Initial Combination of Empagliflozin and Metformin in Patients With Type 2 Diabetes

Samy Hadjadj,[1] Julio Rosenstock,[2] Thomas Meinicke,[3] Hans J. Woerle,[4] and Uli C. Broedl[4]

Diabetes Care 2016;39:1718–1728 | DOI: 10.2337/dc16-0522

OBJECTIVE

This study compared the efficacy and safety of initial combinations of empagliflozin + metformin with empagliflozin and metformin monotherapy in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

The study randomized 1,364 drug-naïve patients (HbA_{1c} >7.5 to ≤12% [>58 to ≤108 mmol/mol]) for 24 weeks to empagliflozin 12.5 mg b.i.d. + metformin 1,000 mg b.i.d., empagliflozin 12.5 mg b.i.d. + metformin 500 mg b.i.d., empagliflozin 5 mg b.i.d + metformin 1,000 mg b.i.d., empagliflozin 5 mg b.i.d. + metformin 500 mg b.i.d., empagliflozin 25 mg q.d., empagliflozin 10 mg q.d., metformin 1,000 mg b.i.d., or metformin 500 mg b.i.d. The primary end point was change from baseline in HbA_{1c} at week 24.

RESULTS

At week 24, reductions in HbA_{1c} (mean baseline 8.6–8.9% [70–73 mmol/mol]) were −1.9 to −2.1% with empagliflozin + metformin twice-daily regimens, −1.4% with both empagliflozin once-daily regimens, and −1.2 to −1.8% with metformin twice-daily regimens. Reductions in HbA_{1c} were significantly greater with empagliflozin + metformin twice-daily regimens than with empagliflozin once-daily regimens ($P < 0.001$) and with metformin twice-daily regimens ($P < 0.01$). Reductions in weight at week 24 were significantly greater with empagliflozin + metformin twice-daily regimens (range −2.8 to −3.8 kg) than with metformin twice-daily regimens (−0.5 to −1.3 kg) ($P < 0.001$ for all). Adverse event (AE) rates were similar across groups (56.7–66.3%). No hypoglycemic AEs required assistance.

CONCLUSIONS

Initial combinations of empagliflozin + metformin for 24 weeks significantly reduced HbA_{1c} versus empagliflozin once daily and metformin twice daily, without increased hypoglycemia, reduced weight versus metformin twice daily, and were well tolerated.

Metformin is the recommended first-line pharmacological treatment for type 2 diabetes (1). Metformin acts mainly by reducing hepatic glucose production via inhibition of gluconeogenesis (2,3) and also increases glucose uptake in peripheral tissue (3). Metformin is associated with a low risk of hypoglycemia and is weight neutral or can lead to weight loss (1). However, as type 2 diabetes progresses, metformin monotherapy often fails to maintain glycemic control (1,4). In such cases, there is often a failure to intensify treatment as appropriate (5). In a retrospective

[1]Centre Hospitalier Universitaire Poitiers and INSERM CIC 1402, Poitiers, France
[2]Dallas Diabetes and Endocrine Center at Medical City, Dallas, TX
[3]Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany
[4]Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany

Corresponding author: Samy Hadjadj, samy.hadjadj@chu-poitiers.fr.

Received 10 March 2016 and accepted 18 July 2016.

Clinical trial reg. no. NCT01719003, clinicaltrials.gov.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc16-0522/-/DC1.

This article is featured in a podcast available at http://www.diabetesjournals.org/content/diabetes-core-update-podcasts.

cohort study of more than 81,000 patients with type 2 diabetes, the median time to the addition of another oral glucose-lowering agent after a patient exceeded his or her HbA_{1c} target ranged from 1.6 to 2.9 years (6). The reasons for this clinical inertia are unclear but likely include a reluctance to initiate more complex drug regimens (7).

Initial combination therapy with oral antidiabetes drugs with complementary modes of action may provide more robust and durable glucose-lowering efficacy compared with the traditional stepwise approach (8). A combination approach to first-line treatment is recommended by the American Diabetes Association/European Association for the Study of Diabetes and the Canadian Diabetes Association for patients whose HbA_{1c} is ≥9% (≥75 mmol/mol) or ≥8.5% (≥69 mmol/mol), respectively (1,9).

Most of the glucose filtered by the kidney is reabsorbed by the sodium glucose cotransporter 2 (SGLT2) (10). SGLT2 inhibitors act by reducing renal glucose reabsorption, thereby increasing urinary glucose excretion and reducing hyperglycemia (10). Empagliflozin is a potent and selective SGLT2 inhibitor (11). When used as an add-on to metformin in patients with type 2 diabetes, empagliflozin (10 mg and 25 mg q.d.) significantly reduced HbA_{1c}, fasting plasma glucose (FPG), and weight and was well tolerated, with a low risk of hypoglycemia (12).

This study was undertaken to compare the efficacy and safety of initial combinations of empagliflozin and metformin immediate release (IR) with those of empagliflozin and metformin IR monotherapy in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study Design

This was a Phase III, randomized, double-blind, parallel-group study conducted from October 2012 to December 2014 in 190 centers in 21 countries. The clinical trial protocol and amendments were approved by the institutional review boards, independent ethics committees, and competent authorities of the participating centers and complied with the Declaration of Helsinki in accordance with the International Conference on Harmonization Harmonized Tripartite Guideline for Good Clinical Practice. All subjects provided informed consent before participation.

Patients

This study enrolled adults with type 2 diabetes with BMI ≤45 kg/m^2 at screening who were drug-naïve (no oral antidiabetes therapy, glucagon-like peptide-1 analog, or insulin for ≥12 weeks before randomization). Before a protocol amendment, patients with HbA_{1c} >7% to ≤10% (>53 to ≤86 mmol/mol) at screening were eligible for randomized treatment and patients with HbA_{1c} >10% (>86 mmol/mol) at screening were eligible for open-label treatment. After the protocol amendment, patients with HbA_{1c} >7.5% to ≤12% (>58 to ≤108 mmol/mol) at screening were eligible for randomized treatment, and enrollment in the open-label arm was stopped; however, patients already enrolled in the open-label arm were allowed to complete the study. The increase in the HbA_{1c} inclusion threshold for randomized treatment was implemented so that the effects of initial therapy with empagliflozin + metformin in patients with high HbA_{1c} could be evaluated in a randomized controlled environment.

Exclusion criteria included uncontrolled hyperglycemia (plasma glucose >240 mg/dL [13.3 mmol/L] after an overnight fast during a 2-week placebo run-in, confirmed by a second measurement); contraindication to metformin according to the local label; renal impairment (estimated creatinine clearance rate <60 mL/min using the Cockcroft-Gault formula) or indication of liver disease (serum alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase >3 times the upper limit of normal) at screening or during the placebo run-in; treatment with antiobesity drugs within 3 months before consent; and any uncontrolled endocrine disorder except type 2 diabetes.

Interventions

After a 2-week placebo run-in period, eligible patients were randomized (1:1:1:1:1:1:1:1) to receive empagliflozin 12.5 mg b.i.d. + metformin 1,000 mg b.i.d., empagliflozin 12.5 mg b.i.d. + metformin 500 mg b.i.d., empagliflozin 5 mg b.i.d. + metformin 500 mg b.i.d., empagliflozin 5 mg b.i.d. + metformin 1,000 mg b.i.d., empagliflozin 10 mg q.d., empagliflozin 25 mg q.d., metformin 500 mg b.i.d., or metformin 1,000 mg b.i.d. for 24 weeks. Patients randomized to receive metformin 1,000 mg b.i.d. underwent dose escalation: 500 mg b.i.d. in the first week, increasing to 850 mg b.i.d. in the second week and to 1,000 mg b.i.d. in the third week; dose adjustment other than this was not permitted. Patients allocated to the open-label arm received empagliflozin 12.5 mg b.i.d. + 1,000 mg b.i.d. for 24 weeks.

Randomization was achieved using a computer-generated random sequence and an interactive voice and Web response system. Randomization was stratified by the following factors: HbA_{1c} (<8.5% [<69 mmol/mol] and ≥8.5% [≥69 mmol/mol]) at screening, renal function (estimated glomerular filtration rate [eGFR] ≤90 mL/min/1.73m^2 and ≥90 mL/min/1.73m^2 using the Modification of Diet in Renal Disease equation) at screening, and region (Europe, Asia, North America, Latin America). Study visits were scheduled at screening, at the start of the placebo run-in, and at weeks 0 (baseline), 6, 12, 18, and 24 of treatment. A follow-up visit occurred 7 days after the last intake of study drug.

Rescue medication could be initiated if, after an overnight fast, a patient had a confirmed blood glucose level >240 mg/dL (13.3 mmol/L) between weeks 1 and 12 or >200 mg/dL (11.1 mmol/L) between weeks 12 and 24. The use of other SGLT2 inhibitors and metformin was not permitted. In cases of hypoglycemia, rescue medication was to be reduced in dose or discontinued. If hyper- or hypoglycemia could not be controlled, the subject was discontinued from the trial.

End Points and Assessments

The primary end point was change from baseline in HbA_{1c} at week 24. Key secondary end points were changes from baseline in FPG and weight at week 24. Exploratory efficacy end points included the proportion of patients with HbA_{1c} ≥7% (≥53 mmol/mol) at baseline who had HbA_{1c} <7% (<53 mmol/mol) at week 24, the proportion of patients with HbA_{1c} ≥7% (≥53 mmol/mol) at baseline who had HbA_{1c} <6.5% (<48 mmol/mol) at week 24 (defined post hoc), the proportion of patients with >5% reduction in weight at week 24 (defined post hoc), and changes from

baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP) at week 24.

Safety end points included clinical laboratory parameters and adverse events (AEs), with preferred terms coded according to the Medical Dictionary for Drug Regulatory Activities (MedDRA) version 17.1. AEs included all events with an onset after the first dose and up to 7 days after the last dose of trial medication. Confirmed hypoglycemic AEs, defined as AEs with plasma glucose ≤70 mg/dL (3.9 mmol/L) and/or requiring assistance, were identified by direct plasma glucose measurements and by home blood glucose monitoring performed by the patient. Other predefined AEs of special interest included events consistent with urinary tract infection (UTI), genital infection, and volume depletion, identified using prospectively defined search categories based on 67, 87, and 8 MedDRA preferred terms, respectively. AEs related to increased urination were assessed based on a post hoc search for the MedDRA preferred terms pollakiuria, polyuria, and nocturia.

Statistical Analysis

The primary analysis was a restricted maximum likelihood–based mixed-model repeated-measures (MMRM) approach assessing changes from baseline in HbA_{1c} at week 24, with treatment, baseline renal function, region, visit, and visit by treatment as fixed effects, and baseline HbA_{1c} as a linear covariate. The analysis was performed on the full analysis set (FAS) (randomized patients treated with ≥1 dose of study drug who had a baseline and ≥1 on-treatment HbA_{1c} assessment) using observed cases (OC). Values observed after a patient started glucose-lowering rescue therapy were set to missing. A sample size of 168 patients per group was required to provide power of 89% to detect a 0.5% treatment difference in HbA_{1c} between empagliflozin + metformin and the individual components, assuming a dropout rate of 2%.

A hierarchical testing procedure was used, beginning with a test for superiority of combination treatment versus the corresponding empagliflozin once-daily regimens and metformin twice-daily doses in change from baseline in HbA_{1c} at week 24. Null/alternative hypotheses were grouped into dose levels (empagliflozin 5 mg b.i.d. + metformin 1,000 mg b.i.d., empagliflozin 5 mg b.i.d. + metformin 500 mg b.i.d., empagliflozin 12.5 mg b.i.d. + metformin 1,000 mg b.i.d., and empagliflozin 12.5 mg b.i.d. + metformin 500 mg b.i.d.). Two hypotheses were tested within each dose level: one tested for superiority of the empagliflozin + metformin combination versus the empagliflozin component, and the other tested whether the combination was superior to the metformin component. The two hypotheses were tested simultaneously, each at the level of $\alpha = 0.05$ (two-sided). If all the steps in the hierarchical testing above were successful, noninferiority testing of change from baseline in HbA_{1c} at week 24 with empagliflozin 25 mg q.d. versus metformin 1,000 mg b.i.d. and empagliflozin 10 mg q.d. versus metformin 1,000 mg b.i.d. was to be performed at the level of $\alpha = 0.025$ (one-sided). If all the steps in the noninferiority testing were successful, then change from baseline to week 24 in FPG and then change from baseline to week 24 in weight (combination treatment vs. metformin twice daily only) were to be analyzed using the same hierarchical testing procedure as for the primary analysis. The baseline value for the end point in question was included as a linear covariate.

Sensitivity analyses of the primary end point were performed using the per protocol set (patients in the FAS without important protocol violations) and FAS completers (patients in the FAS who completed 23 ± 1 weeks' treatment); the same model as for the primary analysis was used. The primary end point at week 24 was also analyzed in the FAS (last observation carried forward) using an ANCOVA model with treatment, baseline renal function, and region as fixed effects and baseline HbA_{1c} as a linear covariate. Categorical changes in HbA_{1c} were analyzed using logistic regression in the FAS with noncompleters considered failure imputation.

Efficacy analyses in the open-label group were descriptive and based on OC.

Safety and lipid parameters were analyzed in the treated set (patients who received ≥1 dose of study drug) and were descriptive.

RESULTS

Patient Disposition

Of 1,364 patients who were randomized, 1,327 were treated and had a baseline and one or more on-treatment HbA_{1c} value, comprising the FAS. Overall, 90.8% of patients who were randomized and treated completed the treatment period. Baseline characteristics were balanced across the randomized treatment groups (Table 1). An additional 53 patients with HbA_{1c} >10% (>86 mmol/mol) were treated with open-label empagliflozin 12.5 mg b.i.d. + 1,000 mg b.i.d., and 49 (92.5%) completed the treatment period (Supplementary Fig. 1).

Efficacy

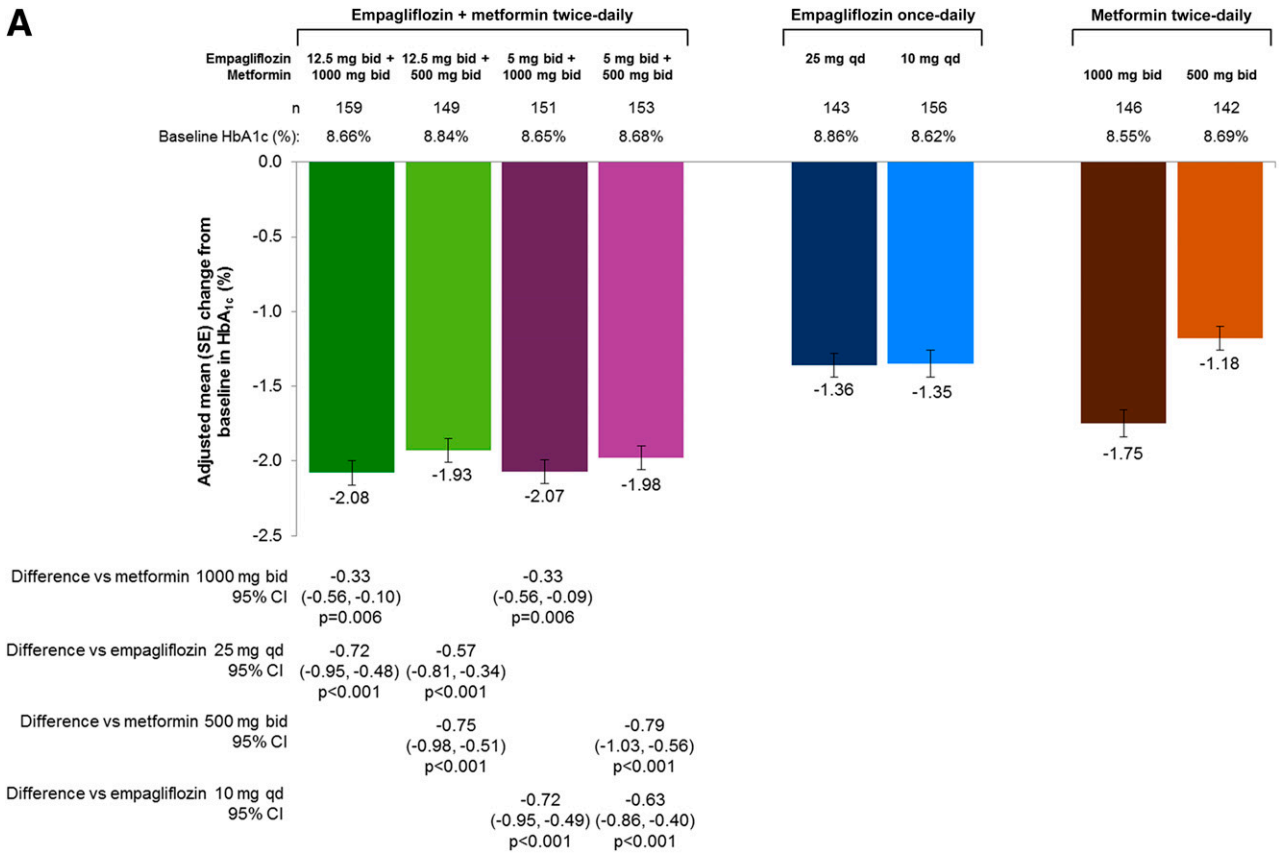
Glycemic Control in Randomized Groups

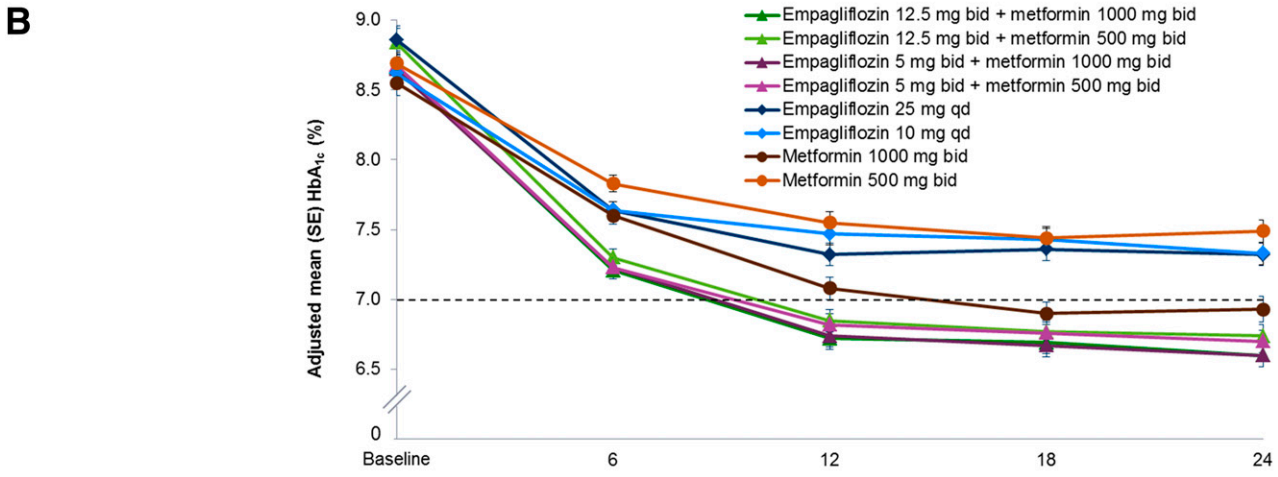
At week 24, pronounced reductions from baseline in HbA_{1c} (mean baseline 8.55–8.86% [70–73 mmol/mol]) were observed in all randomized treatment groups (Fig. 1*A*). Compared with empagliflozin once-daily regimens, the adjusted mean differences in changes from baseline with empagliflozin + metformin twice daily ranged from −0.57 to −0.72% (−6.2 to −7.9 mmol/mol; $P < 0.001$) and compared with metformin twice daily ranged from −0.33 to −0.79% (−3.6 to −8.6 mmol/mol; $P < 0.001$). Adjusted mean HbA_{1c} over the treatment period is shown in Fig. 1*B*. At week 24, adjusted mean HbA_{1c} values with empagliflozin + metformin twice daily ranged from 6.6% (49 mmol/mol) with empagliflozin 5 mg b.i.d. or 12.5 mg b.i.d. + metformin 1,000 mg b.i.d. to 6.7% (50 mmol/mol) with empagliflozin 12.5 mg b.i.d. + metformin 500 mg b.i.d. Values were 7.3% (57 mmol/mol) and 7.3% (56 mmol/mol) for empagliflozin 10 mg q.d. and 25 mg q.d., respectively, and 7.5% (58 mmol/mol) and 6.9% (52 mmol/mol) for metformin 500 mg and 1,000 mg b.i.d., respectively (Fig. 1*B*). The results of sensitivity analyses of changes in HbA_{1c} were consistent with the primary analysis (Supplementary Table 1). Significantly greater proportions of randomized patients with HbA_{1c} ≥7% (≥53 mmol/mol) at baseline reached HbA_{1c} <7% (<53 mmol/mol) and HbA_{1c} <6.5% (<48 mmol/mol) at week 24 with empagliflozin + metformin twice daily than with empagliflozin once daily or metformin twice daily (Fig. 1*C* and Supplementary Fig 2). Empagliflozin did not achieve noninferiority versus metformin 1,000 mg b.i.d. in changes from baseline in HbA_{1c} at

Table 1—Patient demographics and baseline characteristics

Parameter	Empagliflozin 12.5 mg b.i.d. + metformin 1,000 mg b.i.d. (*n* = 169)	Empagliflozin 12.5 mg b.i.d. + metformin 500 mg b.i.d. (*n* = 165)	Empagliflozin 5 mg b.i.d. + metformin 1,000 mg b.i.d. (*n* = 167)	Empagliflozin 5 mg b.i.d. + metformin 500 mg b.i.d. (*n* = 161)	Empagliflozin 25 mg q.d. (*n* = 164)	Empagliflozin 10 mg q.d. (*n* = 169)	Metformin 1,000 mg b.i.d. (*n* = 164)	Metformin 500 mg b.i.d. (*n* = 168)	Open-label empagliflozin 12.5 mg b.i.d. + metformin 1,000 mg b.i.d. (*n* = 53)
Sex									
Male	88 (52.1)	105 (63.6)	99 (59.3)	97 (60.2)	83 (50.6)	97 (57.4)	92 (56.1)	86 (51.2)	41 (77.4)
Female	81 (47.9)	60 (36.4)	68 (40.7)	64 (39.8)	81 (49.4)	72 (42.6)	72 (43.9)	82 (48.8)	12 (22.6)
Age (years)	53.6 ± 10.7	51.0 ± 10.7	52.3 ± 11.3	52.2 ± 11.7	53.3 ± 10.7	53.1 ± 10.7	51.6 ± 10.8	53.4 ± 10.9	50.3 ± 10.0
Race									
White	94 (55.6)	86 (52.1)	93 (55.7)	88 (54.7)	97 (59.1)	100 (59.2)	95 (57.9)	93 (55.4)	39 (73.6)
Asian	39 (23.1)	40 (24.2)	39 (23.4)	39 (24.2)	35 (21.3)	39 (23.1)	35 (21.3)	43 (25.6)	12 (22.6)
American Indian/Alaska Native	29 (17.2)	30 (18.2)	27 (16.2)	27 (16.8)	24 (14.6)	23 (13.6)	27 (16.5)	22 (13.1)	0
Black/African American	7 (4.1)	9 (5.5)	7 (4.2)	7 (4.3)	8 (4.9)	7 (4.1)	7 (4.3)	10 (6.0)	2 (3.8)
Native Hawaiian/Pacific Islander	0	0	1 (0.6)	0	0	0	0	0	0
Time since diagnosis									
≤1 year	98 (58.0)	87 (52.7)	98 (58.7)	95 (59.0)	90 (54.9)	82 (48.5)	90 (54.9)	101 (60.1)	19 (35.8)
>1 to ≤5 years	45 (26.6)	44 (26.7)	40 (24.0)	48 (29.8)	49 (29.9)	61 (36.1)	48 (29.3)	44 (26.2)	20 (37.7)
>5 to ≤10 years	16 (9.5)	21 (12.7)	20 (12.0)	15 (9.3)	21 (12.8)	17 (10.1)	16 (9.8)	19 (11.3)	8 (15.1)
>10 years	10 (5.9)	13 (7.9)	9 (5.4)	3 (1.9)	4 (2.4)	9 (5.3)	10 (6.1)	4 (2.4)	6 (11.3)
Weight (kg)	83.8 ± 19.8	82.9 ± 18.7	83.0 ± 19.1	82.3 ± 19.2	83.1 ± 20.3	83.8 ± 19.8	83.7 ± 20.1	82.7 ± 21.2	93.7 ± 18.9
BMI (kg/m^2)	30.4 ± 5.3	30.2 ± 5.2	30.5 ± 5.0	30.1 ± 5.3	30.6 ± 5.9	30.3 ± 5.2	30.5 ± 5.9	30.3 ± 5.8	31.7 ± 5.5
HbA_{1c} (%)	8.66 ± 1.14	8.84 ± 1.31	8.65 ± 1.23	8.68 ± 1.26	8.86 ± 1.29	8.62 ± 1.24	8.58 ± 1.13	8.69 ± 1.04	11.46 ± 1.57
HbA_{1c} (mmol/mol)	71 ± 12.5	73 ± 14.3	71 ± 13.4	71 ± 13.8	73 ± 14.1	71 ± 13.6	70 ± 12.4	71 ± 11.4	102 ± 17.1
FPG (mmol/L)	9.3 ± 2.3	9.5 ± 2.4	9.1 ± 2.3	9.2 ± 2.2	9.8 ± 2.7	9.4 ± 2.2	9.4 ± 2.7	9.6 ± 2.2	14.6 ± 4.1
SBP (mmHg)	127.0 ± 13.7	127.2 ± 14.5	127.2 ± 13.8	126.3 ± 13.0	128.2 ± 15.8	128.4 ± 14.6	128.6 ± 15.5	127.9 ± 14.0	130.9 ± 12.1
DBP (mmHg)	78.5 ± 8.1	79.2 ± 9.1	78.3 ± 9.1	78.4 ± 8.6	79.3 ± 9.4	79.0 ± 9.6	79.1 ± 9.3	78.5 ± 8.6	81.8 ± 8.8
eGFR*	92.3 ± 19.2	94.9 ± 20.9	93.6 ± 21.9	93.0 ± 20.5	91.7 ± 19.5	94.0 ± 21.5	93.2 ± 20.2	90.9 ± 19.4	95.5 ± 20.8

Data are *n* (%) or mean ± SD in the FAS (patients who received ≥1 dose of study drug and had a baseline HbA_{1c} value). Patients in the open-label group had HbA_{1c} >10% at baseline. *Calculated as mL/min/1.73 m^2 by the Modification of Diet in Renal Disease equation.





Analyzed patients	Baseline	6	12	18	24
Empagliflozin 12.5 mg + metformin 1000 mg bid	169	168	162	159	159
Empagliflozin 12.5 mg + metformin 500 mg bid	165	164	156	153	149
Empagliflozin 5 mg + metformin 1000 mg bid	167	166	160	158	151
Empagliflozin 5 mg + metformin 500 mg bid	161	159	159	156	153
Empagliflozin 25 mg qd	163	160	155	144	143
Empagliflozin 10 mg qd	169	167	167	160	156
Metformin 1000 mg bid	162	160	147	148	146
Metformin 500 mg bid	167	166	155	149	142

Figure 1—Changes in HbA_{1c}. *A*: Change from baseline in HbA_{1c} at week 24 in randomized groups (MMRM in the FAS using OC). *B*: HbA_{1c} over 24 weeks in randomized groups (MMRM, FAS, OC). *C*: Percentage of patients with $HbA_{1c} \geq 7\%$ at baseline who had $HbA_{1c} < 7\%$ at week 24 in randomized groups (FAS; logistic regression with noncompleters considered failure). *D*: HbA_{1c} over 24 weeks in the open-label group (descriptive statistics, OC).

week 24 (adjusted mean difference vs. metformin 1,000 mg b.i.d.: empagliflozin 25 mg, 0.39% [4.3 mmol/mol], $P = 0.625$; empagliflozin 10 mg, 0.40% [4.4 mmol/mol], $P = 0.656$). Owing to failed non-inferiority testing in the hierarchical sequence, the subsequent analyses for FPG and weight are considered exploratory.

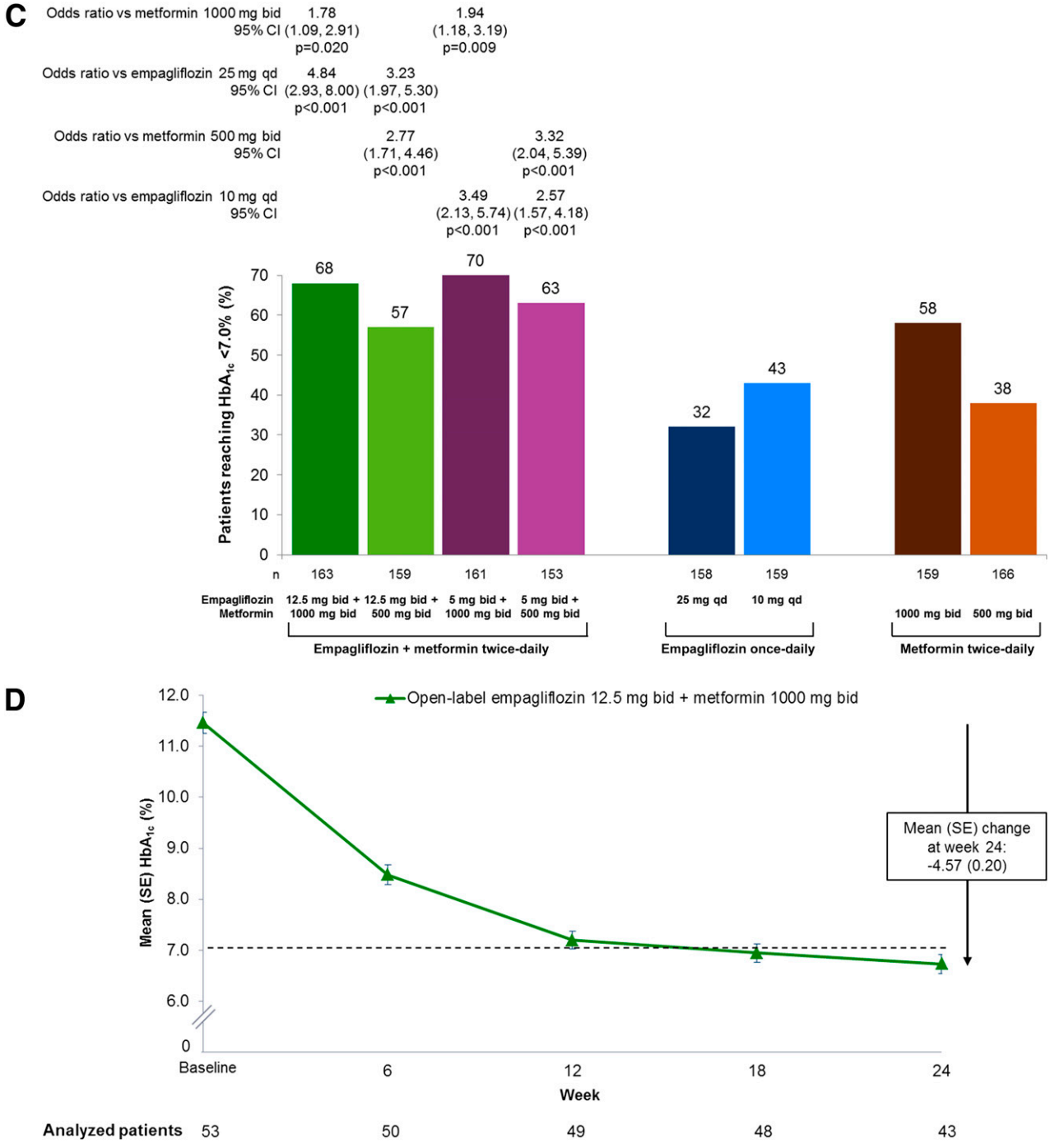


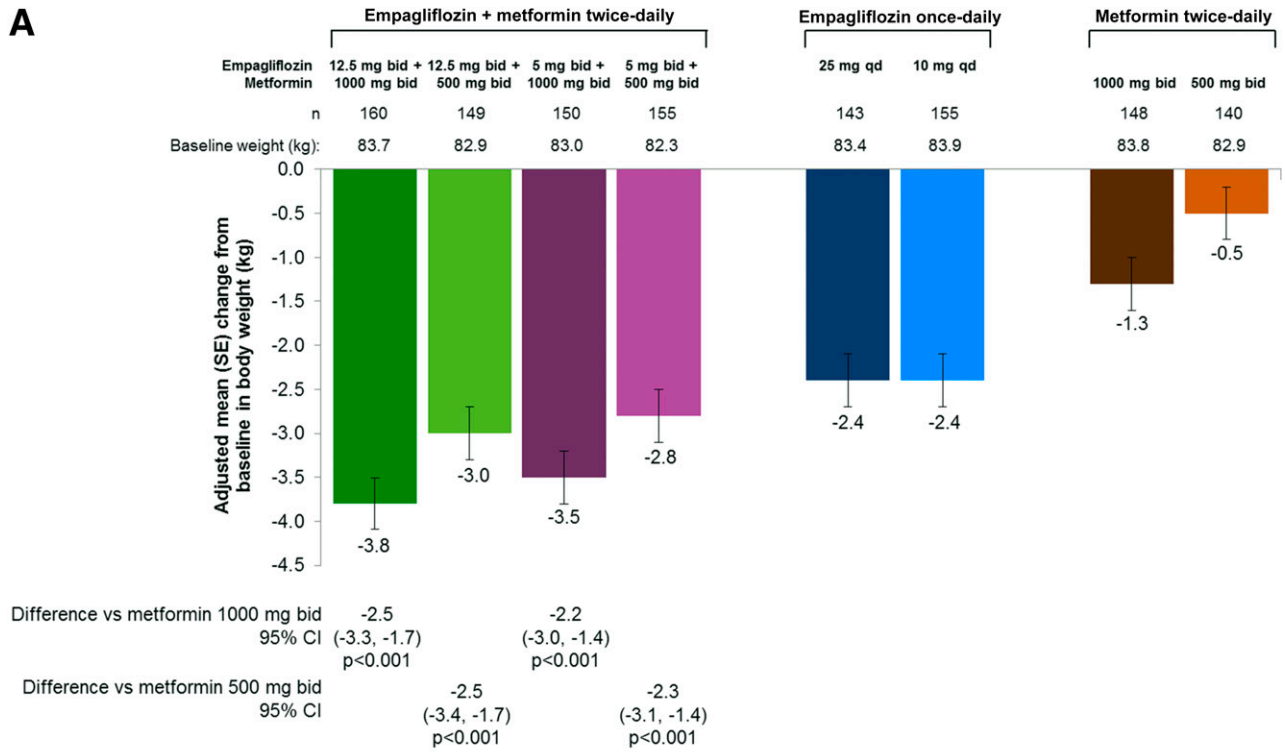
Figure 1—*Continued*.

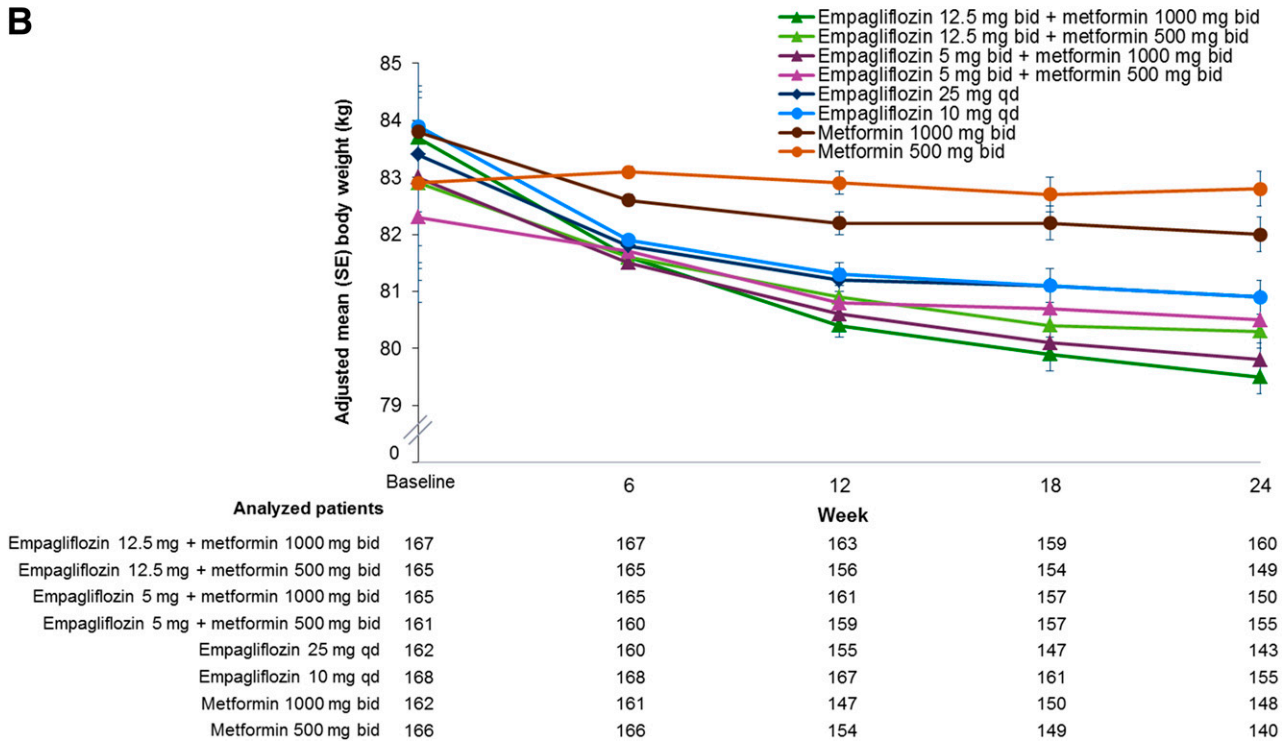
In the randomized treatment groups, empagliflozin + metformin twice daily significantly reduced FPG compared with empagliflozin once-daily and metformin twice-daily regimens at week 24 (Supplementary Fig 3*A*). Adjusted mean differences in changes from baseline with empagliflozin + metformin twice-daily compared with empagliflozin once-daily regimens ranged from −0.7 to −1.3 mmol/L ($P < 0.001$; nonconfirmatory) and compared with metformin twice-daily regimens ranged from −0.9 to −1.6 mmol/L ($P < 0.001$). Adjusted mean FPG over the treatment period is shown in Supplementary Fig 3*B*.

Rescue medication was taken by one patient (0.6%) in each of the groups on empagliflozin + metformin twice daily compared with six (3.7%) on empagliflozin 25 mg q.d., three (1.8%) on empagliflozin 10 mg q.d., seven (4.3%) on metformin 1,000 mg b.i.d., and nine (5.4%) on metformin 500 mg b.i.d.

Body Weight in Randomized Groups

In the randomized treatment groups, there was a pronounced change from baseline in weight at week 24 with empagliflozin + metformin twice-daily regimens (range −2.8 to −3.8 kg) that appeared to be additive, given the changes in weight observed with empagliflozin once daily (−2.4 kg for both regimens) and the small





Analyzed patients					
Empagliflozin 12.5 mg + metformin 1000 mg bid	167	167	163	159	160
Empagliflozin 12.5 mg + metformin 500 mg bid	165	165	156	154	149
Empagliflozin 5 mg + metformin 1000 mg bid	165	165	161	157	150
Empagliflozin 5 mg + metformin 500 mg bid	161	160	159	157	155
Empagliflozin 25 mg qd	162	160	155	147	143
Empagliflozin 10 mg qd	168	168	167	161	155
Metformin 1000 mg bid	162	161	147	150	148
Metformin 500 mg bid	166	166	154	149	140

Figure 2—Changes in weight. *A*: Change from baseline in weight at week 24 in randomized groups (MMRM in the FAS using OC). *B*: Weight over 24 weeks in randomized groups (MMRM, FAS, OC). *C*: Percentage of patients with >5% reduction in weight at week 24 in randomized groups (FAS; logistic regression with noncompleters considered failure).

changes observed with metformin twice-daily regimens (range −0.5 to −1.3 kg) (Fig. 2*A*). Adjusted mean differences in changes from baseline with empagliflozin + metformin twice-daily regimens compared with metformin twice-daily regimens ranged from −2.2 to −2.5 kg ($P < 0.001$; nonconfirmatory). Adjusted mean weight over the treatment period is shown in Fig. 2*B*. A significantly greater proportion of patients achieved a >5% reduction in weight with empagliflozin + metformin twice-daily than with metformin twice-daily regimens at week 24 (Fig. 2*C*).

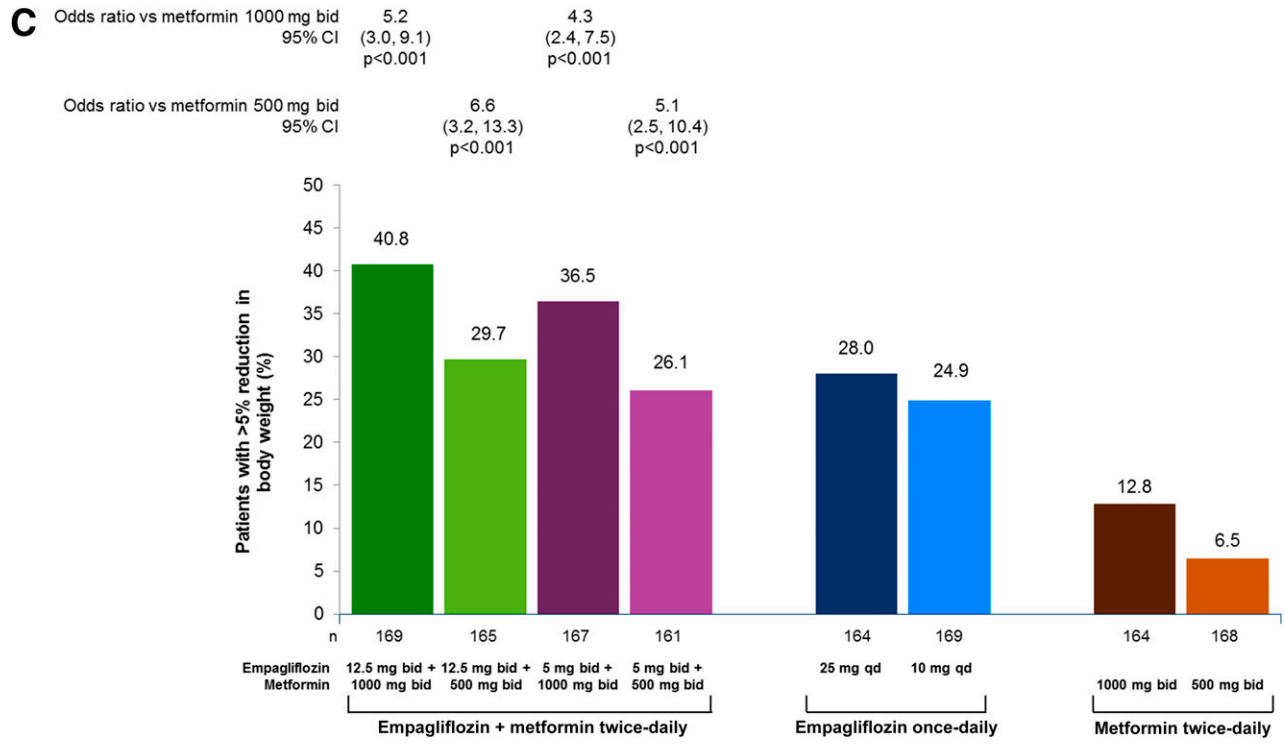


Figure 2—*Continued*.

BP in Randomized Groups

Changes from baseline in BP at week 24 in the randomized treatment groups are reported in Supplementary Table 2. Reductions from baseline in SBP (mean baseline 126.3 mmHg) at week 24 ranged from −2.2 to −3.2 mmHg with empagliflozin + metformin twice-daily regimens, −2.1 to −2.3 mmHg with empagliflozin once-daily regimens, and −0.2 to 0.8 mmHg with metformin twice-daily regimens. Empagliflozin + metformin twice daily significantly reduced SBP compared with metformin twice daily but not compared with empagliflozin once-daily regimens; adjusted mean differences in changes from baseline with empagliflozin + metformin twice daily compared with metformin twice daily ranged from −2.8 to −4.0 mmHg ($P < 0.05$). Reductions from baseline in DBP (mean baseline 78.2–79.4 mmHg) at week 24 ranged from −1.6 to −1.9 mmHg with empagliflozin + metformin twice daily, −1.0 to −1.7 mmHg with empagliflozin once daily, and 0 to 0.6 mmHg with metformin twice-daily regimens. Empagliflozin + metformin twice daily significantly reduced DBP compared with metformin twice daily but not compared with empagliflozin once-daily regimens. The adjusted mean differences in changes from baseline with empagliflozin + metformin twice daily compared with metformin twice daily ranged from −1.9 to −2.3 mmHg ($P < 0.05$).

Open-Label Treatment Group

HbA_{1c} over 24 weeks in the open-label treatment group (empagliflozin 12.5 mg b.i.d. + 1,000 mg b.i.d.) is shown in Fig. 1*D*. Mean HbA_{1c} was reduced from 11.5% (102 mmol/mol) at baseline to 6.7% (50 mmol/mol) at week 24. At week 24, 52.8% of patients in the open-label treatment group had HbA_{1c} <7%. Four (7.5%) patients in the open-label treatment group received glucose-lowering rescue medication.

Safety

The proportion of randomized patients with one or more AE was similar across all randomized treatment groups (Table 2), and 95% of randomized patients with one or more AE reported only events of mild or moderate intensity. Similar proportions of patients discontinued because of AEs across the randomized treatment groups. No patients died. The proportion of patients with confirmed hypoglycemic AEs was low in all randomized treatment groups (0–1.8%).

Events consistent with UTI were reported in 5.9–12.4% of patients across the randomized treatment groups (Table 2) and were reported in a greater proportion of female patients (12.9–23.0%) than male patients (0.0–5.6%) in all groups. None of these events led to hospitalization. Two cases of acute pyelonephritis were reported: one in the empagliflozin 5 mg b.i.d. + metformin 1,000 mg b.i.d. group and one in the empagliflozin 25 mg q.d. group; both events were mild in intensity, were resolved with antibiotics, and did not lead to hospitalization or discontinuation of study drug. Chronic pyelonephritis was reported in one patient in the metformin 500 mg b.i.d. group; this event was mild in intensity and did not lead to discontinuation of study drug. Events consistent with genital infection were reported in 1.8–6.4% of patients across the randomized treatment groups (Table 2) and were reported in a greater proportion of female patients (1.5–8.2%) than in male patients (0.0–6.0%). The proportion of patients with increased urination and volume depletion was low across the randomized treatment groups (Table 2). There were no episodes of diabetic ketoacidosis.

Laboratory measurements are presented in Supplementary Table 3. Hematocrit

Table 2—Summary of AEs

	Empagliflozin 12.5 mg b.i.d. + metformin 1,000 mg b.i.d. (*n* = 170)	Empagliflozin 12.5 mg b.i.d. + metformin 500 mg b.i.d. (*n* = 170)	Empagliflozin 5 mg b.i.d. + metformin 1,000 mg b.i.d. (*n* = 171)	Empagliflozin 5 mg b.i.d. + metformin 500 mg b.i.d. (*n* = 169)	Empagliflozin 25 mg q.d. (*n* = 167)	Empagliflozin 10 mg q.d. (*n* = 172)	Metformin 1,000 mg b.i.d. (*n* = 170)	Metformin 500 mg b.i.d. (*n* = 171)	Open-label empagliflozin 12.5 mg b.i.d. + metformin 1,000 mg b.i.d. (*n* = 53)
≥1 AE(s)	104 (61.2)	110 (64.7)	97 (56.7)	112 (66.3)	99 (59.3)	108 (62.8)	108 (63.5)	101 (59.1)	31 (58.5)
≥1 drug-related* AE(s)	35 (20.6)	23 (13.5)	23 (13.5)	17 (10.1)	16 (9.6)	26 (15.1)	27 (15.9)	13 (7.6)	8 (15.1)
≥1 AE(s) leading to treatment discontinuation	6 (3.5)	5 (2.9)	4 (2.3)	3 (1.8)	4 (2.4)	3 (1.7)	5 (2.9)	5 (2.9)	0
≥1 serious AE(s)	2 (1.2)	6 (3.5)	3 (1.8)	2 (1.2)	3 (1.8)	1 (0.6)	3 (1.8)	3 (1.8)	2 (3.8)
Deaths	0	0	0	0	0	0	0	0	0
AEs with a frequency of ≥5% in any randomized group (by MedDRA preferred term)									
UTI	18 (10.6)	17 (10.0)	12 (7.0)	9 (5.3)	13 (7.8)	12 (7.0)	14 (8.2)	12 (7.0)	0
Upper respiratory tract infection	4 (2.4)	5 (2.9)	8 (4.7)	4 (2.4)	7 (4.2)	5 (2.9)	5 (2.9)	10 (5.8)	3 (5.7)
Dyslipidemia	8 (4.7)	6 (3.5)	8 (4.7)	15 (8.9)	11 (6.6)	15 (8.7)	8 (4.7)	7 (4.1)	2 (3.8)
Dizziness	6 (3.5)	9 (5.3)	4 (2.3)	5 (3.0)	3 (1.8)	4 (2.3)	4 (2.4)	7 (4.1)	3 (5.7)
Diarrhea	12 (7.1)	6 (3.5)	5 (2.9)	9 (5.3)	6 (3.6)	2 (1.2)	24 (14.1)	6 (3.5)	4 (7.5)
Confirmed hypoglycemic AE(s)†	3 (1.8)	3 (1.8)	1 (0.6)	0	1 (0.6)	1 (0.6)	2 (1.2)	0	1 (1.9)
Events requiring assistance	0	0	0	0	0	0	0	0	0
Events consistent with UTI‡	21 (12.4)	19 (11.2)	13 (7.6)	10 (5.9)	14 (8.4)	13 (7.6)	17 (10.0)	14 (8.2)	1 (1.9)
Male	5 (5.6)	5 (4.6)	4 (4.0)	0	3 (3.6)	2 (2.0)	2 (2.1)	1 (1.1)	0
Female	16 (19.8)	14 (23.0)	9 (12.9)	10 (14.9)	11 (13.3)	11 (15.3)	15 (19.7)	13 (15.7)	1 (1.9)
Events consistent with genital infection§	5 (2.9)	9 (5.3)	5 (2.9)	3 (1.8)	8 (4.8)	11 (6.4)	5 (2.9)	4 (2.3)	2 (3.8)
Male	0	4 (3.7)	3 (3.0)	2 (2.0)	3 (3.6)	6 (6.0)	0	0	2 (3.8)
Female	5 (6.2)	5 (8.2)	2 (2.9)	1 (1.5)	5 (6.0)	5 (6.9)	5 (6.6)	4 (4.8)	0
Increased urination									
Pollakiuria	0	1 (0.6)	0	4 (2.4)	2 (1.2)	0	1 (0.6)	0	0
Polyuria	1 (0.6)	0	1 (0.6)	0	1 (0.6)	2 (1.2)	0	0	0
Nocturia	0	0	0	0	0	2 (1.2)	0	1 (0.6)	0
Events consistent with volume depletion¶	3 (1.8)	0	1 (0.6)	2 (1.2)	1 (0.6)	0	2 (1.2)	0	1 (1.9)
Dehydration	1 (0.6)	0	0	0	0	0	1 (0.6)	0	0
Hypotension	1 (0.6)	0	0	1 (0.6)	1 (0.6)	0	1 (0.6)	0	1 (1.9)
Orthostatic hypotension	1 (0.6)	0	1 (0.6)	0	0	0	0	0	0
Syncope	0	0	0	1 (0.6)	0	0	1 (0.6)	0	0

Data are *n* (%) in the treated set (patients treated with ≥1 dose of study drug). *As reported by the investigator; †Plasma glucose ≤3.9 mmol/L and/or assistance required; ‡Based on 67 MedDRA preferred terms; §Based on 87 MedDRA preferred terms; ¶Based on 8 MedDRA preferred terms.

increased from baseline in patients treated with combination therapy or empagliflozin and decreased in patients treated with metformin. Uric acid levels decreased in the combination therapy and empagliflozin groups and increased in the metformin groups. No pattern was observed in changes in eGFR. Small increases in total cholesterol and HDL cholesterol were observed in all treatment groups, except for small decreases in total cholesterol with empagliflozin 12.5 mg b.i.d. + metformin 1,000 mg b.i.d. and metformin 1,000 mg b.i.d. Small increases in LDL cholesterol were observed with empagliflozin and with empagliflozin 12.5 mg b.i.d. + metformin 500 mg b.i.d. but not in other groups. Triglycerides increased with empagliflozin 5 mg b.i.d. + metformin 500 mg b.i.d., empagliflozin 25 mg q.d., and metformin twice daily and decreased in all other treatment groups. There were no clinically relevant changes in electrolytes in any treatment group.

In the open-label treatment group, one patient (1.9%) had a confirmed hypoglycemic AE. No confirmed hypoglycemic events required assistance or led to study discontinuation. One patient (1.9%) had an event consistent with UTI, and two patients (3.8%) had an event consistent with genital infection. Volume depletion (hypotension) occurred in one patient (1.9%) (Table 2).

CONCLUSIONS

Our study found initial combinations of empagliflozin and metformin IR given twice daily for 24 weeks in patients with type 2 diabetes led to statistically significant and clinically meaningful reductions in HbA_{1c} compared with the corresponding empagliflozin once-daily and metformin twice-daily regimens. In the combination therapy groups, changes in HbA_{1c} of ~2% were observed at week 24, irrespective of the dose of empagliflozin or metformin. The results of sensitivity analyses of changes in HbA_{1c} were consistent with the primary analysis and supported the robustness of the results.

Empagliflozin + metformin combinations could be a useful treatment regimen to provide rapid, clinically relevant improvements in glycemic control in newly diagnosed patients with type 2 diabetes. Importantly, 57–70% of patients with $HbA_{1c} \geq 7\%$ at baseline who received combination therapy reached $HbA_{1c} < 7\%$ (<53 mmol/mol) at week 24, and 37–52% reached $HbA_{1c} < 6.5\%$. Even in very poorly controlled patients with type 2 diabetes (mean HbA_{1c} of 11.5% at baseline in the open-label group), 53% reached $HbA_{1c} < 7\%$ (<53 mmol/mol) at week 24, suggesting that an initial combination of empagliflozin and metformin may provide substantial benefits in this patient population.

High-dose metformin IR is known to be efficacious in drug-naïve patients with high baseline HbA_{1c} (13,14), and in this study, noninferiority of empagliflozin 25 mg and 10 mg q.d. compared with metformin 1,000 mg b.i.d. in reducing HbA_{1c} was not demonstrated. However, metformin is commonly associated with gastrointestinal AEs (14,15), and in practice, many patients cannot tolerate metformin at a dose of 1,000 mg b.i.d.

Many antidiabetes treatments are associated with weight gain (1), which can affect patients' satisfaction with and adherence to treatment (16,17). Significant and clinically meaningful reductions in weight were observed with combinations of empagliflozin and metformin compared with metformin regimens, and 26–41% of patients on empagliflozin + metformin combinations had a ≥5% reduction in weight at week 24. Further, changes in weight over time suggested that maximum weight loss for empagliflozin + metformin 1,000 mg b.i.d. may not have been reached by week 24. The weight loss observed with SGLT2 inhibitors is primarily caused by loss of calories as a result of urinary glucose excretion (18) and reflects loss of both visceral and subcutaneous fat (19). In this study, the effects of empagliflozin and metformin on weight appeared to be additive, but the lack of a placebo arm means that this cannot be conclusively assessed.

Our study observed significant reductions in SBP and DBP from baseline at week 24 with empagliflozin + metformin combinations compared with metformin regimens but not compared with empagliflozin alone. This was as expected given that empagliflozin has consistently been shown to reduce BP in patients with type 2 diabetes (20). The mechanisms behind reductions in BP with empagliflozin have not been fully clarified but may reflect weight loss, volume contraction secondary to osmotic diuresis, or arterial stiffness (21–23).

The results of the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) trial showed that in patients with type 2 diabetes and high cardiovascular risk, empagliflozin reduced cardiovascular death, hospitalization for heart failure, and all-cause mortality (24). These findings may encourage earlier use of combinations including empagliflozin in patients with type 2 diabetes and high cardiovascular risk.

All of the treatment regimens used in this study were well tolerated. The risk of hypoglycemia is an important consideration in the management of patients with type 2 diabetes because it can be dangerous and lead to reduced treatment adherence and impairment in health-related quality of life (17,25). The proportion of patients in this study with confirmed hypoglycemic AEs was low, and none required assistance. Patients with type 2 diabetes are at increased risk of UTIs and genital infections (26,27). In the current study, 5.9–12.4% of patients reported events consistent with UTI, and 1.8–6.4% of patients reported events consistent with genital infection across the randomized treatment groups. Overall, the safety profiles of the empagliflozin and metformin twice-daily combinations were consistent with the known safety profiles for empagliflozin and metformin.

In conclusion, twice-daily combinations of empagliflozin and metformin for 24 weeks led to pronounced reductions in HbA_{1c} and weight loss, with 57–70% of patients reaching $HbA_{1c} < 7\%$ and 26–41% achieving weight loss of >5% at week 24. These data suggest that the initial combination of empagliflozin and metformin could represent a valuable treatment option for newly diagnosed patients with type 2 diabetes, particularly those with $HbA_{1c} > 8.5\%$, irrespective of the dose of metformin that a patient can tolerate.

Acknowledgments. The authors are grateful to Melanie Stephens and Wendy Morris of Fleishman-Hillard Group, Ltd. for medical writing assistance.
Duality of Interest. S.H. has served as a consultant and/or on advisory panels for AstraZeneca/Bristol-Myers Squibb, has received honoraria or speaking fees from AstraZeneca/Bristol-Myers

Squibb, Abbott, Boehringer Ingelheim, Eli Lilly, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Sanofi, Servier, and Takeda, has received research grants from Abbott and Takeda, and has received travel grants from Janssen, AstraZeneca/Bristol-Myers Squibb, Merck Sharp & Dohme, and Sanofi. J.R. has served on scientific advisory boards and received honoraria or consulting fees from companies involved in the development of SGLT2 inhibitors, including Bristol-Myers Squibb, AstraZeneca, Janssen, Merck, Boehringer Ingelheim, Eli Lilly, and Lexicon, and has received grants/research support from Pfizer, Merck, Bristol-Myers Squibb, AstraZeneca, Janssen, Boehringer Ingelheim, Eli Lilly, and Lexicon. T.M., H.J.W., and U.C.B. are employees of Boehringer Ingelheim. Medical writing assistance was supported financially by Boehringer Ingelheim. This study was funded by the Boehringer Ingelheim and Eli Lilly and Company Diabetes Alliance. No other potential conflicts of interest relevant to this article were reported.

The authors were fully responsible for all content and editorial decisions, were involved at all stages of manuscript development, and approved the final version.

The authors received no financial compensation for the writing of this manuscript.

Author Contributions. S.H. contributed to the acquisition and interpretation of data and writing of the manuscript. J.R. contributed to the interpretation of data and writing of the manuscript. T.M., U.C.B., and H.J.W. contributed to the study design, interpretation of data, and writing of the manuscript. S.H. 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. Portions of the data in this study were presented at the 75th Scientific Sessions of the American Diabetes Association, Boston, MA, 5–9 June 2015 (Hadjadj S, Jelaska A, Zhang S, Meinicke T, Woerle HJ, Broedl UC et al. Diabetes 2015;64[Suppl. 1]:LB31) and at the 51st European Association for the Study of Diabetes Annual Meeting, Stockholm, Sweden, 14–18 September 2015 (Hadjadj S, Jelaska A, Zhang S, Meinicke T, Woerle HJ, Broedl UC et al. Diabetologia 2015;58[Suppl. 1]:S350).

References

1. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 2015;58:429–442
2. Hundal RS, Krssak M, Dufour S, et al. Mechanism by which metformin reduces glucose production in type 2 diabetes. Diabetes 2000;49:2063–2069
3. Basu R, Shah P, Basu A, et al. Comparison of the effects of pioglitazone and metformin on hepatic and extra-hepatic insulin action in people with type 2 diabetes. Diabetes 2008;57:24–31
4. Turner RC, Cull CA, Frighi V, Holman RR; UK Prospective Diabetes Study (UKPDS) Group. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). JAMA 1999;281:2005–2012
5. Triplitt C. Improving treatment success rates for type 2 diabetes: recommendations for a changing environment. Am J Manag Care 2010; 16(Suppl.):S195–S200
6. Khunti K, Wolden ML, Thorsted BL, Andersen M, Davies MJ. Clinical inertia in people with type 2 diabetes: a retrospective cohort study of more than 80,000 people. Diabetes Care 2013;36:3411–3417
7. Miccoli R, Penno G, Del Prato S. Multidrug treatment of type 2 diabetes: a challenge for compliance. Diabetes Care 2011;34(Suppl. 2): S231–S235
8. DeFronzo RA, Eldor R, Abdul-Ghani M. Pathophysiologic approach to therapy in patients with newly diagnosed type 2 diabetes. Diabetes Care 2013;36(Suppl. 2):S127–S138
9. Cheng AY; Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2013 clinical practice guidelines for the prevention and management of diabetes in Canada. Introduction. Can J Diabetes 2013;37(Suppl. 1):S1–S3
10. Gallo LA, Wright EM, Vallon V. Probing SGLT2 as a therapeutic target for diabetes: basic physiology and consequences. Diab Vasc Dis Res 2015;12:78–89
11. Grempler R, Thomas L, Eckhardt M, et al. Empagliflozin, a novel selective sodium glucose cotransporter-2 (SGLT-2) inhibitor: characterisation and comparison with other SGLT-2 inhibitors. Diabetes Obes Metab 2012;14:83–90
12. Häring HU, Merker L, Seewaldt-Becker E, et al.; EMPA-REG MET Trial Investigators. Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care 2014;37:1650–1659
13. Nichols GA, Conner C, Brown JB. Initial non-adherence, primary failure and therapeutic success of metformin monotherapy in clinical practice. Curr Med Res Opin 2010;26:2127–2135
14. Göke B, Hershon K, Kerr D, et al. Efficacy and safety of vildagliptin monotherapy during 2-year treatment of drug-naïve patients with type 2 diabetes: comparison with metformin. Horm Metab Res 2008;40:892–895
15. Hirst JA, Farmer AJ, Ali R, Roberts NW, Stevens RJ. Quantifying the effect of metformin treatment and dose on glycemic control. Diabetes Care 2012;35:446–454
16. Hauber AB, Mohamed AF, Johnson FR, Falvey H. Treatment preferences and medication adherence of people with Type 2 diabetes using oral glucose-lowering agents. Diabet Med 2009;26:416–424
17. Marrett E, Stargardt T, Mavros P, Alexander CM. Patient-reported outcomes in a survey of patients treated with oral antihyperglycaemic medications: associations with hypoglycaemia and weight gain. Diabetes Obes Metab 2009; 11:1138–1144
18. Barnett AH. Impact of sodium glucose co-transporter 2 inhibitors on weight in patients with type 2 diabetes mellitus. Postgrad Med 2013;125:92–100
19. Ridderstråle M, Andersen KR, Zeller C, Kim G, Woerle HJ, Broedl UC; EMPA-REG H2H-SU trial investigators. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial. Lancet Diabetes Endocrinol 2014; 2:691–700
20. Liakos A, Karagiannis T, Athanasiadou E, et al. Efficacy and safety of empagliflozin for type 2 diabetes: a systematic review and meta-analysis. Diabetes Obes Metab 2014;16:984–993
21. Baker WL, Smyth LR, Riche DM, Bourret EM, Chamberlin KW, White WB. Effects of sodium-glucose co-transporter 2 inhibitors on blood pressure: a systematic review and meta-analysis. J Am Soc Hypertens 2014;8:262–75.e9
22. Cherney DZ, Perkins BA, Soleymanlou N, et al. The effect of empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated type 1 diabetes mellitus. Cardiovasc Diabetol 2014;13:28
23. Dengo AL, Dennis EA, Orr JS, et al. Arterial destiffening with weight loss in overweight and obese middle-aged and older adults. Hypertension 2010;55:855–861
24. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373: 2117–2128
25. Alvarez Guisasola F, Tofé Povedano S, Krishnarajah G, Lyu R, Mavros P, Yin D. Hypoglycaemic symptoms, treatment satisfaction, adherence and their associations with glycaemic goal in patients with type 2 diabetes mellitus: findings from the Real-Life Effectiveness and Care Patterns of Diabetes Management (RECAP-DM) Study. Diabetes Obes Metab 2008;10(Suppl. 1): 25–32
26. Hirji I, Guo Z, Andersson SW, Hammar N, Gomez-Caminero A. Incidence of urinary tract infection among patients with type 2 diabetes in the UK General Practice Research Database (GPRD). J Diabetes Complications 2012;26:513–516
27. Hirji I, Andersson SW, Guo Z, Hammar N, Gomez-Caminero A. Incidence of genital infection among patients with type 2 diabetes in the UK General Practice Research Database. J Diabetes Complications 2012;26:501–505