Empagliflozin as Add-on Therapy in Patients With Type 2 Diabetes Inadequately Controlled With Linagliptin and Metformin: A 24-Week Randomized, Double-Blind, Parallel-Group Trial

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OBJECTIVE

To evaluate the efficacy and safety of empagliflozin versus placebo as add-on therapy in patients with type 2 diabetes and inadequate glycemic control with linagliptin and metformin.

RESEARCH DESIGN AND METHODS

Patients with HbA_{1c} ≥8.0% and ≤10.5% (≥64 and ≤91 mmol/mol) while receiving stable-dose metformin received open-label linagliptin 5 mg (n = 606) for 16 weeks. Subsequently, those with HbA_{1c} ≥7.0 and ≤10.5% (≥53 and ≤91 mmol/mol) were randomized to receive double-blind, double-dummy treatment with empagliflozin 10 mg (n = 112), empagliflozin 25 mg (n = 111), or placebo (n = 110) for 24 weeks; all patients continued treatment with metformin and linagliptin 5 mg. The primary end point was the change from baseline in HbA_{1c} after 24 weeks of double-blind treatment.

RESULTS

At week 24, empagliflozin significantly reduced HbA_{1c} (mean baseline 7.96–7.97% [63–64 mmol/mol]) versus placebo; the adjusted mean differences in the change from baseline with empagliflozin 10 and 25 mg versus placebo were −0.79% (95% CI −1.02, −0.55) (−8.63 mmol/mol [−11.20, −6.07 mmol/mol]) and −0.70% (95% CI −0.93, −0.46) (−7.61 mmol/mol [−10.18, −5.05 mmol/mol]), respectively (both P < 0.001). Fasting plasma glucose and weight were significantly reduced in both empagliflozin groups versus placebo (P < 0.001 for all comparisons). More patients receiving placebo than empagliflozin 10 and 25 mg reported adverse events during double-blind treatment (68.2%, 55.4%, and 51.8%, respectively).

CONCLUSIONS

Empagliflozin treatment for 24 weeks improved glycemic control and weight versus placebo as an add-on to linagliptin 5 mg and metformin and was well tolerated.

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Metformin is recommended as first-line pharmacotherapy for patients with type 2 diabetes who fail to achieve glycemic control through lifestyle modification or in whom this is considered unlikely (1). Although initially effective, metformin treatment alone frequently fails to maintain glycemic control as type 2 diabetes progresses (1,2). When glycemic control can no longer be maintained with metformin monotherapy, additional therapies are required (1). However, there are no uniform recommendations regarding the best agent to combine with metformin, and tolerability, particularly weight gain and hypoglycemia, should be a major consideration according to guidelines from the American Diabetes Association and the European Association for the Study of Diabetes (1).

Dipeptidyl peptidase 4 (DPP-4) inhibitors are one of the recommended second-line treatment options for patients with type 2 diabetes that is uncontrolled with metformin monotherapy (1,3). Linagliptin is a potent and selective DPP-4 inhibitor (4). In a phase III study in patients with type 2 diabetes (5), linagliptin 5 mg given as an add-on to metformin treatment for 24 weeks improved glycemic control without weight gain and was well tolerated, with a low risk of hypoglycemia.

Empagliflozin is a potent and selective sodium–glucose cotransporter 2 (SGLT2) inhibitor. In phase III trials, empagliflozin as monotherapy or add-on to existing therapy was associated with clinically relevant improvements in glycemic control and weight at week 24, which were sustained until week 76, as well as reductions in blood pressure (BP) (6–12). Empagliflozin was well tolerated and associated with a low risk of hypoglycemia (6–12). Furthermore, patients with type 2 diabetes at high cardiovascular risk who received empagliflozin in the EMPA-REG OUTCOME trial had a lower rate of the primary composite cardiovascular outcome (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) and of death from any cause, compared with placebo (13). SGLT2 inhibitors are one of the recommended second- or third-line treatment options for patients with type 2 diabetes, and the combination of SGLT2 inhibitors with DDP-4 inhibitors and metformin is recommended (3).

This study was undertaken to evaluate the efficacy and safety of empagliflozin 10 and 25 mg compared with placebo as add-on therapy in patients with type 2 diabetes uncontrolled after 16 weeks of treatment with linagliptin 5 mg and metformin.

RESEARCH DESIGN AND METHODS

This was a 24-week, phase III, randomized, double-blind, double-dummy, parallel-group study conducted between March 2013 and March 2015 at 90 sites in 10 countries (Australia, Brazil, Canada, France, Korea, New Zealand, Norway, Spain, Taiwan, and the U.S.). The clinical trial protocol was 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 participants provided written informed consent. The trial was registered with clinicaltrials.gov (Clinical trial reg. no. NCT01734785).

Study Design

Adults (≥18 years of age) with type 2 diabetes who had an HbA_{1c} of ≥8.0% and ≤10.5% (≥64 and ≤91 mmol/mol) despite being on a diet and exercise regimen and receiving a stable dose (unchanged for ≥12 weeks prior to screening) of metformin immediate release (≥1,500 mg/day, maximum tolerated dose, or maximum dose according to the local label) and who had a BMI ≤45 kg/m^2 were eligible for participation.

Eligible patients were treated with open-label linagliptin 5 mg for 16 weeks as add-on to background metformin at an unchanged dose. This was followed by a 1-week period during which open-label placebo was added to open-label linagliptin 5 mg and metformin. Patients with an HbA_{1c} ≥7.0 and ≤10.5% (≥53 and ≤91 mmol/mol) measured at the end of the 16-week open-label linagliptin 5 mg and metformin period and who still satisfied the other eligibility/exclusion criteria were then randomized (1:1:1) to receive double-blind, double-dummy treatment with a single-pill combination of empagliflozin 10 mg/linagliptin 5 mg or empagliflozin 25 mg/linagliptin 5 mg, or with placebo plus linagliptin 5 mg, all given in addition to background metformin for 24 weeks. Randomization was undertaken using a third-party interactive voice and web response system and was stratified by HbA_{1c} at the end of the 16-week, open-label linagliptin 5 mg and metformin period (<8.5% [<69 mmol/mol], ≥8.5% [≥69 mmol/mol]); estimated glomerular filtration rate (eGFR) at the end of the 16-week, open-label linagliptin and metformin period (≥90 mL/min/1.73 m^2, or 60–89 mL/min/1.73 m^2 calculated using the Modification of Diet in Renal Disease [MDRD] equation); and region (Europe [including Australia and New Zealand], Asia, North America, and Latin America). Tablets were to be taken once daily in the morning.

Exclusion criteria included, among others, uncontrolled hyperglycemia (glucose level >15.0 mmol/L after an overnight fast during the open-label or placebo add-on periods, confirmed by a second measurement); treatment with any antidiabetes agent except metformin within 12 weeks prior of the start of open-label treatment; treatment with any antidiabetes agent except study drug and metformin prior to randomization to double-blind treatment; eGFR <60 mL/min/1.73 m^2; hereditary galactose intolerance; acute coronary syndrome, stroke, or transient ischemic attack within 3 months prior to consent; any previous (within the past 2 years) or planned bariatric surgery; and treatment with antiobesity drugs within 3 months prior to consent.

Patients requiring rescue therapy for glucose levels >15.0 mmol/L after an overnight fast during the open-label or placebo add-on periods were not eligible for randomization to double-blind treatment. During the double-blind treatment period, rescue therapy could be initiated if, after an overnight fast, a patient had blood glucose levels >15.0 mmol/L until week 6, >13.3 mmol/L during weeks 6–12, and >11.1 mmol/L during weeks 12–24; blood glucose levels had to be confirmed by at least one second measurement. The initiation, choice, and dosage of rescue therapy were at the discretion of the investigator, according to local prescribing information; however, the use of DPP-4 inhibitors, glucagon-like peptide 1 analogs, and SGLT2 inhibitors were not permitted. In cases of hypoglycemia, reduction or discontinuation of rescue therapy was to be considered prior to reducing the dose of background metformin.

End Points and Assessments

The primary end point was the change from baseline (defined as the last

observation before the first intake of any double-blind, randomized treatment) in HbA_{1c} after 24 weeks of double-blind treatment (referred to as week 24). Key secondary end points were the change from baseline in fasting plasma glucose (FPG) and weight at week 24. Additional end points included (for patients with HbA_{1c} level $\geq$7.0% at baseline) the occurrence of HbA_{1c} $<$7.0% at week 24; change from baseline in systolic BP (SBP) and diastolic BP (DBP) at week 24; and change from baseline in HbA_{1c}, FPG, weight, SBP, and DBP over time. Efficacy end points (HbA_{1c}, FPG, weight, SBP, and DBP changes from pretreatment) were also assessed at the end of the 16-week, open-label linagliptin treatment period.

Safety assessments included vital signs, clinical laboratory parameters, and adverse events (AEs; using preferred terms according to the Medical Dictionary for Drug Regulatory Activities [MedDRA] version 17.1). Treatment-emergent AEs included all events with an onset after the first dose of open-label linagliptin and up to 7 days after the last dose of study drug. Confirmed hypoglycemic AEs were defined as events with a plasma glucose concentration of $\leq$3.9 mmol/L and/or requiring assistance. Events consistent with urinary tract infection (UTI), events consistent with genital infection, hypersensitivity reactions, pancreatitis, and diabetic ketoacidosis (identified from AEs reported spontaneously by the investigator using prospectively defined search categories based on 79, 88, 236, 18, and 3 MedDRA preferred terms, respectively) were also assessed.

Statistical Analysis

Separate efficacy analyses were undertaken for the open-label and double-blind treatment periods. Efficacy was analyzed in the full analysis sets (FAS), which were defined separately for each treatment period. For the open-label period, the open-label FAS comprised all patients who received one or more doses of open-label treatment, and who had a pretreatment HbA_{1c} measurement and at least one on-treatment HbA_{1c} measurement during the open-label period (noting that HbA_{1c} measurement was scheduled only after 16 weeks of the open-label period). For the double-blind period, the FAS comprised all patients who received one or more doses of study drug during the double-blind period, and who had an HbA_{1c} measurement at baseline (prior to randomization to double-blind treatment) and at least one on-treatment HbA_{1c} measurement during the double-blind period. Safety was assessed separately in the treated sets for the open-label period (including the placebo add-on period) and the double-blind period (i.e., patients receiving one or more doses of open-label and double-blind treatment, respectively).

The primary end point was analyzed using a restricted maximum likelihood–based mixed-model repeated measures (MMRM) approach in the FAS using observed cases (OC). Values observed after the initiation of rescue therapy were set to missing. The model included baseline HbA_{1c} as a linear covariate, and treatment, baseline eGFR category ($\geq$90 or $<$90 mL/min/1.73 m^2), region, visit, and visit by treatment as fixed effects. Key secondary end points and continuous additional end points were analyzed using the MMRM model described for the primary end point, with the baseline value for the end point in question as an additional linear covariate. HbA_{1c} responder

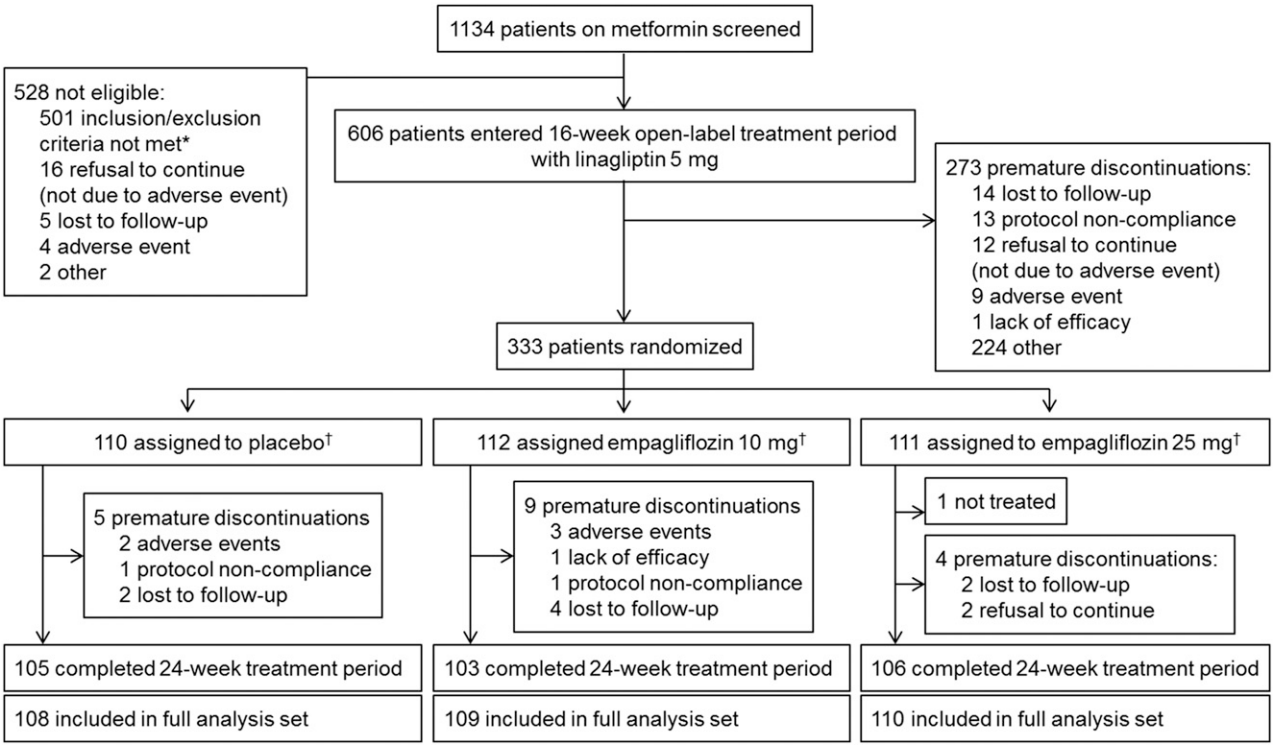


Figure 1—Study flow. During the open-label and double-blind treatment periods, patients had to receive a stable dose of metformin background therapy. *Patients may have had more than one inclusion/exclusion criterion not met; †As add-on therapy to open-label linagliptin 5 mg and metformin.

end points at week 24 were analyzed using logistic regression with noncompleters considered failure imputation. Sensitivity analyses of the changes from baseline in HbA_{1c}, FPG, and weight were performed using an ANCOVA model in the FAS using a last observation carried forward approach to impute missing data. All data after the initiation of rescue therapy were set to missing. The model included baseline HbA_{1c} and the baseline value of the end point in question as linear covariates, and treatment, baseline eGFR, and region as fixed effects.

The null hypotheses of no treatment effect for the primary and key secondary end points were tested hierarchically to control the overall probability of a type 1 error at 0.05: HbA_{1c} then FPG then weight. For each end point, the superiority of empagliflozin 25 mg versus placebo was tested first, followed by empagliflozin 10 mg versus placebo. Confirmatory claims of superiority for each end point/comparison could only be made if the relevant null hypothesis and all preceding null hypotheses in the hierarchy were rejected at the 0.05 level (two sided). Safety analyses were descriptive, except for changes from baseline in lipid parameters during the double-blind period, which were analyzed using MMRM in the treated set, using OC including values after the initiation of rescue therapy.

A sample size of 111 patients per randomized double-blind treatment group was required to provide a 90% power to detect a 0.55% treatment difference in HbA_{1c} change from baseline between empagliflozin and placebo, assuming an SD of 1.1% and a premature double-blind treatment discontinuation rate of ~7%.

RESULTS

Study Population

A total of 606 patients received open-label linagliptin 5 mg (treated set), of whom 564 composed the open-label FAS. In total, 117 patients (20.7%) reached the glycemic goal of HbA_{1c} level <7.0% during 16 weeks of open-label treatment with linagliptin 5 mg and were not eligible for double-blind treatment; these patients composed the majority of the 224 "other" premature discontinuations in Fig. 1. The other major reason for other premature discontinuations was the required number of patients being reached for the double-blind treatment period. Of the 333 patients who entered the double-blind treatment period, the treated set comprised 332 patients, and the FAS comprised 327 patients (Fig. 1).

Baseline demographics and characteristics in the double-blind FAS were balanced between the treatment groups, except for sex, race, and weight; the mean baseline HbA_{1c} level was 7.97% (64 mmol/mol) (Table 1). Pretreatment demographics and characteristics in the open-label FAS are shown in Supplementary Table 1; the mean pretreatment HbA_{1c} was 8.95% (74 mmol/mol).

Efficacy

During the double-blind treatment period, empagliflozin 10 and 25 mg significantly reduced the mean HbA_{1c} from baseline at week 24 compared with placebo (Fig. 2*A*). The adjusted mean differences in change from baseline in HbA_{1c} with empagliflozin 10 and 25 mg versus placebo were −0.79% (95% CI −1.02, −0.55) (−8.63 mmol/mol [−11.20, −6.07 mmol/mol]) and −0.70% (95% CI −0.93, −0.46) (−7.61 mmol/mol [−10.18, −5.05 mmol/mol]), respectively (both $P < 0.001$). Significantly more patients reached HbA_{1c} <7.0% (<53 mmol/mol) at week 24 with empagliflozin compared with placebo (Fig. 2*B*). Changes in HbA_{1c} over time are shown in Fig. 3.

Empagliflozin 10 and 25 mg significantly reduced mean FPG and weight from baseline at week 24 (double-blind treatment period) compared with placebo (Fig. 4*A* and *B*). Changes in FPG and weight over time are shown in Supplementary Fig. 2. Sensitivity analyses of the changes from baseline in HbA_{1c}, FPG, and weight at week 24 were consistent with the results of the primary analyses (Supplementary Table 2). Mean reductions from baseline in both SBP and DBP at week 24 were numerically higher with empagliflozin

Table 1—Demographics and baseline characteristics (double-blind FAS)

	Linagliptin 5 mg and metformin		
	Placebo (*n* = 108)	Empagliflozin 10 mg (*n* = 109)	Empagliflozin 25 mg (*n* = 110)
Male sex, *n* (%)	60 (55.6)	66 (60.6)	71 (64.5)
Age (years)	55.9 (9.7)	54.3 (9.6)	55.4 (9.9)
Race, *n* (%)			
White	59 (54.6)	67 (61.5)	65 (59.1)
Asian	32 (29.6)	26 (23.9)	30 (27.3)
Other	17 (15.7)	16 (14.7)	15 (13.6)
Time since diagnosis of type 2 diabetes, *n* (%)			
≤1 year	9 (8.3)	6 (5.5)	7 (6.4)
>1–5 years	31 (28.7)	30 (27.5)	41 (37.3)
>5–10 years	38 (35.2)	42 (38.5)	35 (31.8)
>10 years	30 (27.8)	31 (28.4)	27 (24.5)
HbA_{1c} (%)	7.97 (0.85)	7.97 (0.84)	7.97 (0.82)
HbA_{1c} (mmol/mol)	64 (9.3)	64 (9.2)	64 (9.0)
HbA_{1c}, *n* (%)			
<8.5%	76 (70.4)	79 (72.5)	81 (73.6)
≥8.5%	32 (29.6)	30 (27.5)	29 (26.4)
FPG (mmol/L)	9.1 (1.8)	9.3 (2.2)	9.4 (2.3)
Weight (kg)	82.3 (19.8)	88.4 (20.8)	84.4 (19.2)
BMI (kg/m^2)	29.6 (5.7)	31.2 (5.9)	29.9 (5.3)
SBP (mmHg)	130.1 (16.3)	130.4 (14.2)	131.0 (14.7)
DBP (mmHg)	77.8 (8.7)	80.0 (8.2)	79.7 (8.7)
eGFR (mL/min/1.73 m^2 [MDRD])	92.7 (16.2)	90.8 (19.1)	93.4 (18.7)
eGFR (MDRD), *n* (%)			
≥90 mL/min/1.73 m^2	57 (52.8)	47 (43.1)	57 (51.8)
60 to <90 mL/min/1.73 m^2	49 (45.4)	60 (55.0)	52 (47.3)
<60 mL/min/1.73 m^2	2 (1.9)	2 (1.8)	1 (0.9)

Data are mean (SD), unless otherwise stated, in the FAS (patients treated with one or more doses of study drug during the double-blind period and who had a baseline and one or more on-treatment HbA_{1c} measurements during the double-blind period).

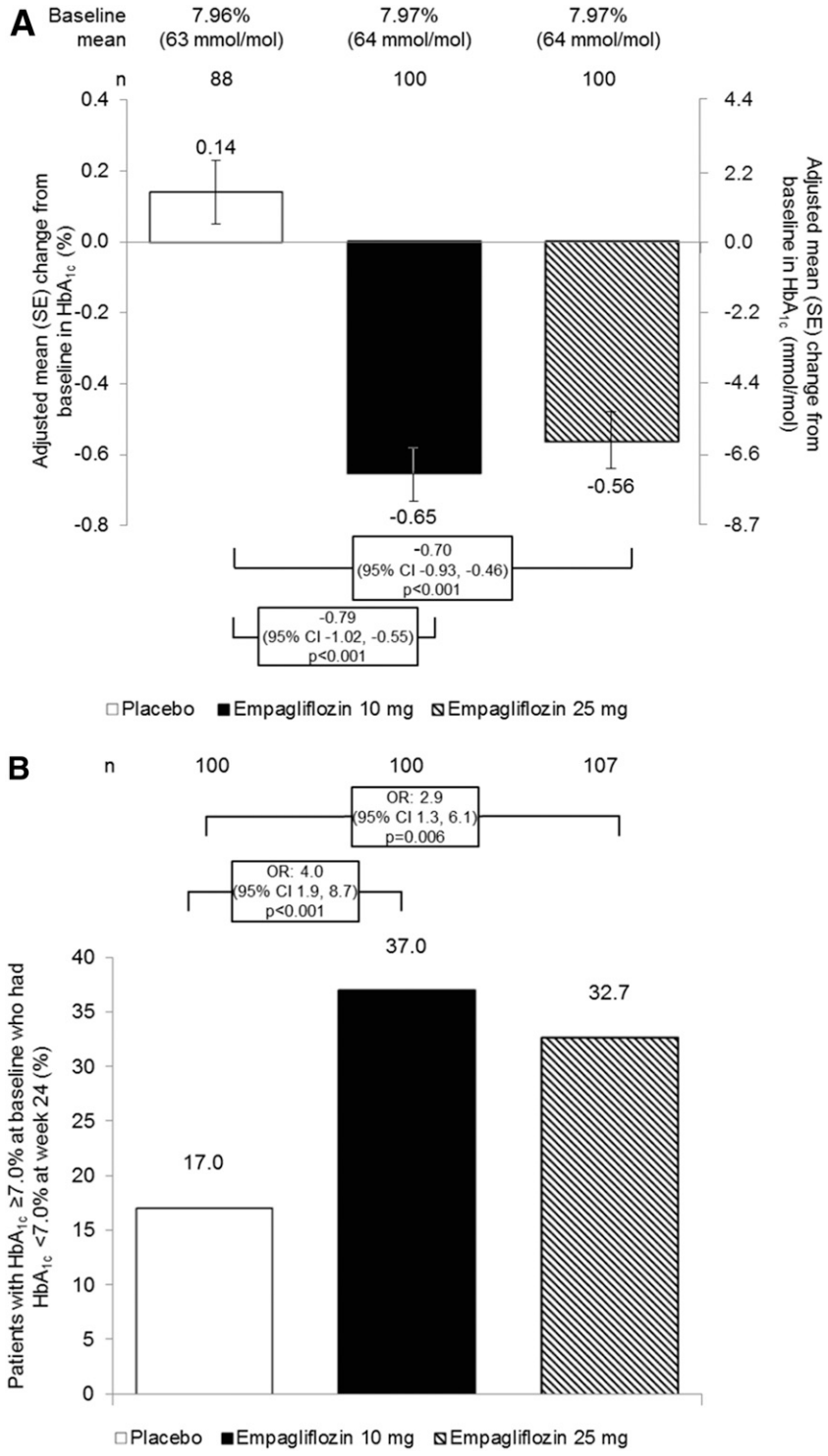


Figure 2—Efficacy parameters: HbA_{1c}. *A*: Change from baseline in HbA_{1c} at week 24 (MMRM in FAS using OC). *B*: Patients with HbA_{1c} ≥7.0% (≥53 mmol/mol) at baseline who reached HbA_{1c} <7.0% (<53 mmol/mol) at week 24 (logistic regression analysis in FAS using noncompleters considered failure). Data are adjusted mean ± SE or percentage. *n*, number of patients with data at week 24. Treatment differences and odds ratios (ORs) are presented as empagliflozin compared with placebo.

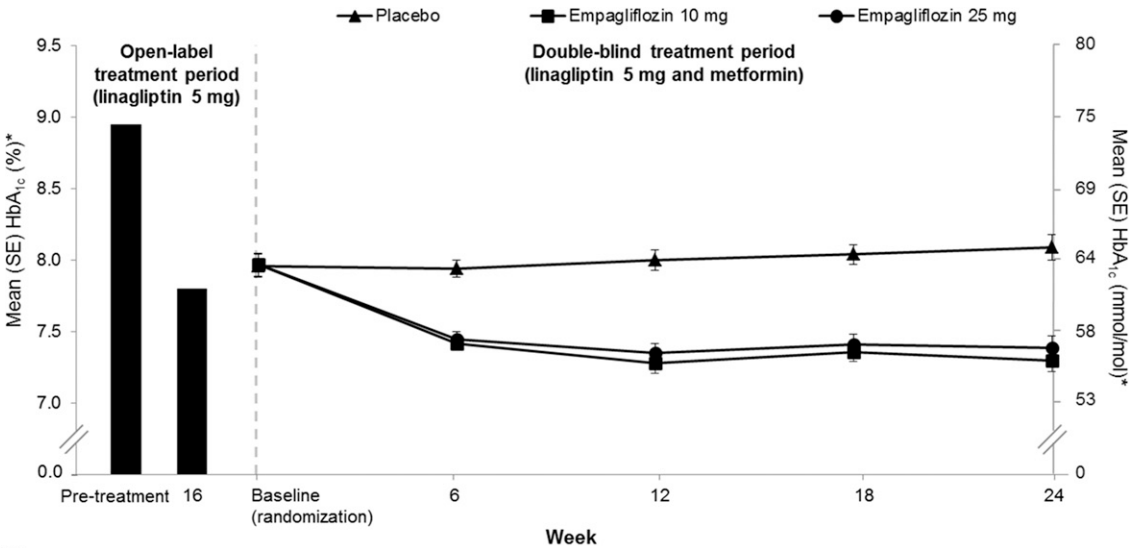
than placebo during the double-blind treatment period, but were not statistically significant (Supplementary Fig. 1*A* and *B*).

During the open-label treatment period, reductions in mean values from pretreatment HbA_{1c} levels were observed at week 16 in patients receiving linagliptin 5 mg and metformin (Fig. 3). Reductions in mean values from pretreatment FPG levels (Supplementary Fig. 2*A*), weight (Supplementary Fig. 2*B*), SBP (Supplementary Fig. 1*C*), and DBP (Supplementary Fig. 1*D*) were also observed at week 16.

Safety

During the double-blind treatment period, the proportion of patients with one or more AEs was lower in the empagliflozin groups than in the placebo group (Table 2). Most events in each treatment group were mild or moderate in intensity. The proportion of patients with serious AEs was lower in the empagliflozin groups than in the placebo group (Table 2). AEs leading to discontinuation were reported in four patients: two patients (1.8%) receiving placebo and two patients (1.8%) receiving empagliflozin 10 mg. Confirmed hypoglycemic AEs (plasma glucose values ≤3.9 mmol/L and/or requiring assistance) were reported in four patients: one patient (0.9%) receiving placebo and three patients (2.7%) receiving empagliflozin 25 mg, one of whom required assistance. Events consistent with UTI were reported in eight patients (7.3%) receiving placebo, eight patients (7.1%) receiving empagliflozin 10 mg, and four patients (3.6%) receiving empagliflozin 25 mg; these events were reported in a larger proportion of female than male patients in each group (Table 2). Events consistent with genital infection were reported in two patients (1.8%) receiving placebo, two patients (1.8%) receiving empagliflozin 10 mg, and five patients (4.5%) receiving empagliflozin 25 mg; these events were reported in a greater proportion of female than male patients in each group (Table 2). There were no reports of pancreatitis or diabetic ketoacidosis. Hypersensitivity reactions were reported in two patients (1.8%) receiving placebo, three patients (2.7%) receiving empagliflozin 10 mg, and five patients (4.5%) receiving empagliflozin 25 mg (Table 2).

AEs during the open-label period are shown in Supplementary Table 3. In total, 48.8% of patients experienced one or more AEs. Most events were mild or moderate in intensity. Serious AEs were reported in 18 patients (3.0%), and the proportion of patients with AEs leading to discontinuation was low. Confirmed hypoglycemic AEs were reported in four patients (0.7%), none of whom required



Number of patients							
Linagliptin 5 mg open-label	564	550	-	-	-	-	-
Placebo	-	-	106	104	103	96	88
Empagliflozin 10 mg	-	-	109	108	106	105	100
Empagliflozin 25 mg	-	-	110	110	106	103	100

Figure 3—HbA_{1c} over time (MMRM in FAS using OC). *Data are adjusted mean ± SE, except for linagliptin open-label data, which are unadjusted mean. *n*, number of patients with data at week 24.

assistance. Events consistent with UTI were reported in 30 patients (5.0%), and again these events were reported in a larger proportion of female than male patients. Two patients (0.3%) had events consistent with genital infection. There were no reports of pancreatitis or diabetic ketoacidosis. Hypersensitivity reactions were reported in 19 patients (3.1%).

Changes from baseline in laboratory measurements during the double-blind treatment period are shown in Supplementary Table 4. Increases in mean hematocrit and decreases in mean serum uric acid from baseline were observed in patients receiving empagliflozin (both doses), compared with placebo. Mean changes from baseline in eGFR and urinary albumin-to-creatinine ratio were small and similar across treatment groups. There were no clinically meaningful changes in electrolyte levels in any treatment group. At week 24, there was a small increase from baseline in mean total cholesterol, HDL cholesterol, and LDL cholesterol with empagliflozin 10 and 25 mg versus placebo. No differences were noted in changes from baseline in mean triglycerides with empagliflozin 10 and 25 mg versus placebo. Changes in laboratory measurements during the open-label treatment period are shown in Supplementary Table 5.

CONCLUSIONS

This phase III trial evaluated the efficacy and safety of empagliflozin compared with placebo as add-on therapy in patients with type 2 diabetes in whom glycemic control was not achieved/maintained with linagliptin and metformin. Treatment with empagliflozin 10 and 25 mg for 24 weeks was associated with statistically significant and clinically relevant improvements in mean HbA_{1c}, FPG, and weight compared with placebo in patients with type 2 diabetes that was inadequately controlled after 16 weeks of treatment with linagliptin 5 mg and metformin alone. The proportion of patients with an HbA_{1c} $\geq$7.0% at baseline who reached HbA_{1c} of $<$7.0% after 24 weeks with empagliflozin 10 mg was more than twice that with placebo as the add-on to linagliptin and metformin, and was almost doubled with empagliflozin 25 mg compared with placebo as the add-on to linagliptin and metformin. Unexpectedly, reductions in mean HbA_{1c} with empagliflozin 10 and 25 mg were similar in this trial, even though a dose-dependent increase in urinary glucose excretion and a dose-dependent decrease in HbA_{1c} level have been reported in phase I/II trials (14–16).

Weight loss with empagliflozin treatment is consistent with data from phase III trials (6–12) and is likely due, primarily, to the loss of calories via the increased urinary glucose excretion associated with empagliflozin (17), whereas linagliptin is considered to be weight neutral (5,18). Weight loss or avoiding weight gain is important to patients (19), with weight gain associated with decreased treatment satisfaction and health-related quality of life (20).

During this study, there were modest reductions in the mean SBP change from baseline at week 24 in both empagliflozin treatment groups compared with placebo. However, this study did not control for changes in the use of antihypertensive drugs, which may have impacted the effects observed on BP. Statistically significant reductions in SBP were demonstrated in phase III trials with empagliflozin as monotherapy or add-on therapy (6–11). Empagliflozin reduces BP via mechanisms that may include diuretic effects, weight loss, and improved glycemic control (21), whereas linagliptin has no effect on BP (22).

Treatment with empagliflozin 10 or 25 mg as add-on to linagliptin and metformin during the double-blind period was well tolerated; AEs were reported for a lower proportion of patients in the empagliflozin groups than in the placebo group. Treatment-induced hypoglycemia

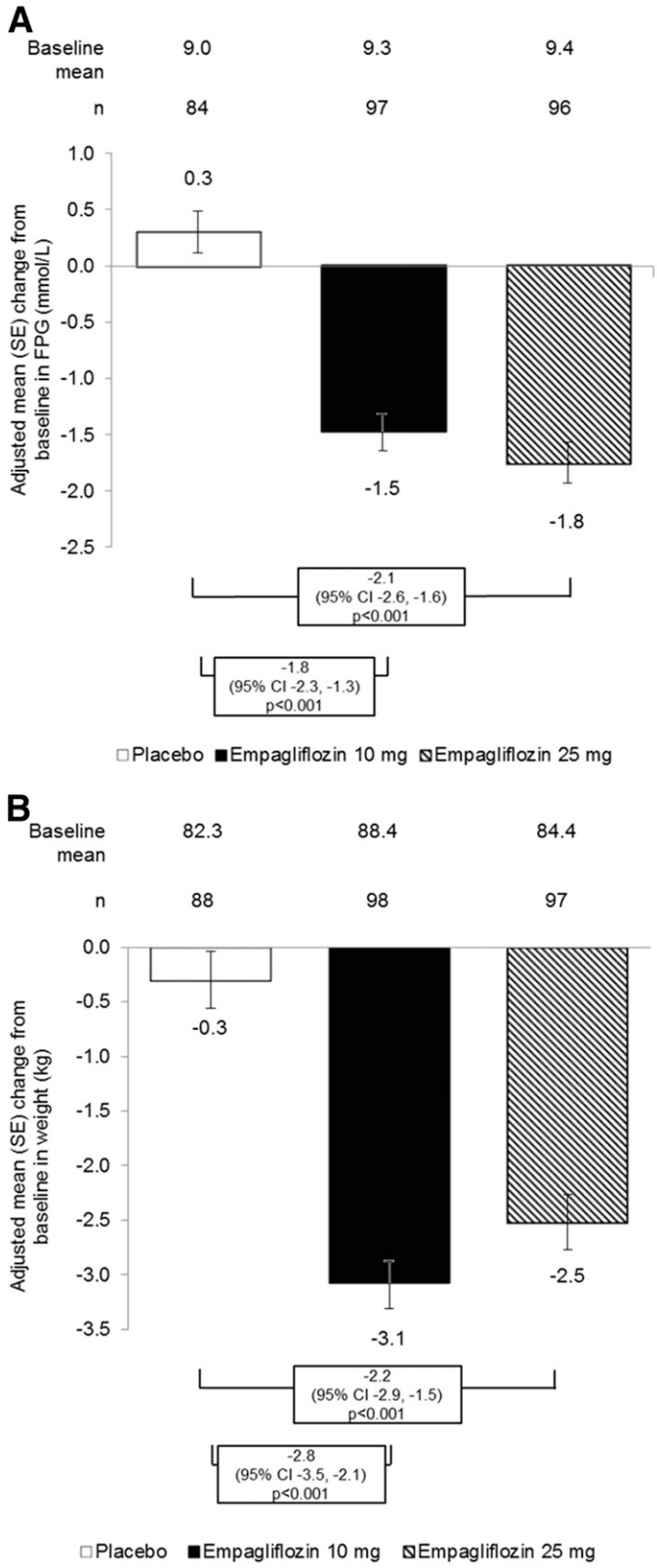


Figure 4—Efficacy parameters: FPG and weight. *A*: Change from baseline in FPG at week 24 (MMRM in FAS using OC). *B*: Change from baseline in weight at week 24 (MMRM in FAS using OC). Data are adjusted mean ± SE. *n*, number of patients with data at week 24.

represents a major concern in patients with diabetes and is associated with increased risk of cardiovascular events, decreased treatment satisfaction and health-related quality of life, and poor glycemic control (20,23). Both empagliflozin and linagliptin are associated with a low risk of hypoglycemia when given as monotherapy (6,18). In this study, confirmed hypoglycemic AEs were reported in a greater proportion of patients receiving empagliflozin 25 mg than placebo as add-on therapy with linagliptin and metformin, although the numbers were small. The low risk of hypoglycemia associated with both empagliflozin and linagliptin is important, given the current treatment recommendations (1). The proportions of patients with events consistent with genital infection were low in all treatment groups, although the incidence of such events was higher in patients treated with empagliflozin 25 mg than placebo. There was no increase in the number of events consistent with UTI. A limitation of our study is the relatively small sample size, which needs to be considered when interpreting small numbers of AEs. Furthermore, the length of exposure and follow-up for AEs in our study was relatively short.

In conclusion, empagliflozin 10 and 25 mg improved glycemic control and weight compared with placebo as add-on therapy with linagliptin and metformin, and were well tolerated in patients with type 2 diabetes. Therefore, empagliflozin may provide a valuable treatment option as add-on therapy for patients with inadequate glycemic control with linagliptin and metformin, with the benefits of weight loss and a low risk of hypoglycemia.

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Duality of Interest. E.S. is an employee of Haukeland University Hospital and has lectured and received other fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Merck Sharp and Dohme, Novartis, Novo Nordisk, and Sanofi. J.J.M. has served as a consultant for AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Merck Sharp and Dohme, Novo Nordisk, and Sanofi; has received grants from Novo Nordisk, Merck Sharp and Dohme, Sanofi, Eli Lilly and Company, and Novartis; and has lectured and received other fees from AstraZeneca, Berlin-Chemie, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly and Company, Merck Sharp and Dohme, Novo Nordisk, Novartis, Roche, and Sanofi. B.V. and U.C.B. are employees of Boehringer Ingelheim. R.T. is a contractor who provides services to Boehringer Ingelheim. M.M.-L. was an employee of

Table 2—AEs during the double-blind treatment period

	Linagliptin 5 mg and metformin		
	Placebo (*n* = 110)	Empagliflozin 10 mg (*n* = 112)	Empagliflozin 25 mg (*n* = 110)
One or more AEs	75 (68.2)	62 (55.4)	57 (51.8)
One or more drug-related* AEs	6 (5.5)	8 (7.1)	12 (10.9)
One or more AEs leading to discontinuation	2 (1.8)	2 (1.8)	0
One or more severe AEs	3 (2.7)	4 (3.6)	1 (0.9)
One or more serious AEs	10 (9.1)	5 (4.5)	4 (3.6)
Deaths	0	0	0
AEs with frequency of >5% in any randomized treatment group (by preferred term)			
Nasopharyngitis	8 (7.3)	5 (4.5)	4 (3.6)
Headache	8 (7.3)	3 (2.7)	2 (1.8)
UTI	7 (6.4)	8 (7.1)	3 (2.7)
Hyperglycemia	7 (6.4)	1 (0.9)	1 (0.9)
Lipase increased	6 (5.5)	4 (3.6)	3 (2.7)
Special interest categories			
Confirmed hypoglycemia†	1 (0.9)	0	3 (2.7)
Events requiring assistance	0	0	1 (0.9)
Events consistent with UTI‡	8 (7.3)	8 (7.1)	4 (3.6)
Male	1 (1.6)	0	1 (1.4)
Female	7 (14.3)	8 (17.4)	3 (7.7)
Events consistent with genital infection#	2 (1.8)	2 (1.8)	5 (4.5)
Male	0	0	3 (4.2)
Female	2 (4.1)	2 (4.3)	2 (5.1)
Hypersensitivity reactions¶	2 (1.8)	3 (2.7)	5 (4.5)
Pancreatitis§	0	0	0

Data are *n* (%) in the treated set (patients who received one or more doses of study drug during the double-blind period). *As reported by the investigator; †Plasma glucose concentration ≤3.9 mmol/L and/or requiring assistance; ‡Based on 79 MedDRA preferred terms; #Based on 88 MedDRA preferred terms; ¶Based on 236 MedDRA preferred terms; §Based on 18 MedDRA preferred terms.

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

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