Dapagliflozin Improves Glycemic Control and Reduces Body Weight as Add-on Therapy to Metformin Plus Sulfonylurea: A 24-Week Randomized, Double-Blind Clinical Trial

*Stephan Matthaei,[1] Keith Bowering,[2] Katja Rohwedder,[3] Anke Grohl,[4] and Shamik Parikh,[5] for the Study 05 Group**

Diabetes Care 2015;38:365–372 | DOI: 10.2337/dc14-0666

OBJECTIVE

To evaluate the efficacy and safety of dapagliflozin in patients with type 2 diabetes inadequately controlled with metformin and sulfonylurea.

RESEARCH DESIGN AND METHODS

Patients with HbA_{1c} of 7.0% (53 mmol/mol) to 10.5% (91 mmol/mol) receiving sulfonylurea and metformin were randomized to receive dapagliflozin 10 mg/day (*n* = 109) or placebo (*n* = 109) for 24 weeks.

RESULTS

HbA_{1c} (baseline: dapagliflozin 8.08% [65 mmol/mol]; placebo 8.24% [67 mmol/mol]) and fasting plasma glucose (baseline: dapagliflozin 167.4 mg/dL [9.29 mmol/L]; placebo 180.5 mg/dL [10.02 mmol/L]) significantly improved from baseline with dapagliflozin (placebo-subtracted change –0.69% [–7.5 mmol/mol], *P* < 0.0001; –33.5 mg/dL [–1.86 mmol/L], *P* < 0.0001, respectively). More patients achieved a therapeutic glycemic response (HbA_{1c} <7.0% [53 mmol/mol]) with dapagliflozin (31.8%) versus placebo (11.1%) (*P* < 0.0001). Body weight and systolic blood pressure were significantly reduced from baseline over 24 and 8 weeks, respectively, with dapagliflozin (placebo-subtracted change –2.1 kg, *P* < 0.0001; –3.8 mmHg, *P* = 0.0250). Patients receiving dapagliflozin showed placebo-subtracted increases in total, LDL, and HDL cholesterol (11.4 mg/dL, *P* = 0.0091; 11.4 mg/dL, *P* = 0.0030; 2.2 mg/dL, *P* = 0.0172, respectively) with no change in LDL/HDL cholesterol ratio (0.1; *P* = 0.2008) or triglycerides (–16.5 mg/dL; *P* = 0.1755). Adverse events occurred in 48.6% of patients receiving dapagliflozin and 51.4% receiving placebo. Significantly more patients with dapagliflozin compared with placebo experienced hypoglycemia (12.8 vs. 3.7%; *P* = 0.024) and genital infections (5.5 vs. 0%; *P* = 0.029). Events of urinary tract infection were reported by 6.4% of patients in both groups.

CONCLUSIONS

Dapagliflozin was well tolerated and effective over 24 weeks as add-on to metformin plus sulfonylurea. Adverse effects included hypoglycemia and genital infections.

[1]*Diabetes-Zentrum Quakenbrück, Quakenbrück, Germany*
[2]*University of Alberta, Edmonton, Alberta, Canada*
[3]*AstraZeneca, Wedel, Germany*
[4]*Aptiv Solutions, Köln, Germany*
[5]*AstraZeneca, Wilmington, DE*

Corresponding author: Stephan Matthaei, s.matthaei@ckq-gmbh.de.

Received 14 March 2014 and accepted 13 December 2014.

Clinical trial reg. no. NCT01392677, clinicaltrials.gov.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc14-0666/-/DC1.

**A complete list of the Study 05 participating personnel can be found in the Supplementary Data online.*

© 2015 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered.

See accompanying articles, pp. 352, 355, 373, 376, 384, 394, 403, 412, 420, 429, and 431.

Metformin is recommended as initial pharmacologic therapy for patients with type 2 diabetes in both the U.S. and the European Union because of its glycemic efficacy, weight neutrality, low risk of hypoglycemia, good tolerability, and relatively low cost (1). However, because of the progressive nature of the disease, there is often a loss of efficacy over time with metformin and a need for a second-line therapy (2,3).

Sulfonylureas are commonly used as add-on therapy for patients inadequately controlled with metformin (4). Dual combination therapy is recommended by the American Diabetes Association and the European Association for the Study of Diabetes should HbA_{1c} levels exceed 9% (75 mmol/mol) (1) and by the Canadian Diabetes Association should HbA_{1c} levels exceed 8.5% (69 mmol/mol) (5). Initially this approach is often effective, but there is a lack of durability in combination therapy with metformin and sulfonylurea. Despite an initial improvement in glycemic control following the addition of sulfonylurea to metformin, deterioration can resume as early as 6 months at a rate comparable to that observed with metformin alone (2,6).

If dual therapy fails to adequately control HbA_{1c} levels, the American Diabetes Association, the European Association for the Study of Diabetes, and the American Association of Clinical Endocrinologists recommend the addition of a third oral therapy as one potential therapeutic option (1,7). This could include the addition of a GLP-1 analog, a dipeptidyl peptidase-4 inhibitor, or basal insulin. Inhibitors of sodium–glucose cotransporter 2 (SGLT2) are another possibility as an add-on to dual therapy. SGLT2 inhibitors are not reliant on β-cell function and can be used across all stages of the disease (8).

Dapagliflozin is a highly selective inhibitor of SGLT2 that improves glycemic control through the elimination of glucose in the urine. The associated caloric loss leads to a reduction in body weight (or prevents weight gain). Dapagliflozin therapy is also accompanied by modest reductions in blood pressure (BP) that are consistent with mild diuresis (9–16).

The aim of this study was to evaluate the safety and efficacy of dapagliflozin as part of a triple combination therapy in patients with type 2 diabetes and inadequate glycemic control with metformin and sulfonylurea.

RESEARCH DESIGN AND METHODS

Study Design

Overall, 46 centers in North America (Canada) and Europe (Czech Republic, Germany, Poland, Slovak Republic, and Spain) enrolled patients, and 45 centers randomized patients.

This was a 24-week, international, multicenter, randomized, double-blind, parallel-group, placebo-controlled, phase 3b study (NCT01392677, clinicaltrials.gov). The study consisted of a screening period of up to 3 weeks; an 8-week, single-blind, placebo lead-in period; and a 24-week, double-blind, placebo-controlled treatment period (Supplementary Fig. 1). During the double-blind treatment period, patients were evaluated by the investigators at weeks 4, 8, 16, and 24.

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonisation/Good Clinical Practice, applicable regulatory requirements, and the AstraZeneca policy on bioethics. All patients gave written informed consent.

Study Treatment

Patients on metformin and sulfonylurea were randomized 1:1 via an interactive response system (web or voice based; Perceptive Services Limited) to receive dapagliflozin 10 mg once daily or matched placebo (identical in size, color, smell, taste, packaging, and labeling).

Key Inclusion/Exclusion Criteria

Men and women who were not of childbearing potential (defined as women who were postmenopausal or who were permanently or surgically sterilized) or women of childbearing potential using a highly effective method of birth control and a negative pregnancy test 72 h prior to the start of medication and at each visit were eligible to enter the study. Patients were at least 18 years of age, had a diagnosis of type 2 diabetes, were receiving a stable-dose combination therapy of metformin ≥1,500 mg/day and a maximum tolerated dose (at least half the maximum dose according to local use) of sulfonylurea for at least 8 weeks prior to enrollment, and had inadequate glycemic control (HbA_{1c} ≥7.0% [53 mmol/mol] to ≤10.5% [91 mmol/mol] at randomization).

Patients were excluded from the study if they had a diagnosis of type 1 diabetes, BMI ≥45.0 kg/m^2, measured serum creatinine value of ≥1.5 mg/dL (133 μmol/L) for men or ≥1.4 mg/dL (124 μmol/L) for women, unstable or rapidly progressing renal disease, cardiovascular events within 2 months prior to enrollment, congestive heart failure (New York Heart Association Class IV), systolic BP (SBP) ≥160 mmHg, or diastolic BP (DBP) ≥100 mmHg at randomization.

End Points

The primary end point was change from baseline to week 24 in HbA_{1c} levels. Prespecified subgroup analyses of the change in HbA_{1c} were performed in patients with baseline HbA_{1c} values <8% (<64 mmol/mol), ≥8% (≥64 mmol/mol) to <9% (<75 mmol/mol), and ≥9% (≥75 mmol/mol). Key secondary end points included change from baseline to week 24 in fasting plasma glucose (FPG) and total body weight, proportion of patients achieving a therapeutic glycemic response (defined as HbA_{1c} <7.0% [53 mmol/mol]) at week 24, and change from baseline to week 8 in seated SBP (average of three measurements taken from the same arm after the patient had been sitting and resting for at least 5 min).

During the placebo lead-in period, concomitant antihypertensive medications could be adjusted in patients with seated SBP ≥160 mmHg or seated DBP ≥100 mmHg, without adding new antihypertensive agents to the patient's regimen. Only those patients with seated SBP <160 mmHg and DBP <100 mmHg at the end of the placebo lead-in period were randomized. There were no changes in antihypertensive medications permitted up to week 8 unless the patient had a confirmed SBP ≥160 mmHg or DBP ≥100 mmHg or had symptomatic hypotension or documented orthostatic hypotension during a study visit. After week 8, changes in antihypertensive medication were made as needed for appropriate BP management.

Other secondary end points included change from baseline to week 24 in fasting lipids (total cholesterol, LDL cholesterol, HDL cholesterol, LDL/HDL cholesterol ratio, and triglycerides) and C-peptide and

proportion of patients who discontinued for lack of efficacy or were rescued for failing to maintain FPG below prespecified rescue criteria.

Rescue Criteria

Rescue therapy was mandated by the study protocol to guard the safety of patients. Open-label rescue therapy was administered with the patients' study medication if FPG exceeded 240 mg/dL (13.32 mmol/L) between weeks 4 and 16 or exceeded 200 mg/dL (11.10 mmol/L) between weeks 16 and 24.

Sulfonylurea Down-Titration

Sulfonylurea could be down-titrated only once during the treatment period to mitigate the risk of recurrent hypoglycemic events at the discretion of the investigator.

Safety and Tolerability

The safety and tolerability of dapagliflozin versus placebo were assessed through the evaluation of adverse events, including cardiovascular events, laboratory values, electrocardiogram, vital signs, hypoglycemic events, calculated creatinine clearance, estimated glomerular filtration rate, and physical examination findings over 24 weeks.

Adverse events were defined as the development, at any time throughout the study, of an undesirable medical condition or the deterioration of a preexisting medical condition whether or not considered causally related to the treatment. Serious adverse events were defined as adverse events that were immediately life threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, were congenital abnormalities or birth defects, were important medical events jeopardizing the patient or requiring medical intervention to prevent one of the outcomes listed above, or resulted in death. Events of urinary tract infection and genital infection were determined using a predefined list of Medical Dictionary for Regulatory Activities terms (MedDRA version 15.1). Patients reported symptoms of genital infection and urinary tract infection spontaneously throughout the study as well as in response to questions posed by the investigators at study visits.

Minor episodes of hypoglycemia were defined as either a symptomatic episode with a capillary or plasma glucose measurement $<$3.5 mmol/L ($<$63 mg/dL), regardless of need for external assistance, or an asymptomatic capillary or plasma glucose measurement $<$3.5 mmol/L ($<$63 mg/dL) that did not qualify as a major episode. A major episode was defined as a symptomatic episode requiring third-party assistance due to severe impairment in consciousness or behavior with a capillary or plasma glucose value $<$3 mmol/L ($<$54 mg/dL) and prompt recovery after glucose or glucagon administration.

Statistical Analyses

Efficacy analyses were based on the full analysis set, which included all randomized patients who received at least one dose of study medication during the 24-week double-blind treatment period with a nonmissing baseline value and one or more postbaseline value for at least one efficacy variable analyzed at week 24. The intention-to-treat principle was preserved despite the exclusion of patients who took no study medication. The primary safety analyses included all data regardless of rescue.

Longitudinal repeated measures analysis was used to evaluate the primary end point using a direct likelihood method with fixed categorical effects of treatment, week, treatment-by-week interaction, as well as the continuous fixed covariates of baseline and baseline-by-week interaction. Data for scheduled time points up to week 24 prior to rescue were included in the longitudinal repeated measures analysis.

Variables other than the primary end point were analyzed using an ANCOVA with treatment group as a fixed effect and the baseline measurement as a covariate, and the last observation carried forward (LOCF) approach (17) was used for all other variables at 24 weeks. LOCF analyses from baseline to 24 weeks were based on measurements available at that time point; if no measurement was available, the last postbaseline measurement prior to 24 weeks was used. Unless otherwise specified, if a patient initiated rescue medication, the last value taken on or before the first rescue dose was used for LOCF analysis. All statistical testing performed was two-sided. A hierarchical closed testing procedure was used to control for type I error rate across the primary and key secondary objectives. Treatment comparisons were individually tested for the primary and key secondary end points at a two-sided significance level of 0.05. For all other variables, including changes from baseline in lipids and C-peptide, nominal *P* values were reported without significance testing. The analysis of percentage changes in lipids is conducted using the logarithms of the absolute lipid values. All analyses were performed with SAS (SAS Institute, Cary, NC) version 8.2 or higher.

RESULTS

Patients

Patient disposition is summarized in Supplementary Fig. 2. Briefly, 219 patients entered study randomization, one of whom died before randomization. Patients were randomized 1:1 to receive placebo (*n* = 109) or dapagliflozin 10 mg/day (*n* = 109) in addition to their metformin and sulfonylurea treatment. Approximately 93% of the patients in each treatment arm completed the 24-week double-blind treatment period. Adverse events leading to patient withdrawal included one event each of somnolence, skin reaction, and renal cell carcinoma in the placebo group and one event of chronic obstructive pulmonary disease in the dapagliflozin group. Three patients in the placebo group and two in the dapagliflozin group discontinued treatment due to reasons classed as "other" and included patient choice, lack of glycemic control determined by the investigator, and the patient moving out of the country in the placebo group and patient choice and patient travel in the dapagliflozin group. Two patients in the placebo group and three in the dapagliflozin group were discontinued from the study for not meeting the prespecified inclusion criteria or for meeting the exclusion criteria (incorrect enrollment). In addition, two patients in the dapagliflozin group withdrew their consent.

Demographics and Baseline Characteristics

The treatment groups were generally balanced with respect to demographics and diabetes-related baseline characteristics, with a higher proportion of women in the dapagliflozin treatment arm (Table 1). Most patients were white, had a mean age of 61 years, had a prior history of cardiovascular

Table 1—Demographics and baseline characteristics

	Placebo (*N* = 108)	Dapagliflozin 10 mg/day (*N* = 108)
Age, mean (SD), years	60.9 (9.2)	61.1 (9.7)
Female, *n* (%)	48 (44.4)	62 (57.4)
Race, *n* (%)		
White	102 (94.4)	104 (96.3)
Weight, mean (SD), kg	90.1 (16.2)	88.6 (17.6)
BMI, mean (SD), kg/m^2	32.0 (4.6)	31.9 (4.8)
SBP, mean (SD), mmHg	136.4 (14.2)	134.5 (12.6)
DBP, mean (SD), mmHg	81.6 (7.9)	80.4 (9.2)
Type 2 diabetes duration, mean (SD), years	9.6 (6.2)	9.3 (6.5)
HbA_{1c}, mean (SD), % [mmol/mol]	8.24 (0.87) [67 (9.5)]	8.08 (0.91) [65 (9.9)]
FPG, mean (SD), mg/dL [mmol/L]	180.2 (43.1) [10.00 (2.39)]	167.4 (43.3) [9.29 (2.40)]
Prior history of cardiovascular disease, *n* (%)	95 (88.0)	91 (84.3)
Concomitant medications, *n* (%)		
Thiazide diuretics	29 (26.6)	30 (27.5)
Antihypertensives	95 (87.2)	89 (81.7)
Angiotensin receptor blocker and/or ACE	83 (76.1)	75 (68.8)

N is the number of patients in the full analysis set.

disease, and were receiving antihypertensive medications (mostly angiotensin receptor blockers and/or ACE inhibitors).

Efficacy

HbA_{1c}

HbA_{1c} levels were significantly reduced from baseline (dapagliflozin 8.08% [65 mmol/mol]; placebo 8.24% [67 mmol/mol]) over 24 weeks in patients treated with dapagliflozin compared with placebo (–0.86% [–9.4 mmol/mol] vs. –0.17% [–1.9 mmol/mol], respectively; $P < 0.0001$) (Table 2 and Fig. 1*A*).

HbA_{1c} Subgroup Analyses

In patients with higher baseline HbA_{1c} values (≥8% [≥64 mmol/mol] to <9% [<75 mmol/mol] and ≥9% [≥75 mmol/mol]), the mean placebo-subtracted decreases in HbA_{1c} seen with dapagliflozin were numerically greater (–0.64% [–7.0 mmol/mol] and –0.82% [–9.0 mmol/mol]) compared with –0.36% (–3.9 mmol/mol) in patients with lower baseline HbA_{1c} values (<8% [<64 mmol/mol]) (Supplementary Table 1). The impact of baseline HbA_{1c} on the reduction in HbA_{1c} from baseline was evaluated using a subgroup-by-treatment interaction analysis and was statistically significant ($P = 0.0038$).

A greater proportion of patients receiving dapagliflozin 10 mg/day compared with placebo achieved a therapeutic glycemic response (defined as HbA_{1c} <7.0% [<53 mmol/mol]) at week 24 (LOCF) (31.8 vs. 11.1%; $P < 0.0001$) (Table 2).

FPG

Greater mean reductions from baseline to week 24 (LOCF) in FPG were observed with dapagliflozin compared with placebo (–34.2 mg/dL [–1.90 mmol/L] vs. –0.8 mg/dL [–0.04 mmol/L], respectively; adjusted mean difference –33.5 mg/dL [–1.86 mmol/L]; $P < 0.0001$) (Table 2 and Fig. 1*B*).

Body Weight

Significantly greater mean reductions from baseline to week 24 (LOCF) in body weight were observed with dapagliflozin compared with placebo (–2.7 vs. –0.6 kg, respectively; adjusted mean difference –2.1 kg; $P < 0.0001$) (Table 2 and Fig. 1*C*).

Seated SBP

Patients in the dapagliflozin group showed a significantly larger reduction in seated SBP from baseline to week 8 (LOCF) compared with placebo (–4.0 vs. –0.3 mmHg, respectively; adjusted mean difference –3.8 mmHg; $P = 0.025$).

Rescue

No patients in the dapagliflozin group and 10 patients in the placebo group (9.3%) were rescued due to lack of glycemic control at week 24 (LOCF).

Lipids

Patients receiving dapagliflozin showed a mean placebo-corrected adjusted increase in total cholesterol ($P = 0.0091$) (Table 2). Increases were also seen with LDL cholesterol ($P = 0.0030$) and HDL cholesterol ($P = 0.0172$). No significant change from baseline was observed in LDL/HDL cholesterol ratio ($P = 0.2008$) or triglyceride levels ($P = 0.1755$).

Mean serum levels of C-peptide did not show any change in either treatment group (placebo-subtracted change –0.11 ng/mL).

Safety

The frequency of adverse events was similar between placebo (51.4%) and dapagliflozin (48.6%) groups (Table 3). The majority of adverse events were mild or moderate and not considered related to treatment by the investigator. Significantly more patients with dapagliflozin compared with placebo experienced events of hypoglycemia (12.8 vs. 3.7%, respectively; $P = 0.024$; post hoc analyses). There were no major episodes of hypoglycemia, and no events of hypoglycemia led to discontinuation in either group.

Over 24 weeks, significantly more events of genital infection were experienced by patients receiving dapagliflozin (six [5.5%]; five women, one man) compared with placebo (0%; $P = 0.029$; post hoc analyses): two events of vulvovaginal candidiasis and one episode each of balanitis candida, genital infection, vaginal infection, and vulvovaginitis. All events of genital infection were single events and were treated with antibiotic agents. Three of the events

Table 2—Change from baseline at week 24 (week 8 for seated SBP) for efficacy end points (excluding data after rescue)

	Placebo (*N* = 108)	Dapagliflozin 10 mg/day (*N* = 108)
HbA_{1c}, % [mmol/mol]†		*P* < 0.0001*
Baseline (SD)	8.24 (0.87) [67 (9.5)]	8.08 (0.91) [65 (9.9)]
Adjusted mean change (95% CI)	−0.17 (–0.31 to –0.02) [–1.9 (–3.4 to –0.2)]	−0.86 (–1.00 to –0.72) [–9.4 (–10.9 to –7.9)]
Adjusted placebo-subtracted mean change (SE)		−0.69 (0.10) [–7.5 (1.1)]
FPG, mg/dL [mmol/L]‡		*P* < 0.0001*
Baseline (SD)	180.5 (43.3) [10.02 (2.40)]	167.4 (43.3) [9.29 (2.40)]
Adjusted mean change (95% CI)	−0.8 (–7.6 to 6.0) [–0.04 (–0.42 to 0.33)]	−34.2 (–41.0 to –27.5) [–1.90 (–2.27 to –1.53)]
Adjusted placebo-subtracted mean change (SE)		−33.5 (4.9) [–1.86 (0.27)]
Body weight, kg‡		*P* < 0.0001*
Baseline (SD)	90.1 (16.2)	88.6 (17.6)
Adjusted mean change (95% CI)	−0.6 (–1.1 to –0.1)	−2.7 (–3.2 to –2.1)
Adjusted placebo-subtracted mean change (SE)		−2.1 (0.4)
Seated SBP at week 8, mmHg‡		*P* = 0.0250*
Baseline (SD)	136.3 (14.4)	134.7 (12.7)
Adjusted mean change (95% CI)	−0.3 (–2.6 to 2.1)	−4.0 (–6.4 to –1.7)
Adjusted placebo-subtracted mean change (SE)		−3.8 (1.7)
Proportion of patients with HbA_{1c} <7.0% (53 mmol/mol), %‡		*P* < 0.0001*
Proportion (95% CI)	11.1 (5.4 to 16.8)	31.8 (23.3 to 40.2)
Adjusted placebo-subtracted mean change (SE)		20.7 (5.06)
Fasting total cholesterol, mg/dL‡		*P* = 0.0091
Baseline (SD)	172.2 (35.6)	179.5 (45.3)
Week 24 (SD)	168.8 (34.1)	184.5 (43.4)
Adjusted mean change (95% CI)	−5.0 (–11.0 to 1.1)	6.4 (0.5 to 12.4)
Adjusted placebo-subtracted mean change (SE)		11.4 (4.3)
Fasting LDL cholesterol, mg/dL‡		*P* = 0.0030
Baseline (SD)	91.3 (29.6)	96.4 (38.4)
Week 24 (SD)	86.6 (28.1)	101.1 (39.4)
Adjusted mean change (95% CI)	−5.7 (–11.0 to –0.4)	5.6 (0.4 to 10.9)
Adjusted placebo-subtracted mean change (SE)		11.4 (3.8)
Fasting HDL cholesterol, mg/dL‡		*P* = 0.0172
Baseline (SD)	45.1 (10.5)	47.6 (12.3)
Week 24 (SD)	45.2 (10.9)	49.5 (12.2)
Adjusted mean change (95% CI)	−0.1 (–1.4 to 1.1)	2.1 (0.8 to 3.3)
Adjusted placebo-subtracted mean change (SE)		2.2 (0.9)
LDL/HDL ratio		*P* = 0.2008
Baseline (SD)	2.1 (0.9)	2.1 (0.9)
Week 24 (SD)	2.0 (0.8)	2.1 (0.9)
Adjusted mean change (95% CI)	−0.1 (–0.2 to 0.0)	0.0 (–0.1 to 0.2)
Adjusted placebo-subtracted mean change (SE)		0.1 (0.1)
Fasting triglycerides, mg/dL‡		*P* = 0.1755
Baseline (SD)	190.9 (148.1)	184.7 (127.5)
Week 24 (SD)	193.1 (115.5)	173.8 (99.1)
Adjusted mean change (95% CI)	3.9 (–13.2 to 20.9)	−12.6 (–29.4 to 4.2)
Adjusted placebo-subtracted mean change (SE)		−16.5 (12.1)
C-peptide, ng/mL‡		*P* = 0.1731
Baseline (SD)	2.50 (0.94)	2.51 (1.07)
Adjusted mean change (95% CI)	−0.04 (–0.16 to 0.07)	−0.16 (–0.27 to –0.04)
Adjusted placebo-subtracted mean change (SE)		−0.11 (0.08)

N is the number of patients in the full analysis set. †Longitudinal analysis. ‡LOCF. *Significant *P* value for primary end point tested at $\alpha = 0.050$ and key secondary end points tested sequentially at $\alpha = 0.050$. For all other variables, including changes from baseline in lipids and C-peptide, nominal *P* values are reported without significance testing. Logistic regression analysis of responses is based on the methodology of Zhang et al., with adjustment for baseline value (27).

occurred within the first 12 weeks of treatment. Two of these events required additional treatment. No patient was discontinued from study medication due to an event of genital infection. Events of urinary tract infection were reported by seven (6.4%) patients in each group (one man and six women receiving placebo and three men and four women receiving dapagliflozin). Three patients in the dapagliflozin group experienced 2 events of urinary tract infection for a total of 10 events. In the placebo group, five of the seven events of urinary tract infection were reported in the first half of the study as well as six of the seven events initially reported in the dapagliflozin group. Antimicrobial

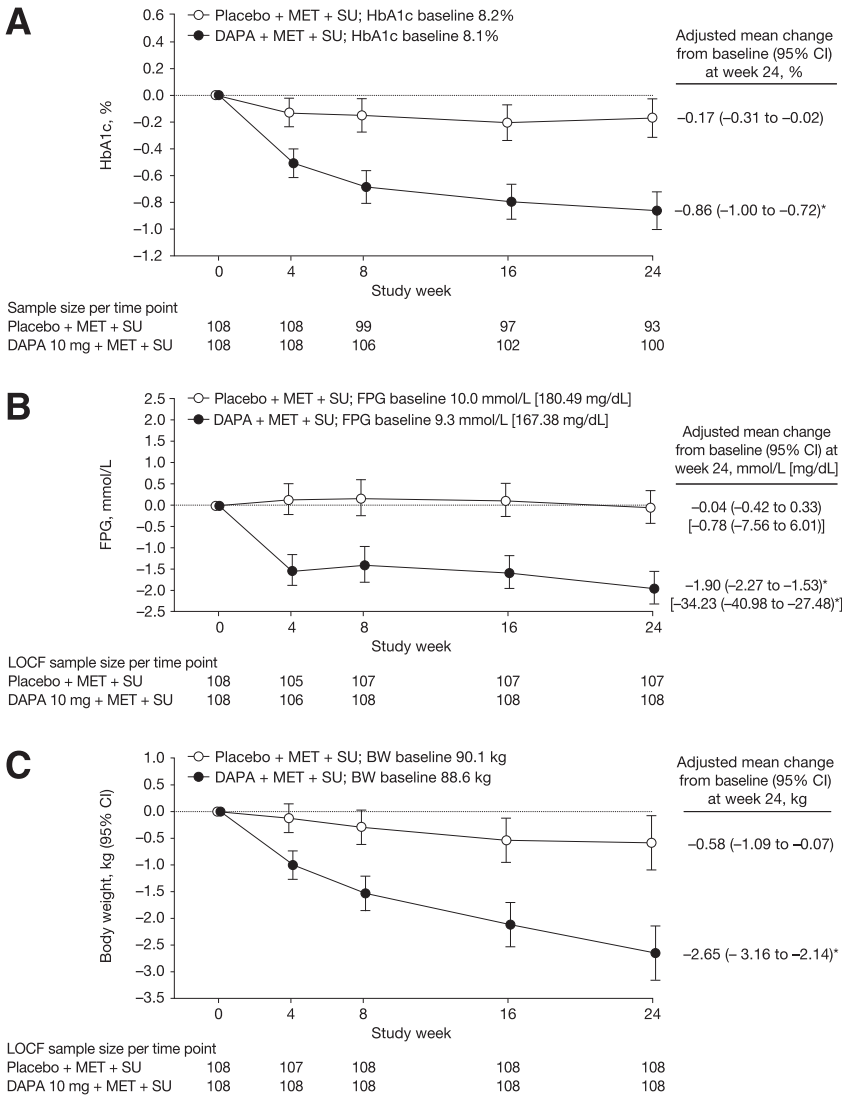

Figure 1—Change from baseline over 24 weeks in (*A*) HbA_{1c} (longitudinal repeated measurements), (*B*) FPG (ANCOVA, LOCF), and (*C*) body weight (ANCOVA, LOCF). Excluding data after rescue. *$P < 0.0001$ vs. placebo. DAPA, dapagliflozin; MET, metformin; SU, sulfonylurea.

treatment was administered for 7 of the 10 events in the dapagliflozin group and 6 of the 7 events in the placebo group. One patient in the dapagliflozin group was given additional treatment owing to an inadequate response to the initial treatment. No patient was discontinued from study medication because of a urinary tract infection event. One event of chronic pyelonephritis was observed in a female patient in the dapagliflozin group that was identified by sonograph while the patient was being investigated for chronic hematuria. The patient experienced no further symptoms and did not receive any specific treatment for the event.

One event of volume depletion was noted over the 24-week treatment period. This was an episode of orthostatic hypotension that resolved without recurrence and occurred in a patient treated with dapagliflozin.

Marked abnormalities of liver function tests were rare (one episode of elevated total bilirubin in a patient receiving dapagliflozin). One nonserious unspecified bladder neoplasm was reported (diagnosis at 3 months) in a female patient in the dapagliflozin group with hematuria at randomization and after 2 months. Approximately 6 months after start of treatment, the patient was diagnosed with bladder cancer.

CONCLUSIONS

Little information is available involving the concomitant use of three oral antidiabetic drugs in patients with type 2 diabetes, although thiazolidinediones and dipeptidyl peptidase-4 inhibitors have been shown to be effective as add-on treatments in patients inadequately controlled with metformin and sulfonylureas (7,18,19).

Dapagliflozin has been shown to be well tolerated and effective when administered as monotherapy or in combination with other antihyperglycemic medications (9–12,15,16,20). The safety and efficacy of dapagliflozin as part of a triple therapy with metformin and sitagliptin have been evaluated previously (13). In addition, preliminary analyses were performed to evaluate dapagliflozin in combination with metformin plus sulfonylurea (prespecified analyses with no multiplicity testing) and with metformin plus insulin (post hoc analyses) (20). The results indicated that dapagliflozin was effective as part of a triple therapy in improving glycemic control and reducing body weight in type 2 diabetes. This study evaluated the safety and efficacy of dapagliflozin administered as part of a triple therapy for patients with type 2 diabetes and inadequate glycemic control with metformin and sulfonylurea. In patients with inadequate glycemic control taking metformin plus a sulfonylurea, dapagliflozin resulted in a significant improvement in glycemic control (reductions in HbA_{1c} and FPG) and reduced body weight when compared with placebo. Similar results have been reported with other SGLT2 inhibitors when administered in combination with metformin and sulfonylurea (21,22). Consistent with the reported diuretic effects of dapagliflozin, seated SBP was also reduced with dapagliflozin compared with placebo. Type 2 diabetes is associated with an increased risk of cardiovascular disease (23), and the weight loss and BP reduction associated with dapagliflozin treatment could provide a significant cardiovascular benefit to patients with type 2 diabetes inadequately controlled with their current antihyperglycemic regimens. However, it should be noted that the effects on lipid parameters observed with dapagliflozin in this study (increases in total cholesterol, LDL cholesterol, and HDL cholesterol but no significant change in LDL vs. HDL cholesterol ratio or triglyceride levels) are consistent with pooled

Table 3—Summary of adverse events over 24 weeks

	Placebo (*N* = 109)	Dapagliflozin 10 mg/day (*N* = 109)
≥1 Adverse event	56 (51.4)	53 (48.6)
Adverse events leading to discontinuation	3 (2.8)	2 (1.8)
≥1 Serious adverse event	6 (5.5)	1 (0.9)
Deaths	0	0
Treatment-related adverse events	8 (7.3)	18 (16.5)
Hypoglycemia*	4 (3.7)	14 (12.8)
Adverse events with frequency ≥3% in any group (by MedDRA preferred term)		
Bronchitis	1 (0.9)	5 (4.6)
Urinary tract infection**	7 (6.4)	5 (4.6)
Hypertension	4 (3.7)	1 (0.9)
Adverse events of special interest		
Patients experiencing events of genital infection†	0	6 (5.5)
Men	0/60	1/46 (2.2)
Women	0/49	5/63 (7.9)
Patients experiencing events of urinary tract infection†	7 (6.4)	7 (6.4)
Men	1/60 (1.7)	3/46 (6.5)
Women	6/49 (12.2)	4/63 (6.3)
Renal impairment/failure‡	0	2 (1.8)
Orthostatic hypotension	0	1 (0.9)
Elevated liver tests	0	1 (0.9)
Elevated bilirubin >2× upper limit of normal	0	1 (0.9)

Data are *n* (%). *N* is the number of patients in the safety analysis set. *No major episodes of hypoglycemia were reported. **Events based on most common MedDRA preferred terms. †Reports were based on a predefined list of MedDRA terms. ‡All events of renal impairment/failure were decreased renal creatinine clearance.

data across the phase 2b/3 program (24).

Patients with type 2 diabetes have an increased susceptibility to asymptomatic bacteriuria, urinary tract infections, and genital infections (25). An increase in the growth of microbiological flora in the genital tract would not be unexpected under conditions of glucosuria such as induced through the inhibition of glucose reabsorption, and as is observed with all SGLT2 inhibitors, dapagliflozin was associated with a higher frequency of genital infection events. These were predominantly mild to moderate in intensity, responded to antibiotic treatment, and did not result in any study discontinuations. Urinary tract infections were reported at a similar frequency in both groups and were also primarily mild to moderate in intensity and responded to antimicrobial treatment. Clinicians prescribing dapagliflozin should advise their patients to report any symptoms suggestive of genital or urinary tract infections and assess suitability for treatment.

Dapagliflozin has a low intrinsic risk of hypoglycemia due to its insulin-independent mode of action. However, there may be a potential to increase this risk when added to therapies known to cause hypoglycemia such as sulfonylureas and insulin. In this trial, hypoglycemia was observed more frequently in patients receiving dapagliflozin compared with placebo when added to preexisting metformin and sulfonylurea treatment. An increase in the frequency of hypoglycemic events was also observed with other SGLT2 inhibitors when administered in combination with metformin and sulfonylurea (21, 22). In clinical practice, when using dapagliflozin in patients already on background sulfonylurea therapy, discontinuation or down-titration of sulfonylurea should be considered in patients at risk (26).

The results presented here indicate that triple combination therapy that includes dapagliflozin 10 mg/day with metformin and sulfonylurea is a suitable treatment option for patients with inadequate glycemic control on metformin and a sulfonylurea, with the added benefits of weight loss and BP reduction. Consistent with other SGLT2 inhibitors, dapagliflozin was associated with an increase in frequency of genital infections and increases in total, LDL, and HDL cholesterol that may necessitate additional lipid management. Further studies are underway to explore the effects of longer-term exposure to dapagliflozin.

Duality of Interest. This study was sponsored by Bristol-Myers Squibb and AstraZeneca. Medical writing assistance was provided by Karen Pemberton of PPSI (a PAREXEL company) and was funded by AstraZeneca. S.M. holds advisory board membership at Abbott, AstraZeneca, Bristol-Myers Squibb (BMS), Boehringer Ingelheim, Janssen, Merck Sharp & Dohme, Novo Nordisk, and Roche and is part of the speakers' bureau at Abbott, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Janssen, Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Roche, and Sanofi. K.B. holds advisory board membership at AstraZeneca, Boehringer Ingelheim, BMS, Eli Lilly, Merck, Novo Nordisk, Pfizer, Johnson & Johnson, and Takeda; is part of the speakers' bureau at AstraZeneca, Boehringer Ingelheim, BMS, Eli Lilly, Merck, and Novo Nordisk; and has performed clinical research for AstraZeneca, Boehringer Ingelheim, Merck, Novartis, Novo Nordisk, and Eli Lilly. K.R. is a full-time employee of AstraZeneca. A.G. is a full-time employee of Aptiv Solutions. S.P. is a full-time employee and stock holder of AstraZeneca. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. S.M. reviewed/edited the manuscript and contributed to the discussion. K.B., K.R., A.G., and S.P. researched data, reviewed/edited the manuscript, and contributed to the discussion. S.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented at the 49th Annual Meeting of the European Association for the Study of Diabetes, Barcelona, Spain, 23–27 September 2013.

References

1. Inzucchi SE, Bergenstal RM, Buse JB, et al.; American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012;35:1364–1379

2. Cook MN, Girman CJ, Stein PP, Alexander CM, Holman RR. Glycemic control continues to deteriorate after sulfonylureas are added to metformin among patients with type 2 diabetes. Diabetes Care 2005;28:995–1000

3. Cook MN, Girman CJ, Stein PP, Alexander CM. Initial monotherapy with either metformin or sulphonylureas often fails to achieve or maintain current glycaemic goals in patients with Type 2 diabetes in UK primary care. Diabet Med 2007;24:350–358

4. Dodd AH, Colby MS, Boye KS, Fahlman C, Kim S, Briefel RR. Treatment approach and HbA1c control among US adults with type 2 diabetes:

NHANES 1999-2004. Curr Med Res Opin 2009; 25:1605–1613
5. Harper W, Clement M, Goldenberg R, et al.; Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Pharmacologic management of type 2 diabetes. Can J Diabetes 2013;37(Suppl. 1):S61–S68
6. Riedel AA, Heien H, Wogen J, Plauschinat CA. Loss of glycemic control in patients with type 2 diabetes mellitus who were receiving initial metformin, sulfonylurea, or thiazolidinedione monotherapy. Pharmacotherapy 2007;27: 1102–1110
7. Hermansen K, Kipnes M, Luo E, Fanurik D, Khatami H, Stein P; Sitagliptin Study 035 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. Diabetes Obes Metab 2007;9:733–745
8. Valentine V. The role of the kidney and sodium-glucose cotransporter-2 inhibition in diabetes management. Clin Diabetes 2012;30:151–155
9. Bailey CJ, Gross JL, Pieters A, Bastien A, List JF. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. Lancet 2010;375:2223–2233
10. Bailey CJ, Gross JL, Hennicken D, Iqbal N, Mansfield TA, List JF. Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial. BMC Med 2013;11:43
11. Ferrannini E, Ramos SJ, Salsali A, Tang W, List JF. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. Diabetes Care 2010;33:2217–2224
12. Henry RR, Murray AV, Marmolejo MH, Hennicken D, Ptaszynska A, List JF. Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomised controlled trial. Int J Clin Pract 2012;66:446–456
13. Jabbour SA, Hardy E, Sugg J, Parikh S; Study 10 Group. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled study. Diabetes Care 2014;37:740–750
14. Nauck MA, Del Prato S, Meier JJ, et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. Diabetes Care 2011;34:2015–2022
15. Rosenstock J, Vico M, Wei L, Salsali A, List JF. Effects of dapagliflozin, an SGLT2 inhibitor, on HbA(1c), body weight, and hypoglycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy. Diabetes Care 2012;35:1473–1478
16. Wilding JP, Woo V, Rohwedder K, Sugg J, Parikh S; Dapagliflozin 006 Study Group. Dapagliflozin in patients with type 2 diabetes receiving high doses of insulin: efficacy and safety over 2 years. Diabetes Obes Metab 2014;16:124–136
17. Shao J, Zhong B. Last observation carry-forward and last observation analysis. Stat Med 2003;22:2429–2441
18. Rosenstock J, Sugimoto D, Strange P, Stewart JA, Soltes-Rak E, Dailey G. Triple therapy in type 2 diabetes: insulin glargine or rosiglitazone added to combination therapy of sulfonylurea plus metformin in insulin-naive patients. Diabetes Care 2006;29:554–559
19. Tran MT, Navar MD, Davidson MB. Comparison of the glycemic effects of rosiglitazone and pioglitazone in triple oral therapy in type 2 diabetes. Diabetes Care 2006;29:1395–1396
20. Jabbour S, Hardy E, DeBruin T, et al. Dapagliflozin as part of triple combination therapy helps reduce HbA1c and body weight in patients with type 2 diabetes (Abstract). Diabetes 2013; 62(Suppl. 1):A306
21. Häring HU, Merker L, Seewaldt-Becker E, et al.; EMPA-REG METSU Trial Investigators. Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care 2013;36:3396–3404
22. Wilding JP, Charpentier G, Hollander P, et al. Efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sulphonylurea: a randomised trial. Int J Clin Pract 2013;67:1267–1282
23. The DCCT Research Group. Weight gain associated with intensive therapy in the diabetes control and complications trial. Diabetes Care 1988;11:567–573
24. Hardy E, Ptaszynska A, DeBruin T, Johnsson E, Parikh S, List J. Dapagliflozin effects on the lipid profile of patients with type 2 diabetes mellitus (Abstract). Diabetes 2013;62(Suppl. 1): A310
25. Geerlings S, Fonseca V, Castro-Diaz D, List J, Parikh S. Genital and urinary tract infections in diabetes: impact of pharmacologically-induced glucosuria. Diabetes Res Clin Pract 2014;103: 373–381
26. Farxiga [package insert]. Princeton, NJ, Bristol-Myers Squibb, 2014
27. Zhang M, Tsiatis AA, Davidian M. Improving efficiency of inferences in randomized clinical trials using auxiliary covariates. Biometrics 2008;64:707–715