseline ± 95% confidence intervals derived from ANCOVA and exclude data after rescue therapy. N is the number of patients in the full analysis set; n is the number of patients in the full analysis set with non-missing baseline and week 24 (last observation carried forward) values. *Significant after sequential testing procedure at $\alpha = 0.05$. DAPA, dapagliflozin; GLI, glimepiride; PLA, placebo.

However, no patient discontinued study treatment as a result of hypoglycaemia (Table 2c). Higher proportions of patients in the dapagliflozin treatments groups compared with the placebo group reported signs, symptoms and other reports suggestive of genital infections. All of these events were of mild or moderate intensity and none led to discontinuation from the study. Rates for signs, symptoms and other reports suggestive of UTI were similar across groups (Table 2c). One patient receiving dapagliflozin 10 mg discontinued the study because of an AE of UTI. No kidney infections were reported. One patient receiving dapagliflozin 2.5 mg developed mild renal impairment assessed as related to the study medication, which resolved after 22 days following discontinuation of dapagliflozin. One patient receiving dapagliflozin 2.5 mg experienced an episode of mild asymptomatic hypotension and one patient receiving dapagliflozin 10 mg experienced an episode of syncope (Table 2c). Proportions of patients with a vital sign examination indicating orthostatic hypotension were low at week 24 in placebo [4/133 (3.0%)] and dapagliflozin groups [2.5 mg, 6/139 (4.3%); 5 mg, 5/134 (3.7%); 10 mg, 5/141 (3.6%)].

Changes from baseline in selected laboratory parameters are shown in Table 3. At week 24, dapagliflozin treatment was associated with modest increases in haematocrit and

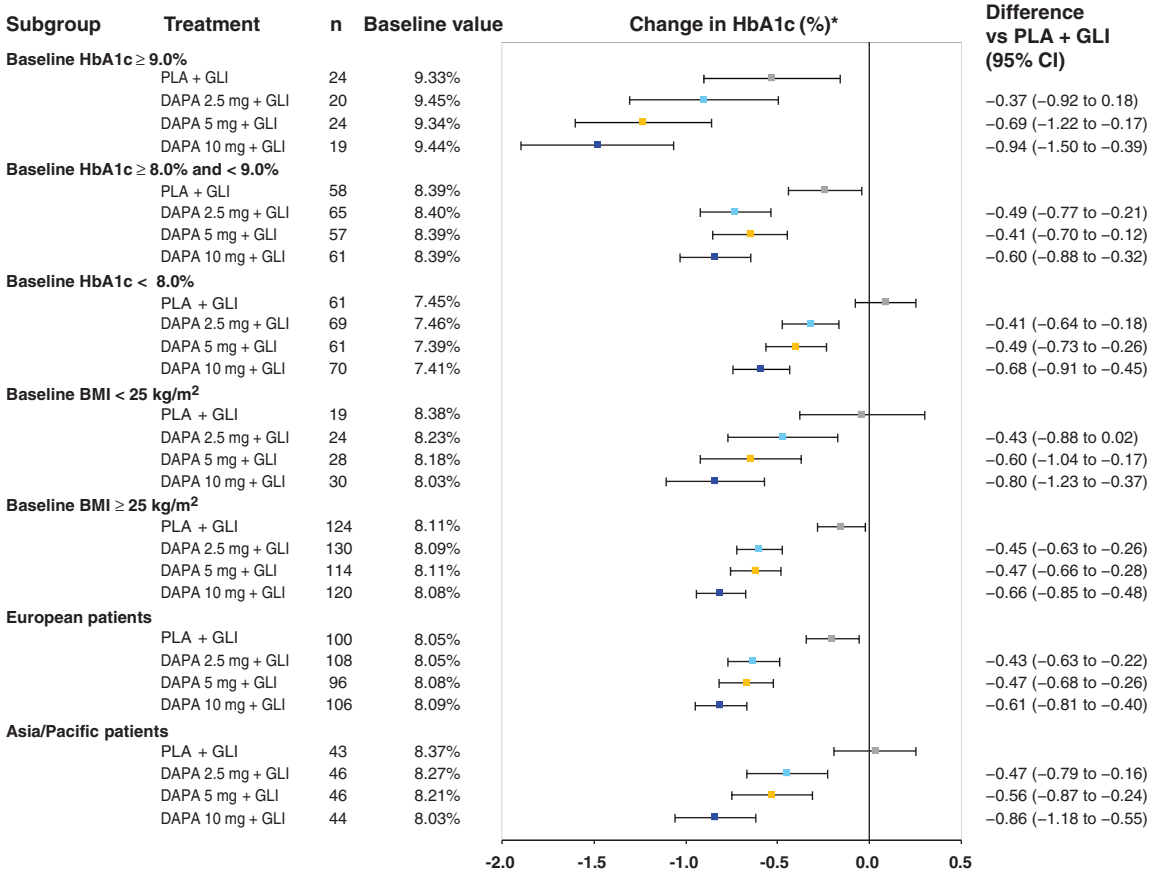


Figure 4. Change in haemoglobin A1c (HbA1c) by baseline HbA1c level, BMI level or geographical area. Data are last observation carried forward (LOCF) adjusted mean changes from baseline using the full analysis set and exclude data after rescue therapy. n = number of patients in the full analysis set with non-missing baseline and week 24 LOCF values. DAPA, dapagliflozin; GLI, glimepiride; PLA, placebo.

blood urea nitrogen, a small increase in serum creatinine and a small decrease in calculated creatinine clearance but without meaningful change in estimated glomerular filtration rate (eGFR), and a modest decrease in uric acid. Values for these parameters at 8 weeks versus those at 24 weeks showed no evidence of progressive change in haematocrit or renal function with dapagliflozin therapy (Table 3). Haematocrit >55% was observed in 11 (2.4%) patients treated with dapagliflozin versus 1 (0.7%) patient treated with placebo. However, none of these patients reported an AE associated with haemoconcentration such as transient ischaemic attack, stroke or venous thromboembolism. Dapagliflozin treatment produced dose-related increases in urinary glucose excretion and urinary glucose : creatinine ratio, which remained constant for the duration of the study (Table 3 and figure S2), consistent with its mechanism of action.

Discussion

The baseline patient characteristics in this study, for example, mean disease duration of 7.4 years and mean HbA1c of 8.1%, are typical of the general population of patients with T2DM. In addition, 30.6% of patients were recruited from the Asia/Pacific region, enabling the efficacy of dapagliflozin in combination with a sulphonylurea to be assessed in patients from this region whose initial treatment is commonly with a sulphonylurea [17].

Dapagliflozin improved a broad range of glycaemic parameters, with significant reductions in HbA1c at all doses and significant improvements at the 5 and 10 mg doses for proportions of patients achieving a therapeutic glycaemic response of HbA1c <7.0%, PPG rise 2 h after OGTT and FPG. Although hypoglycaemic events occurred more frequently in patients receiving dapagliflozin plus glimepiride (7.1–7.9%) versus placebo plus glimepiride (4.8%), an increase in these events is commonly observed when antidiabetes therapies are added to sulphonylureas. For example, in patients with inadequately controlled T2DM receiving glimepiride, rates of any hypoglycaemic event were 12.2% with add-on sitagliptin 100 mg versus 1.8% with placebo [18] and 5.2–9.2% with add-on liraglutide 0.6–1.8 mg versus 2.6% with placebo [19].

In addition to the primary analysis, subgroup analyses suggested that dapagliflozin has broad applicability, reducing HbA1c at all levels of baseline HbA1c and producing equivalent efficacy in patients with high versus low baseline BMI and in patients from the Asia/Pacific region versus those from Europe.

Dapagliflozin 5 and 10 mg/day significantly reduced both FPG and PPG. Combined fasting and postprandial efficacy

Table 2. Overall summary of patients with an adverse event (a); patients with adverse events with frequency ≥3% in any group (b); and patients with special interest adverse events (c).

Preferred term	Placebo + glimepiride (N = 146)	Dapagliflozin 2.5 mg + glimepiride (N = 154)	Dapagliflozin 5 mg + glimepiride (N = 145)	Dapagliflozin 10 mg + glimepiride (N = 151)
(a) Overall summary of number (%) of patients with an adverse event				
One or more AE	69 (47.3%)	80 (51.9%)	70 (48.3%)	76 (50.3%)
One or more drug-related AE*	5 (3.4%)	12 (7.8%)	11 (7.6%)	14 (9.3%)
AE leading to discontinuation	3 (2.1%)	5 (3.2%)	5 (3.4%)	4† (2.6%)
One or more SAE	7 (4.8%)	11 (7.1%)	10 (6.9%)	9 (6.0%)
SAE leading to discontinuation	2 (1.4%)	3 (1.9%)	1 (0.7%)	1 (0.7%)
Deaths	0	1 (0.6%)	0	1 (0.7%)
(b) Number (%) of patients with adverse events with frequency ≥3% in any group (by MedDRA preferred term)				
Back pain	4 (2.7%)	3 (1.9%)	3 (2.1%)	7 (4.6%)
Upper respiratory tract infection	4 (2.7%)	5 (3.2%)	6 (4.1%)	7 (4.6%)
Bronchitis	1 (0.7%)	2 (1.3%)	3 (2.1%)	5 (3.3%)
Nasopharyngitis	4 (2.7%)	3 (1.9%)	8 (5.5%)	5 (3.3%)
Urinary tract infection‡	5 (3.4%)	4 (2.6%)	4 (2.8%)	4 (2.6%)
Hypertension	6 (4.1%)	8 (5.2%)	2 (1.4%)	2 (1.3%)
Arthralgia	4 (2.7%)	6 (3.9%)	0	1 (0.7%)
Diarrhoea	5 (3.4%)	4 (2.6%)	2 (1.4%)	0
(c) Number (%) of patients with a special interest adverse event				
One or more hypoglycaemic event§	7 (4.8%)	11 (7.1%)	10 (6.9%)	12 (7.9%)
Events suggestive of genital infection‖, §				
Total	1/146 (0.7%)	6/154 (3.9%)	9/145 (6.2%)	10/151 (6.6%)
Males	0	0	2/72 (2.8%)	4/66 (6.1%)
Females	1/75 (1.3%)	6/77 (7.8%)	7/73 (9.6%)	6/85 (7.1%)
Events suggestive of urinary tract infection‖				
Total	9/146 (6.2%)	6/154 (3.9%)	10/145 (6.9%)	8/151 (5.3%)
Males	0	0	4/72 (5.6%)	2/66 (3.0%)
Females	9/75 (12.0%)	6/77 (7.8%)	6/73 (8.2%)	6/85 (7.1%)¶
Renal impairment/failure**	2 (1.4%)††	1 (0.6%)‡‡, ¶	1 (0.7%)§§	0
Hypotension/dehydration/hypovolaemia**, §	0	1 (0.6%)	0	1 (0.7%)

AE, adverse event; N, number of patients in the safety analysis set and includes data after rescue; SAE, serious adverse event.
*Events with certain, probable, possible or unknown relation to study drug were deemed to be drug-related adverse events.
†Includes one patient who discontinued secondary to a serious adverse event and who subsequently died. No SAE was assessed as drug-related.
‡Based on definitive MedDRA preferred terms.
§None led to study discontinuation.
‖Events suggestive of genital infection or urinary tract infection were identified in the database using the prespecified lists of preferred terms. These events included signs, symptoms and other reports suggestive of genital infection or urinary tract infection, as well as definitive terms for genital infection or urinary tract infection.
¶One patient discontinued the study.
**These events were also identified in the database using prespecified lists of preferred terms, but which also included, for example, laboratory values such as serum creatinine.
††One renal impairment and one renal failure.
‡‡Renal impairment.
§§Obstructive uropathy.

appears to be important for optimal glycaemic control because: (i) postprandial hyperglycaemia increases earlier and faster than fasting hyperglycaemia during the progression of T2DM [20]; and (ii) postprandial hyperglycaemia influences HbA1c more than fasting hyperglycaemia when HbA1c levels approach target values [21]. Dapagliflozin OGTT response was similar at all dapagliflozin dose levels. In contrast, dose-related differences were apparent for longer-term outcomes such as reduction in HbA1c and weight.

Regarding non-glycaemic parameters, dapagliflozin 5 and 10 mg/day produced dose-related reductions in weight and systolic blood pressure. Given that sulphonylurea treatment is usually associated with weight gain [22,23], these reductions represent a potentially beneficial effect of dapagliflozin as add-on therapy to sulphonylurea treatment. The mechanism by which dapagliflozin induces weight loss may relate to caloric loss from glucosuria leading to fat loss, osmotic diuresis or a combination of both factors. Studies of body composition are under way to confirm a potential mechanism. The mechanism

Table 3. Laboratory values of interest: change from baseline at weeks 8 and 24.

	Placebo + glimepiride (N = 146)	Dapagliflozin 2.5 mg + glimepiride (N = 154)	Dapagliflozin 5 mg + glimepiride (N = 145)	Dapagliflozin 10 mg + glimepiride (N = 151)
Haematocrit (%)				
Baseline	41.83 (3.47)	41.97 (4.11)	41.98 (3.23)	42.25 (3.72)
Change at week 8	0.04 [0.20]	1.56 [0.18]	1.89 [0.19]	1.92 [0.18]
Change at week 24	0.01 [0.17]	1.93 [0.20]	2.28 [0.22]	2.19 [0.20]
Serum creatinine (μmol/l)				
Baseline	78.3 (19.6)	77.9 (18.9)	75.3 (16.1)	75.2 (17.0)
Change at week 8	1.06 [0.82]	1.94 [0.68]	1.77 [0.79]	2.21 [0.78]
Change at week 24	0.09 [0.97]	1.59 [0.77]	0.44 [0.83]	0.71 [0.71]
Calculated creatinine clearance (ml/min)				
Baseline	97.6 (30.5)	100.5 (37.3)	100.5 (32.3)	101.3 (32.6)
Change at week 8	−2.1 [1.19]	−3.8 [0.96]	−2.7 [1.16]	−5.7 [1.16]
Change at week 24	−1.3 [1.06]	−3.5 [1.01]	−2.4 [1.02]	−4.8 [1.08]
Estimated GFR (ml/min/1.73 m^2)				
Baseline	80.2 (19.1)	80.9 (18.6)	83.5 (19.6)	82.2 (17.9)
Change at week 8	−1.0 [1.19]	−2.2 [0.83]	−1.2 [1.03]	−2.7 [0.98]
Change at week 24	0.0 [0.94]	−1.5 [0.89]	−0.1 [1.02]	−1.2 [1.03]
Blood urea nitrogen (mmol/l)				
Baseline	5.8 (1.72)	5.6 (1.69)	5.6 (1.62)	5.5 (1.54)
Change at week 8	0.14 [0.11]	0.25 [0.12]	0.43 [0.11]	0.43 [0.11]
Change at week 24	0.04 [0.13]	0.36 [0.12]	0.43 [0.12]	0.61 [0.11]
Serum uric acid (μmol/l)				
Baseline	315.2 (93.6)	301.6 (81.2)	303.9 (79.8)	301.0 (82.4)
Change at week 8	−3.57 [4.04]	−19.03 [4.26]	−26.17 [4.40]	−27.36 [5.15]
Change at week 24	1.19 [4.77]	−21.41 [4.29]	−26.17 [5.37]	−26.17 [4.90]
Urine glucose (mmol/l)				
Baseline	26.0 (58.0)	19.2 (47.7)	21.1 (55.3)	21.7 (48.4)
Change at week 8	−3.72 [6.32]	103.13 [7.50]	132.06 [7.84]	163.48 [9.59]
Change at week 24	−13.96 [5.68]	98.53 [8.40]	119.90 [8.45]	155.14 [9.28]
Urinary glucose : creatinine ratio (g/g)				
Baseline	6.21 (19.12)	3.63 (9.8)	4.55 (12.38)	4.96 (13.58)
Change at week 8	−2.0 [1.69]	20.9 [1.96]	28.5 [2.17]	34.2 [2.36]
Change at week 24	−3.4 [1.58]	20.7 [2.40]	30.0 [2.79]	35.2 [2.40]

Data are mean (s.d.) or mean [s.e.] using the safety analysis set. Measures for urinary glucose and glucose : creatinine ratio were derived from a urinary spot-check performed in the morning fasting state. GFR, glomerular filtration rate; N, number of patients at baseline in the safety analysis set; s.d., standard deviation; s.e., standard error.

for systolic blood pressure reduction is unclear, but may involve osmotic diuresis or sodium loss.

The study had a number of potential limitations. First, the use of a fixed dose of glimepiride with resort to other forms of rescue medication in the event of inadequate glycaemic control may arguably not have provided a valid assessment of the efficacy of dapagliflozin as add-on therapy without having first titrated glimepiride to maximum effect. Although the fixed dose of half-maximal glimepiride was based upon the US recommended maximum dose of 8 mg [24], in Europe, the manufacturer's summary of product characteristics states that doses of more than 4 mg should only be used in exceptional circumstances [25]. Moreover, the glucose-lowering effect of sulphonylureas is virtually fully realized at half-maximal doses and higher doses are not recommended because of excessive hypoglycaemia risk [5]. Thus, the patients in this study were highly likely to have been exposed to a dose of glimepiride reflective of maximal clinical efficacy. Second, the administration of glimepiride just prior to conducting the OGTT limits the interpretability of the results of this key secondary endpoint. Third, the study design did not control use of antihypertensive medication or lipid-lowering agents throughout the trial, limiting the interpretability of changes in blood pressure and lipids with dapagliflozin.

Dapagliflozin was well tolerated; however, signs, symptoms and other reports suggestive of genital infections were reported more frequently in patients receiving dapagliflozin than in those receiving placebo. All of these events were mild to moderate in intensity and responded to standard treatment, and none led to discontinuation of study medication. Although the relative risk of genital infection is increased in patients with diabetes [26], which may relate to the level of glycaemic control, glucosuria and changes in immune function [27], the higher frequency observed with dapagliflozin is being investigated further in longer-term studies to acquire more detailed information. In this study, no increased frequency of events suggestive of UTI was found.

Although dapagliflozin was associated with modest rises in haematocrit and blood urea nitrogen, there were no progressive changes in serum creatinine or eGFR (Table 3) or increase in proportions of patients experiencing AEs of renal impairment/failure or AEs of hypotension/dehydration/hypovolaemia (Table 2c). This suggests that dapagliflozin treatment was not associated with clinically relevant dehydration or impairment in kidney function. The increase in haematocrit was not associated with an increase in proportion of patients experiencing vascular events in this study. However, any potential link between vascular events and dapagliflozin-induced rises in haematocrit awaits further long-term study.

In conclusion, dapagliflozin is an effective and safe therapy for patients with T2DM who have inadequate glycaemic control on glimepiride monotherapy. Longer-term follow-up studies are ongoing to further characterize the efficacy and safety profile of dapagliflozin as a novel treatment option for patients with T2DM.

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Conflict of Interest

K. S. received honoraria for speaking engagements and participation in clinical trials from the following companies: Eli Lilly, Novo Nordisk, Bristol-Myers Squibb, Bioton (Poland), Merck-Serono, AstraZeneca. K. H. Y. received honoraria for speaking engagements and participation in clinical trials from the following companies: Eli Lilly, Novo Nordisk, Bristol-Myers Squibb, Merck-Serono, AstraZeneca, Merck, GSK, Takeda. V. H., A. M. L. and S. P. are full-time employees of AstraZeneca Pharmaceuticals. M. E. is an employee of ClinResearch, which is contracted to support data analysis for AstraZeneca.

K. S., V. H., M. E., A. M. L. and S. P. participated in the analysis and interpretation of data. V. H., M. E. and S. P. participated in the study concept and design. K. S., K. H. Y., V.H., M. E. and A. M. L. participated in acquisition of data. M. E. participated in the statistical verification of data. V. H. participated in study supervision. K. S., K. H. Y., V. H., M. E., A. M. L. and S. P. contributed to writing and revising the report.

Supporting Information

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

Table S1. Cumulative absolute numbers of patients receiving rescue therapy for failing to reach prespecified glycaemic targets or discontinuing for lack of efficacy.

Table S2. Adjusted proportion of patients discontinued for lack of efficacy or rescued due to inadequate glycaemic control by week 24.

Table S3. Exploratory endpoints at week 24: data are LOCF adjusted mean changes from baseline using the full analysis set and excluding data after rescue.

Figure S1. Change in secondary glycaemic endpoints with treatment. (a) Proportion of patients with a therapeutic glycaemic response, defined as an HbA1c $< 7.0\%$ at week 24; (b) OGTT 2-h post-challenge plasma glucose level response and (c) fasting plasma glucose (i) over study period and (ii) at week 24 secondary endpoint. Data for (a) are adjusted percent $\pm$ 95% confidence intervals derived from logistic regression analysis and exclude data after rescue therapy. Data for (b) and (c) are adjusted mean change from baseline $\pm$ 95% confidence intervals derived from ANCOVA and exclude data after rescue therapy. N is the number of patients in the full analysis set; x the number of patients showing a response; n the number of patients in the full analysis set with non-missing baseline and week 24 (LOCF) values. NT, not tested under sequential testing procedure because first secondary endpoint (total body weight) was not statistically significant at the 2.5 mg dose. *Significant after sequential testing procedure at $\alpha = 0.05$. DAPA, dapagliflozin; FPG, fasting plasma glucose; GLI, glimepiride; PLA, placebo; PPG, post-challenge plasma glucose.

Figure S2. (a) Urinary glucose excretion (mmol/l) and (b) urinary glucose:creatinine ratio (g/g) during the 24-week study period. Data obtained from urinary spot-check performed in the morning fasting state. Data are mean and standard deviation. DAPA, dapagliflozin; GLI, glimepiride; PLA, placebo.

Appendix S1. Exclusion criteria.

Appendix S2. Oral glucose tolerance test.

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