Initial Combination of Empagliflozin and Linagliptin in Subjects With Type 2 Diabetes

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OBJECTIVE

To evaluate the efficacy and safety of empagliflozin/linagliptin in subjects with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Subjects not receiving antidiabetes therapy for ≥12 weeks were randomized to empagliflozin 25 mg/linagliptin 5 mg (*n* = 137), empagliflozin 10 mg/linagliptin 5 mg (*n* = 136), empagliflozin 25 mg (*n* = 135), empagliflozin 10 mg (*n* = 134), or linagliptin 5 mg (*n* = 135) for 52 weeks. The primary end point was change from baseline in HbA_{1c} at week 24.

RESULTS

Mean HbA_{1c} at baseline was 7.99–8.05% (64 mmol/mol). At week 24, adjusted mean (SE) changes from baseline in HbA_{1c} with empagliflozin 25 mg/linagliptin 5 mg, empagliflozin 10 mg/linagliptin 5 mg, empagliflozin 25 mg, empagliflozin 10 mg, and linagliptin 5 mg were −1.08 (0.06)% (−11.8 [0.7] mmol/mol), −1.24 (0.06)% (−13.6 [0.7] mmol/mol), −0.95 (0.06)% (−10.4 [0.7] mmol/mol), −0.83 (0.06)% (−9.1 [0.7] mmol/mol), and −0.67 (0.06)% (−7.3 [0.7] mmol/mol), respectively. Reductions in HbA_{1c} were significantly greater for empagliflozin 25 mg/linagliptin 5 mg compared with linagliptin 5 mg ($P < 0.001$) but not compared with empagliflozin 25 mg and were significantly greater for empagliflozin 10 mg/linagliptin 5 mg compared with the individual components ($P < 0.001$ for both). At week 24, 55.4%, 62.3%, 41.5%, 38.8%, and 32.3% of subjects with baseline HbA_{1c} ≥7% (≥53 mmol/mol) reached HbA_{1c} <7% with empagliflozin 25 mg/linagliptin 5 mg, empagliflozin 10 mg/linagliptin 5 mg, empagliflozin 25 mg, empagliflozin 10 mg, and linagliptin 5 mg, respectively. Efficacy was maintained at week 52. The proportion of subjects with adverse events (AEs) over 52 weeks was similar across groups (68.9–81.5%), with no confirmed hypoglycemic AEs.

CONCLUSIONS

Reductions from baseline in HbA_{1c} with empagliflozin/linagliptin were significantly different versus linagliptin and empagliflozin 10 mg but not versus empagliflozin 25 mg. Empagliflozin/linagliptin was well tolerated.

Empagliflozin is a potent and selective sodium–glucose cotransporter 2 (SGLT2) inhibitor (1) approved for the treatment of type 2 diabetes. Empagliflozin reduces renal glucose reabsorption, thereby increasing urinary glucose excretion, leading to a reduction in plasma glucose levels in subjects with type 2 diabetes in an insulin-independent manner (2). In a phase 3 trial in subjects with type 2 diabetes,

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empagliflozin 10 mg and 25 mg once daily as monotherapy for 24 weeks reduced HbA_{1c}, fasting plasma glucose (FPG), weight, and blood pressure (BP) compared with placebo and were well tolerated, with a low risk of hypoglycemia (3). In a double-blind extension of this trial, the reductions in HbA_{1c}, FPG, and weight achieved with empagliflozin were sustained up to week 76 (4).

Linagliptin is a potent and selective dipeptidyl peptidase-4 (DPP-4) inhibitor (5) approved for the treatment of patients with type 2 diabetes. Linagliptin prevents the inactivation of incretin peptides such as glucagon-like peptide 1 (GLP-1), stimulates insulin release, and inhibits glucagon secretion (6). In a phase 3 trial in subjects with type 2 diabetes, linagliptin 5 mg given as monotherapy for 24 weeks improved glycemic control without weight gain and was well tolerated, with a low risk of hypoglycemia (7). In an open-label extension of this trial, reductions in HbA_{1c} with linagliptin were sustained up to week 102 (8).

Guidelines for the management of type 2 diabetes recommend metformin as first-line pharmacological treatment (9), but initial combination therapy with oral antidiabetes drugs with complementary modes of action may provide more robust and durable glucose-lowering efficacy with enhanced outcomes compared with the traditional stepwise approach (10). Initial combination therapies typically include metformin (9); however, contraindications to metformin, such as renal impairment, are common among patients with type 2 diabetes (11–13), and 5–10% of patients cannot tolerate metformin owing to gastrointestinal side effects (14). The complementary mechanisms of action of SGLT2 inhibitors and DPP-4 inhibitors suggest that the combination of empagliflozin and linagliptin may offer sustained treatment benefits. Therefore, this study was undertaken to evaluate the efficacy and safety of the initial combination of empagliflozin/linagliptin in subjects with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study Design

This was a phase 3, randomized, double-blind, parallel-group study conducted from August 2011 to September 2013 in 197 centers in 22 countries. 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 Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice. All subjects provided written informed consent.

Inclusion and Exclusion Criteria

This study enrolled subjects aged ≥18 years with type 2 diabetes with BMI ≤45 kg/m^2 and HbA_{1c} >7% to ≤10.5% (>53 to ≤91 mmol/mol) at screening despite a diet and exercise regimen who had not received treatment with oral antidiabetes therapy, GLP-1 analog, or insulin for ≥12 weeks prior to randomization.

Exclusion criteria included uncontrolled hyperglycemia (glucose level >240 mg/dL after an overnight fast during the placebo run-in, confirmed by a second measurement); estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 (using the MDRD equation); acute coronary syndrome, stroke, or transient ischemic attack within 3 months prior to consent; bariatric surgery in the last 2 years; and treatment with antiobesity drugs within 3 months prior to consent.

Treatment and Interventions

After a 2-week placebo run-in period, subjects were randomized (1:1:1:1:1) to receive empagliflozin 25 mg/linagliptin 5 mg as a fixed-dose combination (FDC) tablet, empagliflozin 10 mg/linagliptin 5 mg as an FDC tablet, empagliflozin 25 mg, empagliflozin 10 mg, or linagliptin 5 mg for 52 weeks. All study drugs were taken once daily in the morning. Randomization was performed using a third-party interactive voice and web response system and was stratified by HbA_{1c} at screening (<8.5% [<69 mmol/mol], ≥8.5% [≥ 69 mmol/mol]), eGFR at screening (≥90 mL/min/1.73 m^2, 60–89 mL/min/1.73 m^2), and region (Asia, Europe, North America, South America). Study visits were scheduled at screening, at the start of the placebo run-in, at baseline, and at weeks 6, 12, 18, 24, 32, 40, and 52 of treatment. A follow-up visit occurred 4 weeks after the last dose of study drug for subjects who completed the treatment period or within 7 days after the last administration of study drug for those who discontinued treatment before week 52.

Rescue medication was to be initiated if a subject had blood glucose >240 mg/dL after an overnight fast between weeks 1 and 12, blood glucose >200 mg/dL after an overnight fast between weeks 12 and 24, or blood glucose >180 mg/dL or HbA_{1c} >8% (>63.9 mmol/mol) after an overnight fast between weeks 24 and 52. The initiation, choice, and dosage of rescue medication were at the discretion of the investigator, according to local prescribing information, but the use of DPP-4 inhibitors, GLP-1 analogs, and SGLT2 inhibitors 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 the change from baseline in HbA_{1c} at week 24. Key secondary end points were change from baseline in FPG at week 24, change from baseline in weight at week 24, and the proportion of subjects with baseline HbA_{1c} ≥7% (≥53 mmol/mol) who had HbA_{1c} <7% (<53 mmol/mol) at week 24. Exploratory end points were as follows: changes from baseline in HbA_{1c} at week 24 in subgroups of subjects with HbA_{1c} ≥8.5% (≥ 69 mmol/mol) and <8.5% (<69 mmol/mol) at baseline; changes from baseline in HbA_{1c}, FPG, weight, systolic BP (SBP), and diastolic BP (DBP) at week 52; and the proportion of subjects with baseline HbA_{1c} ≥7% (≥53 mmol/mol) who had HbA_{1c} <7% (<53 mmol/mol) at week 52.

Safety end points included vital signs, clinical laboratory parameters, and adverse events (AEs) (preferred terms coded according to the Medical Dictionary for Regulatory Activities [MedDRA], version 16.0). AEs included all events with an onset after the first dose and up to 7 days after the last dose of study medication. Confirmed hypoglycemic AEs were defined as AEs with plasma glucose ≤70 mg/dL and/or requiring assistance. Events consistent with urinary tract infection (UTI), events consistent with genital infection, and events consistent with volume depletion (identified from AEs reported spontaneously by the investigator using prospectively defined search categories based

on 77, 89, and 8 preferred terms, respectively), hypersensitivity reactions (based on three standardized MedDRA queries), and pancreatitis (based on one standardized MedDRA query and one preferred term) were assessed.

Statistical Analysis

Efficacy analyses were performed on the full analysis set (FAS), which included subjects treated with ≥1 dose of study drug who had a baseline and ≥1 on-treatment HbA_{1c} value. Safety was assessed in the treated set, which comprised subjects treated with ≥1 dose of study drug.

The primary end point was assessed using an ANCOVA model, with treatment, region, and eGFR at baseline as fixed-effects and baseline HbA_{1c} as a linear covariate. Values observed after a subject started rescue medication were set to missing. A last observation carried forward (LOCF) approach was used to impute missing continuous efficacy data. Continuous key secondary end points were analyzed using the ANCOVA model described for the primary end point with the baseline value for the end point in question as an additional linear covariate. Sensitivity analyses of the change from baseline in HbA_{1c} and FPG at week 24 were performed using restricted maximum likelihood–based mixed-model repeated measures (MMRM) in the FAS using observed cases and included treatment, region, visit, visit-by-treatment interaction, and eGFR as fixed-effects and baseline HbA_{1c} as a linear covariate. HbA_{1c} over 52 weeks was analyzed using the same MMRM analysis. Subgroup analyses at week 24 and changes from baseline at week 52 were analyzed using the ANCOVA model described for the primary end point. Categorical changes in HbA_{1c} at week 24 and week 52 were analyzed using logistic regression with noncompleters considered failure imputation.

Treatment differences in the primary and key secondary end points were tested hierarchically in the following order: HbA_{1c}, FPG, body weight (empagliflozin/linagliptin versus linagliptin only), and the percentage of subjects who reached HbA_{1c} <7% (<53 mmol/mol). For each end point, the superiority of empagliflozin 25 mg/linagliptin 5 mg versus the individual components was tested followed by the test of empagliflozin 10 mg/linagliptin 5 mg versus the individual components. Each test was at a significance level of 5% (two-sided). A test of superiority was confirmatory only if the previous tests were positive. With this procedure, the family-wise error rate was preserved at 5% (two-sided). Safety analyses were descriptive, except for changes in lipid parameters, which were analyzed using ANCOVA.

A sample size of 133 subjects per group was required to provide power of 89% to detect a 0.5% difference in change from baseline in HbA_{1c} between empagliflozin/linagliptin and the individual components, assuming a common SD of 1.05% and using a significance level of 2.5% (one-sided).

RESULTS

Subjects

In total, 677 subjects were randomized and treated, of whom 667 comprised the FAS (Supplementary Fig. 1). Baseline characteristics of the FAS were balanced between treatment groups (Table 1).

Efficacy

At week 24, reductions from baseline in HbA_{1c} were significantly greater with empagliflozin/linagliptin compared with the individual components, except for empagliflozin 25 mg/linagliptin 5 mg versus empagliflozin 25 mg (Fig. 1*A*). In subjects with HbA_{1c} ≥8.5% (≥69 mmol/mol) at baseline (mean baseline 9.08–9.39% [76–79 mmol/mol]), reductions from baseline in HbA_{1c} at week 24 were significantly greater with empagliflozin/linagliptin compared with the individual components, except for empagliflozin 25 mg/linagliptin 5 mg versus empagliflozin 25 mg (Fig. 1*B*). In subjects with HbA_{1c} <8.5% (<69 mmol/mol) at baseline (mean baseline 7.41–7.63% [57–60 mmol/mol]), reductions from baseline in HbA_{1c} were significantly greater with empagliflozin 10 mg/linagliptin 5 mg compared with the individual components but were not significantly different with empagliflozin 25 mg/linagliptin 5 mg compared with the individual components (Supplementary Fig. 2). Significantly more subjects with baseline HbA_{1c} ≥7% (≥53 mmol/mol) reached HbA_{1c} <7% (<53 mmol/mol) at week 24 with empagliflozin/linagliptin compared with the individual components (Fig. 1*C*). Reductions from baseline in FPG at week 24 were significantly greater with empagliflozin/linagliptin compared with linagliptin but were not significantly different compared with the respective empagliflozin components (Fig. 1*D*). Sensitivity analyses of changes from baseline in HbA_{1c} and FPG at week 24 were consistent with the results of the primary analyses (Supplementary Table 1). Reductions from baseline in weight at week 24 were significantly greater with empagliflozin/linagliptin compared with linagliptin but not compared with the respective empagliflozin components (Fig. 1*E*).

Reductions in HbA_{1c} with empagliflozin/linagliptin were sustained at week 52 (Fig. 2*A* and *B*). Significantly greater proportions of subjects with baseline HbA_{1c} ≥7% (≥53 mmol/mol) had HbA_{1c} <7% (<53 mmol/mol) at week 52 with empagliflozin/linagliptin compared with the individual components, except for empagliflozin 25 mg/linagliptin 5 mg compared with empagliflozin 25 mg (Fig. 2*C*). At week 52, reductions from baseline in FPG were significantly greater with empagliflozin/linagliptin compared with linagliptin but were not significantly different compared with the respective empagliflozin components (Supplementary Table 2).

Over 52 weeks, 6 (4.5%), 5 (3.7%), 6 (4.5%), 12 (9.1%), and 27 (20.3%) subjects on empagliflozin 25 mg/linagliptin 5 mg, empagliflozin 10 mg/linagliptin 5 mg, empagliflozin 25 mg, empagliflozin 10 mg, and linagliptin 5 mg, respectively, received rescue therapy. Most subjects who received rescue therapy received metformin or sulfonylurea.

Reductions from baseline in weight at week 52 were significantly greater with empagliflozin/linagliptin compared with linagliptin but were not significantly different compared with the respective empagliflozin components (Fig. 2*D*).

Changes from baseline in SBP and DBP at week 52 were not significantly different between empagliflozin/linagliptin and the individual components (Fig. 2*E* and *F*). Reductions in BP in the empagliflozin/linagliptin and empagliflozin monotherapy groups were not associated with relevant changes in pulse rate: mean ± SD changes from baseline at week 52 were 0.15 ± 8.83 bpm with empagliflozin 25 mg/linagliptin 5 mg, 0.24 ± 9.44 bpm with empagliflozin 10 mg/linagliptin 5 mg, −0.38 ± 8.52 bpm with empagliflozin 25 mg, −1.33 ± 8.16 bpm

Table 1—Demographics and baseline characteristics

	Empagliflozin 25 mg/ linagliptin 5 mg	Empagliflozin 10 mg/ linagliptin 5 mg	Empagliflozin 25 mg	Empagliflozin 10 mg	Linagliptin 5 mg
n	134	135	133	132	133
Male, *n* (%)	70 (52.2)	73 (54.1)	77 (57.9)	64 (48.5)	75 (56.4)
Age, years	54.2 (10.0)	55.2 (9.8)	56.0 (9.3)	53.9 (10.5)	53.8 (11.5)
Race, *n* (%)					
White	104 (77.6)	100 (74.1)	93 (69.9)	99 (75.0)	103 (77.4)
Asian	12 (9.0)	14 (10.4)	19 (14.3)	13 (9.8)	17 (12.8)
Other	18 (13.4)	21 (15.6)	21 (15.8)	20 (15.2)	13 (9.8)
Time since diagnosis of type 2 diabetes, *n* (%)					
≤1 years	41 (30.6)	46 (34.1)	48 (36.1)	43 (32.6)	50 (37.6)
>1 to 5 years	53 (39.6)	48 (35.6)	48 (36.1)	60 (45.5)	57 (42.9)
>5 to 10 years	28 (20.9)	30 (22.2)	25 (18.8)	15 (11.4)	22 (16.5)
>10 years	12 (9.0)	11 (8.1)	12 (9.0)	14 (10.6)	4 (3.0)
HbA_{1c}, %	7.99 (0.95)	8.04 (0.96)	7.99 (0.97)	8.05 (1.03)	8.05 (0.89)
HbA_{1c}, mmol/mol	64 (10.4)	64 (10.5)	64 (10.6)	64 (11.3)	64 (9.7)
HbA_{1c}, *n* (%)					
<8.5% (<69 mmol/mol)	88 (65.7)	95 (70.4)	97 (72.9)	94 (71.2)	99 (74.4)
≥8.5% (≥69 mmol/mol)	46 (34.3)	40 (29.6)	36 (27.1)	38 (28.8)	34 (25.6)
FPG, mg/dL	156.1 (35.8)	157.2 (35.4)	152.8 (39.0)	160.3 (41.2)	156.0 (37.1)
BMI, kg/m^2	31.8 (5.3)	31.5 (5.6)	31.2 (5.7)	31.5 (5.7)	31.9 (5.9)
Body weight, kg	87.9 (18.2)	87.3 (18.4)	86.7 (19.7)	87.8 (24.0)	89.5 (20.1)
SBP, mmHg	128.3 (14.7)	127.4 (14.1)	129.1 (14.7)	129.1 (15.8)	127.7 (14.4)
DBP, mmHg	77.9 (9.0)	78.4 (8.3)	78.7 (9.1)	79.4 (8.7)	78.2 (8.9)
eGFR, mL/min/1.73 m^2	90.1 (19.6)	87.8 (17.7)	88.5 (18.3)	88.4 (19.0)	89.5 (20.3)
eGFR, *n* (%)					
≥90 mL/min/1.73 m^2	62 (46.3)	54 (40.0)	58 (43.6)	59 (44.7)	57 (42.9)
60 to <90 mL/min/1.73 m^2	67 (50.0)	76 (56.3)	72 (54.1)	70 (53.0)	75 (56.4)
<60 mL/min/1.73 m^2	5 (3.7)	5 (3.7)	3 (2.3)	3 (2.3)	1 (0.8)

Data are means (SD), unless otherwise indicated, in the full analysis set (subjects treated with ≥1 dose of study drug who had a baseline and ≥1 on-treatment HbA_{1c} measurement).

with empagliflozin 10 mg, and 1.28 ± 9.23 bpm with linagliptin 5 mg.

Safety

Similar proportions of subjects in every treatment group had one or more AEs (Table 2). Most events were mild or moderate in intensity; severe events were reported in 5.9% of subjects in each of the combination therapy groups, 7.4% in each of the empagliflozin groups, and 0.7% on linagliptin 5 mg. There was one death in the empagliflozin 10 mg/linagliptin 5 mg group (hemorrhagic stroke), two deaths in the empagliflozin 25 mg group (meningitis tuberculosis and hepatic mass), and one death in the empagliflozin 10 mg group (brain edema).

No subjects receiving empagliflozin/linagliptin had confirmed hypoglycemic AEs. Confirmed hypoglycemic AEs were reported in one subject each in the empagliflozin 25 mg and linagliptin 5 mg groups and in four subjects in the empagliflozin 10 mg group; no events required assistance. Events consistent with UTI were reported in 12.5% of subjects on empagliflozin 25 mg/linagliptin 5 mg, 15.4% on empagliflozin 10 mg/linagliptin 5 mg, 10.4% on empagliflozin 25 mg, 16.3% on empagliflozin 10 mg, and 10.4% on linagliptin 5 mg; these events were reported in a greater proportion of female than male subjects in every group (Table 2). Only one subject (receiving empagliflozin 25 mg) reported an event consistent with UTI of severe intensity; this event did not lead to discontinuation of study drug. Chronic pyelonephritis was reported in one subject (receiving empagliflozin 10 mg); this event was mild in intensity and was not considered to be related to study drug. Events consistent with genital infection were reported in 5.9% of subjects on empagliflozin 25 mg/linagliptin 5 mg, 2.9% on empagliflozin 10 mg/linagliptin 5 mg, 4.4% on empagliflozin 25 mg, 5.2% on empagliflozin 10 mg, and 3% on linagliptin 5 mg; these events were reported in a greater proportion of female than male subjects in all groups except empagliflozin 25 mg/linagliptin 5 mg (Table 2). No severe events consistent with genital infection were reported, but two subjects (one on empagliflozin 25 mg/linagliptin 5 mg and one on empagliflozin 10 mg) discontinued study drug due to these events. Hypersensitivity reactions were reported in two subjects on empagliflozin 25 mg/linagliptin 5 mg (asthmatic crisis and eyelid edema), one on empagliflozin 10 mg/linagliptin 5 mg (asthma), two on empagliflozin 25 mg (urticaria), two on empagliflozin 10 mg (asthma), and none on linagliptin 5 mg. Pancreatitis (pancreatitis acute) was reported in one subject (empagliflozin 25 mg/linagliptin 5 mg). No subjects experienced worsening of heart failure or were hospitalized due to heart failure.

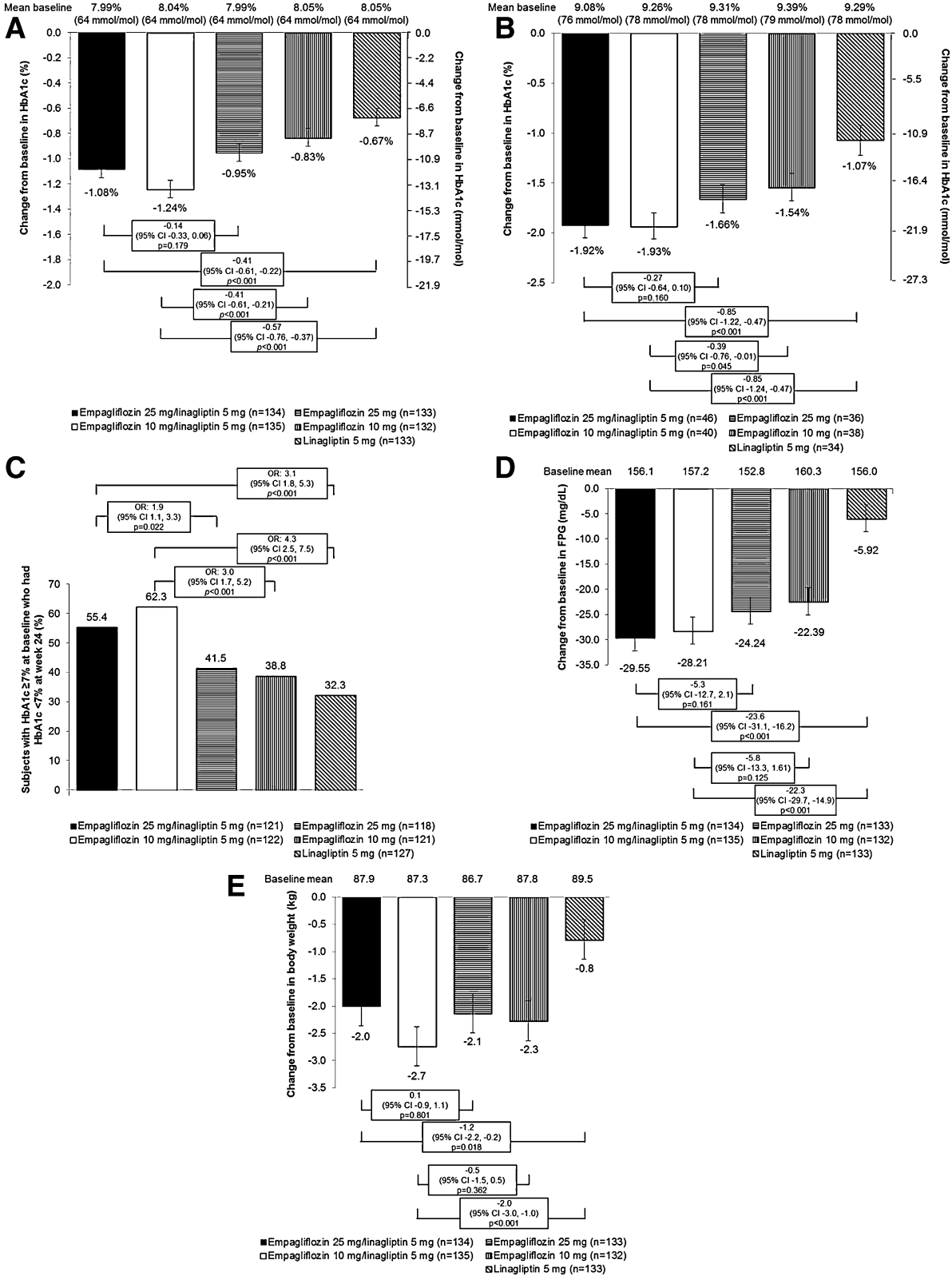

Figure 1—Efficacy parameters at week 24. *A*: Change from baseline in HbA_{1c} at week 24 (ANCOVA using LOCF). *B*: Change from baseline in HbA_{1c} at week 24 in subjects with baseline HbA_{1c} ≥8.5% (≥69 mmol/mol) (ANCOVA, LOCF). *C*: Subjects with HbA_{1c} ≥7% (≥53 mmol/mol) at baseline who reached HbA_{1c} <7% (<53 mmol/mol) at week 24 (logistic regression). *D*: Change from baseline in FPG at week 24 (ANCOVA, LOCF). *E*: Change from baseline in body weight at week 24 (ANCOVA, LOCF). Data are adjusted means ± SE or *n* (%) in the full analysis set. OR, odds ratio.

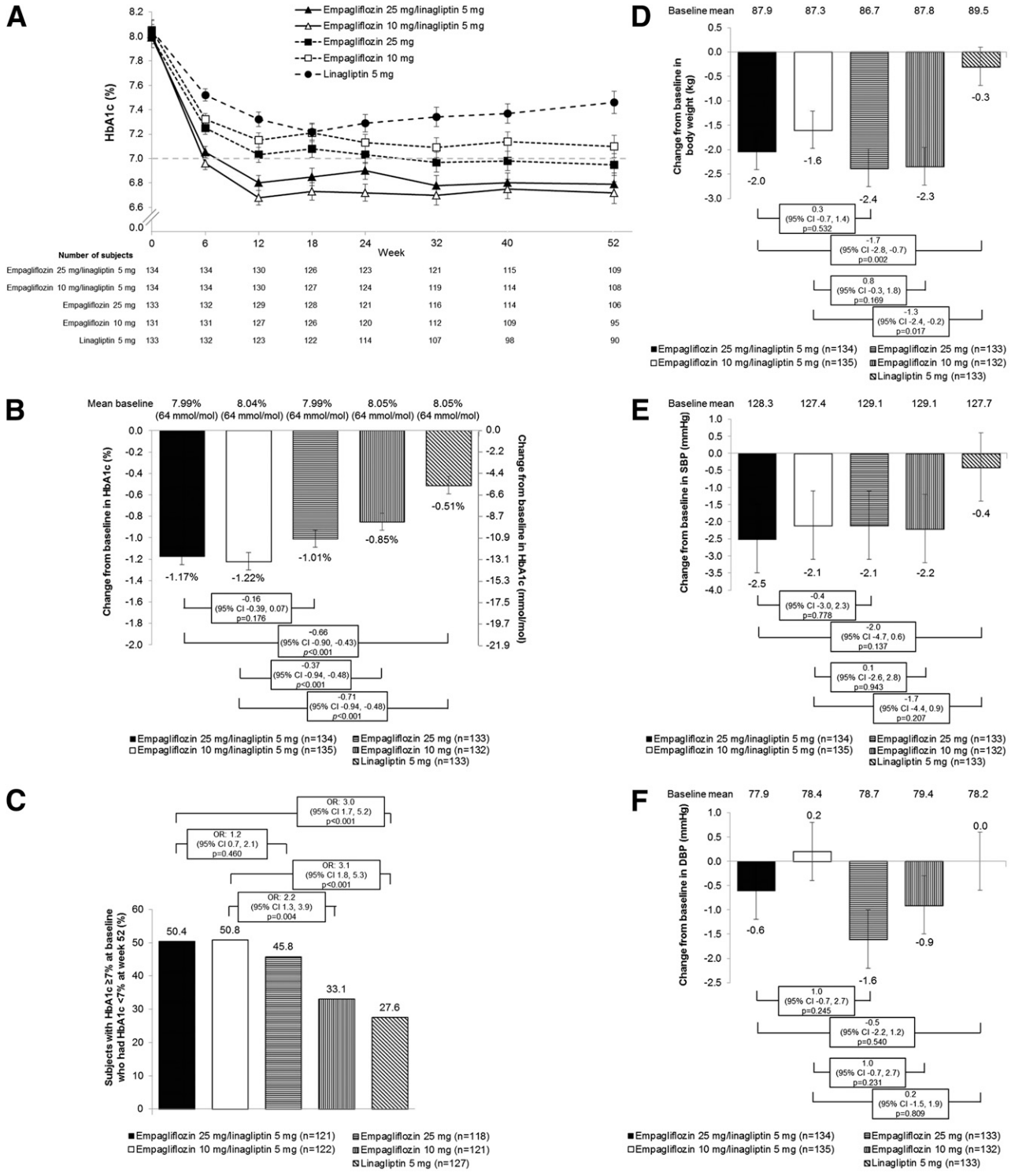

Figure 2—Changes in efficacy parameters at week 52. *A*: HbA_{1c} over 52 weeks (MMRM analysis using observed cases). *B*: Change from baseline in HbA_{1c} at week 52 (ANCOVA using LOCF). *C*: Subjects with $HbA_{1c} \geq 7\%$ (≥ 53 mmol/mol) who reached $HbA_{1c} < 7\%$ (< 53 mmol/mol) at week 52 (logistic regression). *D*: Change from baseline in body weight at week 52 (ANCOVA, LOCF). *E*: Change from baseline in SBP at week 52 (ANCOVA, LOCF). *F*: Change from baseline in DBP at week 52 (ANCOVA, LOCF). Data are adjusted means ± SE or *n* (%) in the full analysis set. OR, odds ratio.

Changes from baseline in laboratory measurements at week 52 are shown in Supplementary Table 3. Changes from baseline in eGFR observed at week 52 and follow-up were small in all groups. Mean changes from baseline in hematocrit were 4.2–4.8% in the empagliflozin/linagliptin and empagliflozin groups and 1.3% in the linagliptin group. Mean changes from baseline in uric acid were −56.5 to −71.4 μmol/L in the empagliflozin/linagliptin and empagliflozin groups and 3.0 μmol/L in the linagliptin group. There were no clinically meaningful changes in electrolytes. There

Table 2—AEs

	Empagliflozin 25 mg/linagliptin 5 mg	Empagliflozin 10 mg/linagliptin 5 mg	Empagliflozin 25 mg	Empagliflozin 10 mg	Linagliptin 5 mg
n	136	136	135	135	135
One or more AEs	103 (75.7)	99 (72.8)	93 (68.9)	110 (81.5)	97 (71.9)
One or more drug-related AEs*	23 (16.9)	14 (10.3)	22 (16.3)	16 (11.9)	17 (12.6)
One or more AEs leading to discontinuation	9 (6.6)	8 (5.9)	5 (3.7)	7 (5.2)	2 (1.5)
One or more severe AEs	8 (5.9)	8 (5.9)	10 (7.4)	10 (7.4)	1 (0.7)
One or more serious AEs	6 (4.4)	7 (5.1)	9 (6.7)	10 (7.4)	2 (1.5)
Deaths	0	1 (0.7)	2 (1.5)	1 (0.7)	0
AEs with frequency of ≥5% in any group (by preferred term)					
UTI	15 (11.0)	17 (12.5)	8 (5.9)	17 (12.6)	12 (8.9)
Upper respiratory tract infection	8 (5.9)	5 (3.7)	9 (6.7)	2 (1.5)	12 (8.9)
Nasopharyngitis	10 (7.4)	5 (3.7)	5 (3.7)	9 (6.7)	8 (5.9)
Influenza	7 (5.1)	7 (5.1)	3 (2.2)	6 (4.4)	2 (1.5)
Hyperglycemia	8 (5.9)	5 (3.7)	4 (3.0)	10 (7.4)	14 (10.4)
Dyslipidemia	9 (6.6)	9 (6.6)	4 (3.0)	8 (5.9)	3 (2.2)
Headache	9 (6.6)	8 (5.9)	7 (5.2)	9 (6.7)	16 (11.9)
Dizziness	7 (5.1)	3 (2.2)	4 (3.0)	5 (3.7)	6 (4.4)
Constipation	2 (1.5)	2 (1.5)	8 (5.9)	4 (3.0)	2 (1.5)
Back pain	5 (3.7)	4 (2.9)	9 (6.7)	4 (3.0)	3 (2.2)
Arthralgia	4 (2.9)	8 (5.9)	6 (4.4)	7 (5.2)	6 (4.4)
Weight decrease	1 (0.7)	1 (0.7)	7 (5.2)	0	0
Confirmed hypoglycemic AEs†	0	0	1 (0.7)	4 (3.0)	1 (0.7)
Events requiring assistance	0	0	0	0	0
Events consistent with UTI‡	17 (12.5)	21 (15.4)	14 (10.4)	22 (16.3)	14 (10.4)
Male	4 (5.6)	5 (6.8)	3 (3.8)	6 (9.2)	2 (2.7)
Female	13 (20.3)	16 (25.8)	11 (19.3)	16 (22.9)	12 (20.0)
Events consistent with genital infection§	8 (5.9)	4 (2.9)	6 (4.4)	7 (5.2)	4 (3.0)
Male	5 (6.9)	1 (1.4)	1 (1.3)	2 (3.1)	1 (1.3)
Female	3 (4.7)	3 (4.8)	5 (8.8)	5 (7.1)	3 (5.0)
Events consistent with volume depletion‖	1 (0.7)	3 (2.2)	0	0	0
Hypersensitivity reactions¶	2 (1.5)	1 (0.7)	2 (1.5)	2 (1.5)	0
Pancreatitis#	1 (0.7)	0	0	0	0

Data are *n* (%) in the treated set (subjects who received ≥1 dose of study drug). *As assessed by the investigator. †Plasma glucose ≤70 mg/dL and/or requiring assistance. ‡Based on 77 MedDRA preferred terms. §Based on 89 MedDRA preferred terms. ‖Based on 8 MedDRA preferred terms. ¶Based on 3 standardized MedDRA queries. #Based on 1 standardized MedDRA query and 1 preferred term.

were no significant differences in changes from baseline in total cholesterol, LDL cholesterol, and triglycerides between empagliflozin/linagliptin and the individual components, except for a greater increase in total cholesterol with empagliflozin 25 mg/linagliptin 5 mg compared with linagliptin 5 mg (Supplementary Table 3). There were no significant differences in changes from baseline in HDL cholesterol between empagliflozin/linagliptin and the empagliflozin components, but there was a greater increase in HDL cholesterol with empagliflozin/linagliptin than with linagliptin (Supplementary Table 3). There were no consistent patterns in the proportions of subjects on empagliflozin/linagliptin with shifts in albuminuria categories from baseline to the end of treatment compared with the respective components (Supplementary Table 4).

CONCLUSIONS

This is the first randomized controlled trial to evaluate the efficacy and safety of the initial combination of an SGLT2 inhibitor and a DPP-4 inhibitor in subjects with type 2 diabetes. Initial combination of empagliflozin/linagliptin led to clinically meaningful reductions from baseline in HbA_{1c} in subjects with type 2 diabetes, with >50% of subjects reaching HbA_{1c} <7% (<53 mmol/mol) at week 52. Greater reductions from baseline in HbA_{1c} (of up to 1.93% [21.1 mmol/mol]) were observed with empagliflozin/linagliptin in subjects with baseline HbA_{1c} ≥8.5% (≥69 mmol/mol) compared with those with baseline HbA_{1c} <8.5% (<69 mmol/mol) who had reductions of up to 0.96% (10.5 mmol/mol). Initial combination of empagliflozin/linagliptin may be an option in patients presenting with marked hyperglycemia, as achieving glycemic targets may be challenging with traditional stepwise treatment escalation, and treatment escalation in clinical practice is often delayed. In a retrospective analysis of >3,000 patients on sulfonylurea monotherapy and >500 patients on metformin monotherapy, patients spent an average of 20.5 months with HbA_{1c} >8% (>64 mmol/mol) on sulfonylurea monotherapy and 14.5 months with HbA_{1c} >8% (>64 mmol/mol) on metformin monotherapy before a new treatment was initiated (15).

Unexpectedly, while empagliflozin 10 mg/linagliptin 5 mg demonstrated greater efficacy compared with

empagliflozin 10 mg and compared with linagliptin, empagliflozin 25 mg/linagliptin 5 mg showed greater efficacy compared with linagliptin 5 mg but not compared with empagliflozin 25 mg. There were no imbalances in baseline characteristics, dropouts, or outliers between treatment groups that explained this finding, and the reasons behind it are unclear. However, although subjects did not receive treatment for ≥12 weeks before randomization, we cannot rule out the possibility that subjects who had previously received treatment had different responses compared with "true" drug-naïve subjects.

Empagliflozin consistently leads to weight loss, likely due to loss of calories via increased urinary glucose excretion (16), while linagliptin treatment is weight neutral (7). As expected, the effect of empagliflozin on body weight was maintained when empagliflozin was used in combination with linagliptin, with both combinations significantly reducing weight compared with linagliptin monotherapy. Empagliflozin reduces SBP via mechanisms that may include osmotic diuretic effects, weight loss, reduced arterial stiffness, or direct vascular effects (17–19), while linagliptin has no effect on blood pressure (20). In this study, treatment with empagliflozin/linagliptin and empagliflozin alone resulted in a consistent, modest reduction in SBP from baseline, but reductions with empagliflozin/linagliptin were not statistically significant compared with linagliptin monotherapy.

Slightly higher percentages of subjects had AEs leading to discontinuation, severe AEs, and serious AEs with empagliflozin/linagliptin or empagliflozin compared with linagliptin, but all the treatments were well tolerated. The overall safety profiles of empagliflozin/linagliptin were similar to the known safety profiles of the individual components. In patients with type 2 diabetes, hypoglycemia is associated with increased risk of cardiovascular events, reduced quality of life, and deterioration in glucose control (21). Empagliflozin and linagliptin are associated with a low risk of hypoglycemia when given as monotherapy (3,8), and no confirmed hypoglycemic AEs were observed with empagliflozin/linagliptin. Guidelines recommend that the potential for hypoglycemic events should play a major role in the selection of first-line therapy if metformin is not used and in the selection of combination therapies (9). Therefore, the low risk of hypoglycemic AEs with empagliflozin/linagliptin in this study is a particularly important finding.

Strengths of this study include the 52-week trial duration to assess the sustainability of the effect of empagliflozin/linagliptin. Limitations include the lack of a placebo arm, which means that the additive efficacy of empagliflozin/linagliptin compared with the individual components cannot be conclusively assessed, and the fact that the patient population studied may not have been a homogenous population of drug-naïve patients.

In conclusion, initial combination of empagliflozin/linagliptin led to clinically meaningful reductions from baseline in HbA_{1c} in subjects with type 2 diabetes. Reductions with empagliflozin 10 mg/linagliptin 5 mg were significantly greater than with the individual components, and reductions with empagliflozin 25 mg/linagliptin 5 mg were significantly greater compared with linagliptin 5 mg but not compared with empagliflozin 25 mg. Empagliflozin/linagliptin was well tolerated, with a low risk of hypoglycemia. Initial combination of empagliflozin/linagliptin may provide a treatment option for patients with type 2 diabetes who are intolerant to metformin and/or have marked hyperglycemia, without the side effects of weight gain or increased risk of hypoglycemia.

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