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ORIGINAL ARTICLE

Empagliflozin as add-on to linagliptin in a fixed-dose combination in Japanese patients with type 2 diabetes: Glycaemic efficacy and safety profile in a 52-week, randomized, placebo-controlled trial

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Aims: This double-blind, randomized, placebo-controlled trial (ClinicalTrials.gov NCT02453555) evaluated the efficacy and safety of empagliflozin (Empa) 10 or 25 mg as add-on to linagliptin (Lina) 5 mg (fixed-dose combination, Empa/Lina 10/5 or 25/5) in insufficiently controlled Japanese type 2 diabetes patients.

Methods: The trial (40 sites; May 2015-March 2017) involved screening 433 adults (≥20 years) who were treatment-naive or were using one oral antidiabetic drug for ≥12 weeks, which was discontinued at enrolment. Patients with HbA1c 7.5%-10.0% after ≥16 weeks of using Lina (pre-enrolment or during a 16-week, open-label period) and 2 weeks of using placebo (Plc) for Empa/Lina 10/5, plus Lina, were randomized (2:1) to once-daily Empa/Lina 10/5 (n = 182) or Plc/Lina 10/5 (n = 93) for 24 weeks. Patients with HbA1c ≥ 7.0% at Week 24 received Empa/Lina up-titrated to 25/5 (n = 126) or the corresponding placebo (n = 80), per randomization, from Week 28; 172 Empa/Lina and 84 Plc/Lina patients completed 52 weeks.

Results: Change from baseline in HbA1c was greater ($P < .0001$) with Empa/Lina than with Plc/Lina at Week 24 (primary outcome, −0.93% vs 0.21%; adjusted mean difference, −1.14%) and Week 52 (−1.16% vs 0.06%; adjusted mean difference, −1.22%). More patients with HbA1c < 7.0% and greater decreases in fasting plasma glucose, body weight and systolic blood pressure were seen in the Empa/Lina group than in the Plc/Lina group. Empa/Lina was well tolerated. The adverse events that were more frequent with Empa/Lina were known empagliflozin-associated events (eg, increased urination, increased blood ketones). There were no adjudication-confirmed diabetic ketoacidosis events or lower limb amputations.

Conclusions: These results support the notion that empagliflozin-linagliptin in fixed-dose combination is a therapeutic option for Japanese patients with type 2 diabetes.

KEYWORDS

empagliflozin, glycaemic control, linagliptin, phase III study, randomized trial, type 2 diabetes

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1 | INTRODUCTION

Treatment guidelines for type 2 diabetes mellitus (T2DM) recommend initiating pharmacotherapy with an oral antidiabetic drug (OAD) to reduce hyperglycaemia when diet and exercise are inadequate.[1,2] International guidelines recommend metformin as the first OAD,[1] whereas Japanese guidelines[2] recognize that other OADs may be more appropriate in Japanese patients.[3–5] Irrespective of the first-line OAD, most patients eventually require an additional OAD with a complementary mechanism to maintain glycaemic control.[1]

Dipeptidyl peptidase-4 (DPP-4) inhibitors stimulate glucose-dependent insulin secretion via increased levels of active glucagon-like peptide-1 (GLP-1),[6] resulting in lower glycated haemoglobin (HbA1c) and fasting plasma glucose (FPG), with low risk of hypoglycaemia.[6,7] DPP-4 inhibitors improve glycaemic control in Asian patients,[8] possibly because Asian patients have reduced insulin secretion capacity,[3–5] and are the most commonly prescribed OAD in Japan.[9,10] Linagliptin is a potent and selective DPP-4 inhibitor, with demonstrated efficacy and safety,[7] including in Japanese patients.[11] Unlike other DPP-4 inhibitors, linagliptin is primarily excreted by non-renal elimination routes.[6]

Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce plasma glucose by blocking renal glucose reabsorption, thus increasing urinary glucose excretion.[12] The SGLT2 inhibitor empagliflozin is efficacious as monotherapy and as add-on to other OADs, including in Japanese patients.[12–14] In addition to reducing HbA1c and FPG, empagliflozin reduces body weight, systolic blood pressure (SBP)[12–14] and the risk of cardiovascular mortality in high-risk patients with T2DM.[15]

Randomized trials have demonstrated that single-pill, fixed-dose combinations (FDCs) of empagliflozin and linagliptin reduce HbA1c more than either component alone in treatment-naive patients[16] and as add-on to metformin.[17] Empagliflozin/linagliptin FDCs are also effective in patients who are inadequately controlled with empagliflozin plus metformin[18] or linagliptin plus metformin.[19] However, empagliflozin as add-on to linagliptin has not yet been fully evaluated in Japanese patients in a double-blind, placebo-controlled trial.

The primary objective of this double-blind, randomized, placebo-controlled trial was to evaluate the efficacy and safety of empagliflozin 10 mg and linagliptin 5 mg FDC (Empa/Lina 10/5) vs linagliptin 5 mg for 24 weeks in Japanese patients who were inadequately controlled with linagliptin. A secondary objective was to evaluate the efficacy and safety of FDCs of empagliflozin (10 or 25 mg) and linagliptin 5 mg vs placebo during a 24-week, up-titration period.

2 | MATERIALS AND METHODS

2.1 | Study details

This was a 52-week, multicentre, phase III, double-blind, double-dummy, randomized, placebo-controlled trial of once-daily empagliflozin/linagliptin FDC compared with linagliptin plus placebo in Japanese patients with T2DM with insufficient glycaemic control after ≥16 weeks of linagliptin 5 mg (Figure S1). The study (ClinicalTrials.gov NCT02453555) was conducted at 40 sites in Japan between May 2015 and March 2017. The study was in compliance with the Japanese Ethical Guideline for Clinical Studies and the Declaration of Helsinki, and was approved by the institutional review board at each site. All patients provided prior written informed consent.

2.2 | Study population

Inclusion criteria included: male and female adults (≥20 years) with a body mass index (BMI) ≤ 40.0 kg/m^2 and a diagnosis of T2DM who had been on a diet and exercise regimen for ≥12 weeks and were either treatment-naive or using a stable dosage of one OAD (sulfonylurea up to half the maximum approved dosage) for ≥12 weeks (≥18 weeks for thiazolidinedione); OADs (except linagliptin) were discontinued at screening. Required HbA1c levels (National Glycohaemoglobin Standardization Programme % units; mmol/mol = [10.93 × %] − 23.5) at screening were ≥ 8.0% and ≤ 10.5% for treatment-naive patients, ≥7.5% and ≤10.5% for OAD-pretreated (except linagliptin) patients, and ≥7.5% and ≤10.0% for linagliptin-pretreated patients.

Exclusion criteria included: uncontrolled hyperglycaemia, defined as FPG > 270 mg/dL (>15 mmol/L; mmol/L = [mg/dL]/18) during the open-label period (confirmed by two measurements); acute coronary syndrome, stroke or transient ischemic attack within 3 months; treatment with insulin, GLP-1 agonists, anti-obesity drugs or any other treatment leading to unstable body weight within 12 weeks before informed consent; indication of liver disease (alanine aminotransferase, aspartate aminotransferase or alkaline phosphatase >3 × upper limit of normal); and estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73 m^2.

2.3 | Study design

To ensure that all patients were pre-treated with linagliptin for ≥16 weeks before switching, treatment-naive and OAD (except linagliptin)-pre-treated patients entered a 16-week, open-label stabilization period of linagliptin 5 mg (Lina 5; Boehringer Ingelheim Roxane, Inc., USA) treatment. Patients who had been pre-treated with linagliptin before study enrolment were not involved in this period. All patients then received placebo matching Empa/Lina 10/5 (Temmler Werke GmbH, Germany), plus Lina 5, during a 2-week run-in period.

Patients with HbA1c ≥7.5% and ≤10.0% after ≥16 weeks of linagliptin monotherapy (ie, immediately before run-in) were randomized 2:1 to receive Empa/Lina 10/5 (Boehringer Ingelheim Pharma GmbH & Co. KG, Germany) plus placebo matching Lina 5 (Empa/Lina 10/5 group) or placebo matching Empa/Lina 10/5 plus Lina 5 (Plc/Lina 10/5 group) for 24 weeks. Treatment assignment was determined by a computer-generated random sequence using a web-based interactive response system and was stratified by HbA1c (<8.5% or ≥8.5%), by eGFR (≥ 45 and <60, ≥60 and <90 or ≥90 mL/min/1.73 m^2) and by prior OAD (none, linagliptin or other). All study drugs were taken orally once daily in the morning.

Patients with HbA1c ≥7.0% after 24 weeks of Empa/Lina 10/5 or Plc/Lina 10/5 received empagliflozin up-titrated to 25 mg/linagliptin 5 mg (Empa/Lina 25/5) or matching placebo (Plc/Lina 25/5), according to randomization group, starting at Week 28. This up-titration aligns with the Japanese package insert for empagliflozin and with clinical

guidance for patients inadequately controlled with low-dose OADs.[2] Patients with HbA1c < 7.0% at Week 24 continued their original treatment. Patients with confirmed FPG > 270 mg/dL (Weeks 0-8), FPG > 240 mg/dL (Weeks 8-12), FPG > 200 mg/dL (Weeks 12-24) or FPG > 180 mg/dL and/or HbA1c > 8.0% (Weeks 24-52) were eligible for rescue medication. With the exception of DPP-4 inhibitors, SGLT2 inhibitors and GLP-1 agonists, which were prohibited, the choice of rescue medication and dosage were at the investigator's discretion.

2.4 | Efficacy outcome measures

The primary endpoint was change in HbA1c from baseline (randomization) to Week 24 for Empa/Lina 10/5 vs Plc/Lina 10/5. Secondary endpoints included change in HbA1c from baseline to Week 52 for All Empa/Lina 5 (Empa/Lina 10/5 group at randomization; includes Empa/Lina 10/5 and Empa/Lina 25/5 groups for Weeks 28-52) vs All Plc/Lina 5 (Plc/Lina 10/5 group at randomization; includes Plc/Lina 10/5 and Plc/Lina 25/5 groups for Weeks 28-52) and change in HbA1c from Week 28 to Week 52 in patients who received Empa/Lina up-titrated to 25/5. Exploratory endpoints included: proportion of patients achieving HbA1c < 7.0% at Weeks 24 and 52; changes in FPG, body weight, SBP, diastolic blood pressure (DBP), fasting plasma insulin and plasma glucagon from baseline to Weeks 24 and 52; and proportion of patients achieving a composite endpoint (decreases from baseline in HbA1c ≥ 0.5%, SBP > 3 mm Hg and body weight > 2%) at Weeks 24 and 52.

2.5 | Safety outcome measures

The type and frequency of adverse events (AEs; coded using Medical Dictionary for Regulatory Activities [MedDRA], version 19.1), serious AEs (SAEs) and AEs of special interest (AESIs) were assessed. AESIs were selected based on the mechanism of action of SGLT2 and DPP-4 inhibitors, or on previous safety concerns for these drugs,[6,20] and included: arthralgia; bone fracture; cardiac failure; confirmed hypoglycaemia (plasma glucose levels ≤70 mg/dL or requiring assistance); acute kidney injury; embolic/thrombotic events; genital infection; hepatic injury; hypersensitivity; increased urination; infections; influence on safety of weight decrease; intestinal obstruction; lower limb amputation; malignancies; metabolic acidosis, ketoacidosis or diabetic ketoacidosis (DKA); pancreatitis; skin lesions; urinary tract infection; and volume depletion. Urinary and blood laboratory parameters were measured centrally every 4 weeks. Independent external committees were established for adjudication of cardiovascular, pancreatic, hepatic and DKA events. Any new, unexpected and unfavourable safety finding not previously seen in studies of Empa/Lina FDC or the monocomponents would be evaluated as a possible safety signal.

2.6 | Statistical analysis

Based on previous experience, the between-group difference in HbA1c change from baseline at Week 24 was assumed to be 0.5%, with a standard deviation (SD) of 1.1%. Assuming that 7% of patients discontinued before the up-titration period, 25% would receive up-titrated medication and 3% would be excluded from analysis, randomization of 182 and 91 patients to the Empa/Lina 10/5 and Plc/Lina 10/5 groups, respectively, would provide 80% probability of detecting a further decrease in HbA1c from Week 28 to Week 52 in Empa/Lina 10/5 patients who received Empa/Lina up-titrated to 25/5. This sample size provides 93% power for the primary endpoint.

The primary endpoint was analysed using a restricted maximum likelihood-based mixed-model repeated measures (MMRM) approach in all randomized patients who received ≥1 dose of study drug and underwent both baseline and ≥1 on-treatment HbA1c assessment during the 24-week double-blind period. The model included treatment, baseline renal function, prior OAD use, visit and visit-by-treatment interaction as fixed effects, and baseline HbA1c as a linear covariate. The model was used to estimate differences in means between treatment groups and their 95% confidence intervals (CI). Missing data were handled implicitly by the model (observed cases) rather than by imputation. Data obtained after use of rescue medication were treated as missing values. Other continuous efficacy endpoints were analysed using the same MMRM model, with the respective baseline parameter as an additional covariate. Binary efficacy endpoints were analysed using a logistic regression model, with treatment, baseline renal function, prior OAD use and baseline HbA1c as covariates, to obtain odds ratios, 95% CIs and *P* values. Safety was analysed in randomized patients who received ≥1 dose of study drug and was presented using descriptive statistics. Two-sided *P* values <.05 were considered significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina).

3 | RESULTS

3.1 | Patient disposition

Among 433 screened patients, 52 were ineligible, mostly because they did not meet HbA1c inclusion criteria. Of the remainder, 169 linagliptin-naive patients received Lina 5 during the stabilization period, whereas 212 linagliptin-pre-treated patients directly entered the run-in period (Figure S2). A total of 182 patients were randomized to Empa/Lina 10/5 and 93 patients to Plc/Lina 10/5; 106 patients discontinued before randomization, mostly because they no longer met HbA1c inclusion criteria. At Week 28, 126 patients (71%) in the Empa/Lina 10/5 group and 80 patients (93%) in the Plc/Lina 10/5 group received Empa/Lina up-titrated to 25/5 and Plc/Lina to 25/5, respectively.

3.2 | Demographic and baseline clinical characteristics

Most (214/275; 78%) patients were men with a mean age of ~60 years and ~9 years since T2DM diagnosis (Table 1). Mean baseline values were HbA1c, ~8.3%; FPG, ~178 mg/dL; body weight, ~72 kg; SBP, ~132 mm Hg; DBP, ~80 mm Hg; BMI, ~26-27 kg/m^2; and eGFR, ~87-88 mL/min/1.73 m^2. Approximately 61.5% (169/275) of patients were pre-treated with linagliptin and 32% (88/275) with

TABLE 1 Patient demographics and baseline characteristics

Variable	Plc/Lina 10/5 (n = 93)	Empa/Lina 10/5 (n = 182)
Male	72 (77.4)	142 (78.0)
Age, years	59.8 ± 10.8	60.0 ± 9.9
Weight, kg	73.1 ± 15.9	71.2 ± 12.6
Body mass index, kg/m^2	26.6 ± 4.5	26.0 ± 3.8
HbA1c, %[a]	8.36 ± 0.74	8.27 ± 0.65
FPG, mg/dL[b,c]	178.4 ± 33.1	177.5 ± 34.3
SBP, mm Hg	133.1 ± 15.7	131.7 ± 14.5
DBP, mm Hg	80.4 ± 11.1	80.1 ± 10.6
eGFR, mL/min/1.73 m^2	86.3 ± 15.2	89.3 ± 18.3
Time since diagnosis of T2DM		
Mean years	8.7 ± 6.1	9.0 ± 7.2
≤1 year	7 (7.5)	10 (5.5)
>1 to 5 years	22 (23.7)	53 (29.1)
>5 to 10 years	29 (31.2)	58 (31.9)
>10 years	35 (37.6)	61 (33.5)
Prior use of OADs		
No treatment	6 (6.5)	12 (6.6)
Pre-treated with 1 OAD, excluding linagliptin	30 (32.3)	58 (31.9)
Pre-treated with linagliptin	57 (61.3)	112 (61.5)

Abbreviations: DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate by Modification of Diet in Renal Disease equation; Empa/Lina 10/5, empagliflozin 10 mg/linagliptin 5 mg fixed-dose combination; FPG, fasting plasma glucose; HbAc1, glycated haemoglobin; OAD, oral antidiabetic drug; Plc/Lina 10/5, placebo for empagliflozin 10 mg/linagliptin 5 mg fixed-dose combination plus linagliptin 5 mg; SBP, systolic blood pressure; SD, standard deviation; T2DM, type 2 diabetes mellitus. Data are presented as n (%) or mean ± SD in patients who received ≥1 dose of study drug and had baseline and at least one post-baseline HbA1c measurement.

[a] Conversion factor: mmol/mol = (10.93 × %) – 23.5.

[b] Conversion factor: mmol/L = (mg/dL)/18.

[c] Empa 10/Lina 5: n = 181.

another OAD; approximately 6.5% (18/275) of patients were treatment-naive.

3.3 | Change in HbA1c

Compared with linagliptin monotherapy, empagliflozin/linagliptin resulted in significantly greater decreases in HbA1c at Weeks 24 (primary endpoint) and 52 (Figure 1A). At Week 24, the adjusted mean (standard error [SE]) change from baseline in HbA1c was significantly greater in the Empa/Lina 10/5 group (−0.93% [0.06%]) than in the Plc/Lina 10/5 group (0.21% [0.09%]; adjusted mean difference [95% CI], −1.14% [−1.36%, −0.91%]; P < .0001). A further decrease was seen at Week 52 (adjusted mean difference [95% CI], −1.22% [−1.45%, −0.99%]; P < .0001). The greater decrease in HbA1c with empagliflozin/linagliptin compared with linagliptin monotherapy was evident from Week 4 and was sustained through 52 weeks (Figure 1B). A decrease in HbA1c was also seen in patients who received Empa/Lina up-titrated from 10/5 to Empa/Lina 25/5 (adjusted mean [SE] change from pre-titration to Week 52, −0.21% [0.03%]). Significantly greater proportions of patients treated with empagliflozin/linagliptin achieved HbA1c levels <7.0% at Weeks 24 (27.5% vs 5.4%) and 52 (43.4% vs 7.5%; P < .0001 at both timepoints) compared with linagliptin monotherapy (Figure 2).

3.4 | Fasting plasma glucose

Empagliflozin/linagliptin treatment resulted in significantly greater decreases in FPG at Weeks 24 (adjusted mean difference [SE], −40.18 [3.33] mg/dL) and 52 (−40.11 [3.48] mg/dL) compared with linagliptin monotherapy (P < .0001 at both timepoints) (Figure 3A). The greater decrease in FPG with empagliflozin/linagliptin occurred by Week 4 and was sustained (Figure 3B).

3.5 | Other efficacy outcomes

Compared with linagliptin monotherapy, empagliflozin/linagliptin resulted in significantly greater decreases in body weight and SBP, but not DBP, at Weeks 24 and 52 (Figure S3). Adjusted mean [SE] differences between groups in the change from baseline were: body weight, −1.68 [0.24] kg at Week 24 and −1.53 [0.34] kg at Week 52 (P < .0001 at both timepoints); SBP, −4.8 [1.6] mm Hg at Week 24 (P = .0025) and −3.8 [1.7] mm Hg at Week 52 (P = .0280); DBP, −1.1 [0.9] mm Hg at Week 24 (P = .2374) and −1.8 [1.1] mm Hg at Week 52 (P = .0986). Significantly greater proportions of patients receiving empagliflozin/linagliptin, compared with linagliptin monotherapy, achieved the composite endpoint at Weeks 24 (31.9% vs 2.2%) and 52 (36.3% vs 3.2%; P < .0001 at both timepoints) (Figure S4). Significantly fewer patients receiving empagliflozin/linagliptin, compared with linagliptin monotherapy, required rescue medication at Weeks 24 (1.1% vs 31.2%) and 52 (6.0% vs 53.8%; P < .0001 at both timepoints) (Table S1).

3.6 | Insulin and glucagon

Mean fasting plasma insulin concentrations were significantly lower with empagliflozin/linagliptin (66.3-71.8 pmol/L) than with linagliptin monotherapy (72.8-91.6 pmol/L) throughout the double-blind treatment period, except Week 52 (Figure S5A). Mean plasma glucagon concentrations were numerically lower in patients treated with empagliflozin/linagliptin, but between-group differences were significant only at Weeks 8 and 48 (Figure S5B).

3.7 | Safety and tolerability measures

The incidence of AEs was lower in patients receiving empagliflozin/linagliptin than in patients receiving linagliptin monotherapy (Table 2). Discontinuation because of an AE was similar in both groups (1.1% at Week 24, 2.2% at Week 52). Drug-related AEs over 52 weeks were more common in the All Empa/Lina 5 group than in the All Plc/Lina 5 group, primarily because of increased blood ketone bodies (4.4% vs 1.1%), pollakiuria (frequent daytime urination) (2.2% vs 0%) and cystitis (2.2% vs 1.1%); all were AEs associated with SGLT2 inhibitors.[20]

Over 52 weeks, nine SAEs were reported by eight patients (4.4%) receiving empagliflozin/linagliptin (three SAEs of neoplasm [different organs], one each of cerebral haemorrhage, prinzmetal angina, cholelithiasis, glaucoma, foot fracture and knee fracture). Three SAEs

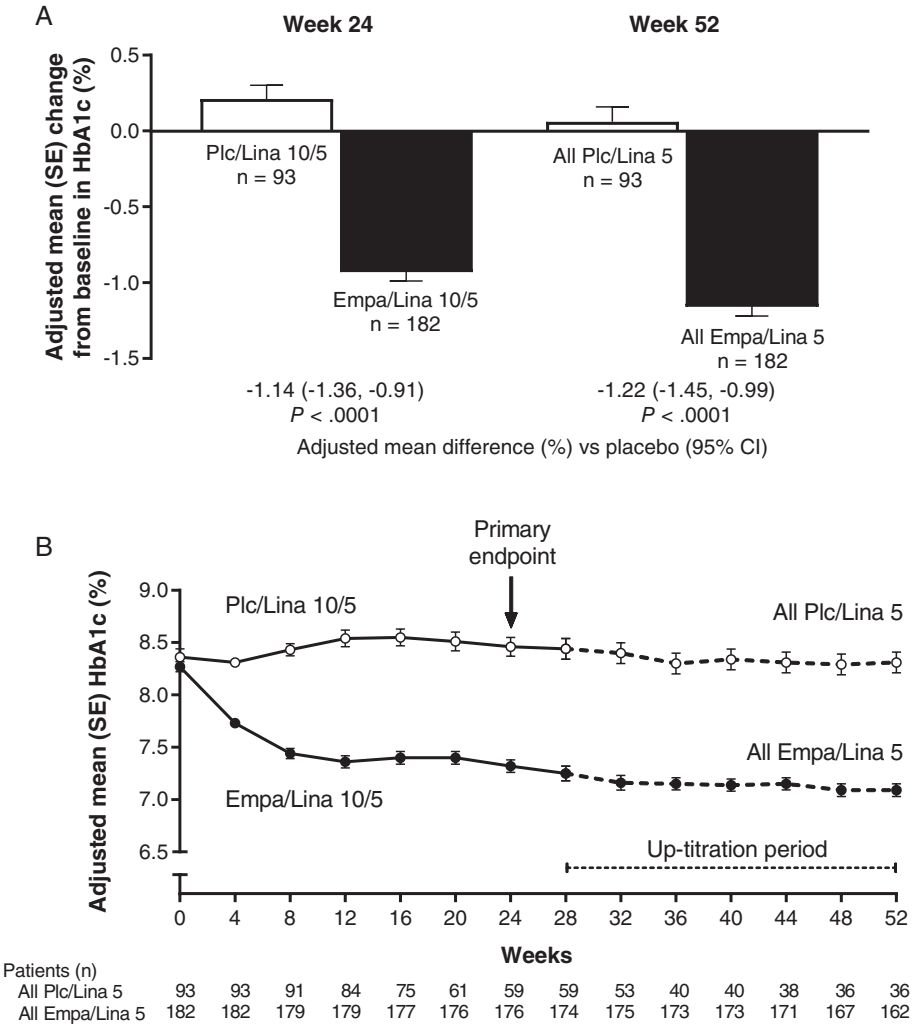

FIGURE 1 Change from baseline in HbA1c during the 52-week double-blind treatment period. A, Adjusted mean (±SE) change from baseline in HbA1c at weeks 24 and 52. B, Adjusted mean (±SE) HbA1c levels during the 52-week double-blind treatment period. HbA1c conversion factor: mmol/mol = (10.93 × %) – 23.5. Abbreviations: All Empa/Lina 5, combined empagliflozin 10 mg/linagliptin 5 mg and empagliflozin 25 mg/linagliptin 5 mg groups; All Plc/Lina 5, combined placebo for empagliflozin 10 mg/linagliptin 5 mg and placebo for empagliflozin 25 mg/linagliptin 5 mg groups; CI, confidence interval; Empa/Lina 10/5, empagliflozin 10 mg/linagliptin 5 mg fixed-dose combination; HbA1c, glycated haemoglobin; Plc/Lina 10/5, placebo for empagliflozin 10 mg/linagliptin 5 mg fixed-dose combination plus linagliptin 5 mg; SE, standard error

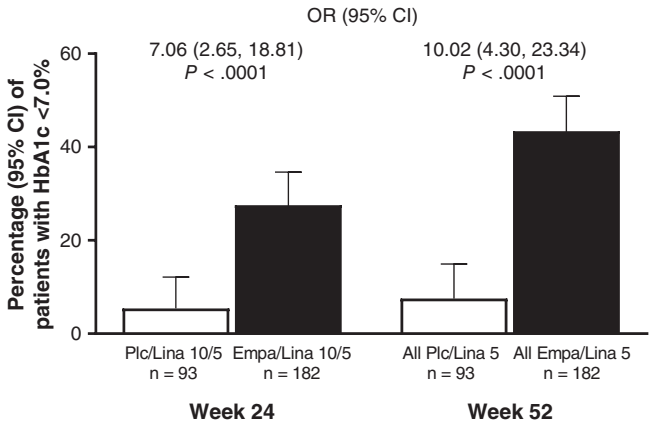

FIGURE 2 Proportion of patients achieving HbA1c <7.0% at weeks 24 and 52. Error bars are 95% CIs. Abbreviations: All Empa/Lina 5, combined empagliflozin 10 mg/linagliptin 5 mg and empagliflozin 25 mg/linagliptin 5 mg groups; All Plc/Lina 5, combined placebo for empagliflozin 10 mg/linagliptin 5 mg and placebo for empagliflozin 25 mg/linagliptin 5 mg groups; CI, confidence interval; HbA1c, glycated haemoglobin; OR, odds ratio

(adrenal neoplasm, lung neoplasm and cerebral haemorrhage), all during the up-titration period, were assessed by the investigators to be drug-related. Of these, the patient with cerebral haemorrhage was receiving Empa/Lina 10/5 during the up-titration period and died atraumatically at home. Although the investigator considered this SAE to be drug-related, the cardiovascular adjudication committee could not confirm the event because of insufficient information (death confirmed by an emergency doctor; no autopsy). There were no other deaths. One patient in the All Plc/Lina 5 group experienced lumbar spinal stenosis during the up-titration period, which was not considered drug-related.

The most common AESIs included infections (primarily nasopharyngitis), urinary tract infection, hypersensitivity, arthralgia and increased urination (Table 2). Of these, hypersensitivity and increased urination were more common with the empagliflozin/linagliptin combination than with linagliptin monotherapy. There were no events of urinary tract infection with complications (ie, pyelonephritis, urosepsis). All events relating to "metabolic acidosis, ketoacidosis or DKA" were, according to the MedDRA Preferred Term, "blood ketone body increased" and were reported by investigators as mild and non-serious. All these events were independently adjudicated, and none were considered DKA. The rate of confirmed hypoglycaemia was low (All Empa/Lina 5, 0%; All Plc/Lina 5, 1.1%). There were no reports of pancreatitis, cardiac failure, acute kidney injury, lower limb amputation, intestinal obstruction or embolic/thrombotic events (Table 2).

There were no confirmed cardiovascular or hepatic events, as judged by the adjudicating committees. Five patients in the All Empa/

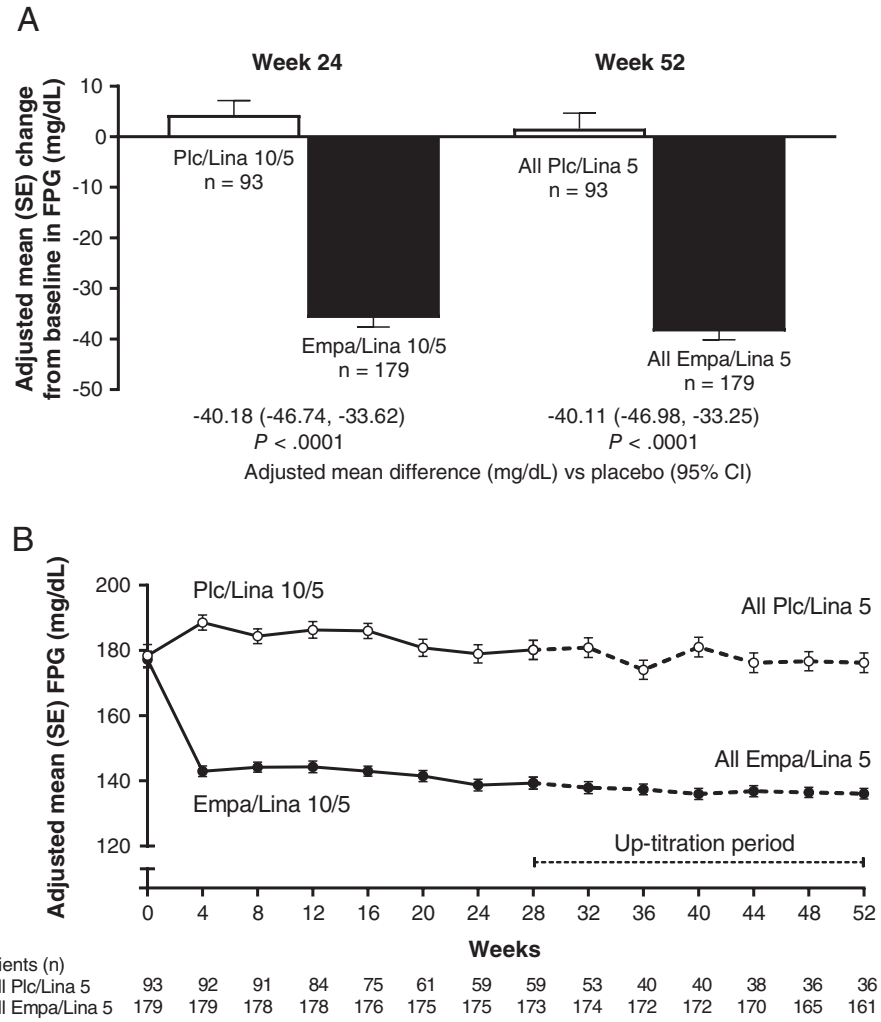

FIGURE 3 Change from baseline in FPG during the 52-week double-blind treatment period. A, Adjusted mean (±SE) change from baseline in FPG at weeks 24 and 52. B, Adjusted mean (±SE) FPG levels during the 52-week double-blind treatment period. FPG conversion factor: mmol/L = (mg/dL)/18. Abbreviations: All Empa/Lina 5, combined empagliflozin 10 mg/linagliptin 5 mg and empagliflozin 25 mg/linagliptin 5 mg groups; All Plc/Lina 5, combined placebo for empagliflozin 10 mg/linagliptin 5 mg and placebo for empagliflozin 25 mg/linagliptin 5 mg groups; CI, confidence interval; Empa/Lina 10/5, empagliflozin 10 mg/linagliptin 5 mg fixed-dose combination; FPG, fasting plasma glucose; Plc/Lina 10/5, placebo for empagliflozin 10 mg/linagliptin 5 mg fixed-dose combination plus linagliptin 5 mg; SE, standard error

Lina 5 group and three patients in the All Plc/Lina 5 group experienced confirmed pancreatic events (all asymptomatic pancreatic hyperenzymaemia); seven were reported as AEs. Up-titration to Empa/Lina 25/5 (n = 126) did not result in increased AEs, with the exception of drug-related AEs (10.3% vs 3.9% for patients continuing with Empa/Lina 10/5 [n = 51]), increased ketone bodies (2.4% vs 0%), arthralgia (2.4% vs 0%), hypersensitivity (4.8% vs 2.0%) and urinary tract infection (4.8% vs 2.0%); none led to DKA, anaphylaxis or urosepsis.

4 | DISCUSSION

In this double-blind, randomized, placebo-controlled trial, switching to an empagliflozin/linagliptin fixed-dose combination provided greater glycaemic control than continuing with linagliptin monotherapy in Japanese patients with T2DM. This was the first randomized trial to evaluate empagliflozin/linagliptin FDC specifically in Japanese patients, and the first to include an up-titration extension period. Compared with linagliptin alone, empagliflozin/linagliptin FDC treatment resulted in statistically significant and clinically relevant reductions in HbA1c of 1.14% at 24 weeks and 1.22% at 52 weeks, as well as improvements in FPG, weight and SBP. Both doses of empagliflozin/linagliptin FDC were well tolerated, with safety profiles consistent with the individual components and without new safety signals. These results suggest that switching from linagliptin monotherapy to empagliflozin/linagliptin FDC is an effective, second-line option for long-term therapy in Japanese patients with T2DM. Moreover, previous studies suggest that the single-pill FDC formulation may improve adherence as compared with dual therapy.[21,22]

Both the reduction in HbA1c and the proportion of patients reaching HbA1c targets were significantly greater with empagliflozin/linagliptin FDC compared with linagliptin monotherapy, consistent with previous trials of empagliflozin/linagliptin FDCs[16–19] and the monocomponents.[7,11–14] Interestingly, HbA1c reduction in this trial (−1.14% at 24 weeks) appeared to be larger than that in a previous,

TABLE 2 Adverse events during the 24-week and 52-week double-blind treatment periods

Adverse event	24 Weeks		52 Weeks	
	Plc/Lina 10/5 (n = 93)	Empa/Lina 10/5 (n = 182)	All Plc/Lina 5 (n = 93)	All Empa/Lina 5 (n = 182)
≥1 AE	64.5% (60)	55.5% (101)	75.3% (70)	70.3% (128)
≥1 severe AE	0% (0)	0% (0)	0% (0)	0.5% (1)
≥1 drug-related AE	3.2% (3)	15.4% (28)	7.5% (7)	20.3% (37)
≥1 AE leading to discontinuation	1.1% (1)	1.1% (2)	2.2% (2)	2.2% (4)
≥1 serious AE	0% (0)	1.6% (3)	1.1% (1)	4.4% (8)
Fatal AE	0% (0)	0% (0)	0% (0)	0.5% (1)
AE of special interest categories				
Acute kidney injury (19 PTs)	0% (0)	0% (0)	0% (0)	0% (0)
Arthralgia (98 PTs)	2.2% (2)	0.5% (1)	6.5% (6)	2.2% (4)
Bone fracture (80 PTs)	1.1% (1)	2.2% (4)	2.2% (2)	2.7% (5)
Cardiac failure (30 PTs)	0% (0)	0% (0)	0% (0)	0% (0)
Confirmed hypoglycaemia[a]	1.1% (1)	0% (0)	1.1% (1)	0% (0)
Embolic and thrombotic events (85 PTs)	0% (0)	0% (0)	0% (0)	0% (0)
Genital infection (88 PTs)	0% (0)	1.1% (2)	0% (0)	1.1% (2)
Hepatic injury (166 PTs)	0% (0)	0.5% (1)	2.2% (2)	1.1% (2)
Protocol-specified[b]	0% (0)	0% (0)	0% (0)	0% (0)
Hypersensitivity (270 PTs)	3.2% (3)	5.5% (10)	4.3% (4)	8.2% (15)
Increased urination (3 PTs)[c]	0% (0)	2.7% (5)	0% (0)	3.3% (6)
Infection (1887 PTs)	37.6% (35)	30.2% (55)	50.5% (47)	41.8% (76)
Influence on safety caused by weight decrease (9 PTs)	NA	NA	0% (0)	0% (0)
Intestinal obstruction (32 PTs)	NA	NA	0% (0)	0% (0)
Lower limb amputation	0% (0)	0% (0)	0% (0)	0% (0)
Malignancies (1689 PTs)	0% (0)	0% (0)	0% (0)	1.6% (3)
Metabolic acidosis, ketoacidosis, or DKA (17 PTs)[d]	0% (0)	4.9% (9)	1.1% (1)	6.6% (12)
DKA (3 PTs)[e]	0% (0)	0% (0)	0% (0)	0% (0)
Pancreatitis (19 PTs)	0% (0)	0% (0)	0% (0)	0% (0)
Skin lesions (56 PTs)	NA	NA	2.2% (2)	2.2% (4)
Urinary tract infection (75 PTs)	5.4% (5)	4.9% (9)	7.5% (7)	7.7% (14)
Acute pyelonephritis	NA	NA	0% (0)	0% (0)
Asymptomatic bacteriuria	NA	NA	6.5% (6)	7.1% (13)
Urosepsis	NA	NA	0% (0)	0% (0)
Volume depletion (8 PTs)	1.1% (1)	0.5% (1)	1.1% (1)	0.5% (1)

Abbreviations: AE, adverse event; All Empa/Lina 5, combined empagliflozin 10 mg/linagliptin 5 mg and empagliflozin 25 mg/linagliptin 5 mg groups; All Plc/Lina 5, combined placebo for empagliflozin 10 mg/linagliptin 5 mg and placebo for empagliflozin 25 mg/linagliptin 5 mg groups; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DKA, diabetic ketoacidosis; Empa/Lina 10/5, empagliflozin 10 mg/linagliptin 5 mg fixed-dose combination; MedDRA, Medical Dictionary for Regulatory Activities; NA, not available; Plc/Lina 10/5, placebo for empagliflozin 10 mg/linagliptin 5 mg fixed-dose combination plus linagliptin 5 mg; PT, MedDRA preferred term; ULN, upper limit of normal. To account for the 2:1 randomization ratio, data are presented as % (n) of patients who received ≥1 dose of study drug.

[a] Hypoglycaemic AE accompanied by a plasma glucose level ≤ 70 mg/dL (≤3.9 mmol/L) or the need for assistance.

[b] AST and/or ALT >3-fold ULN combined with total bilirubin >2-fold ULN or AST and/or ALT >5-fold ULN.

[c] Preferred terms included "pollakiuria", "polyuria" and "nocturia".

[d] Preferred terms were "acetonemia", "acidosis", "anion gap abnormal", "anion gap increased", "blood pH abnormal", "blood pH decreased", "diabetic hyperglycaemic coma", "ketonuria", "ketosis", "Kussmaul respiration", "metabolic acidosis", "blood ketone body", "blood ketone body increased", "urine ketone body present", "blood ketone body present", "urine ketone body", and "diabetic metabolic decompensation"; all observed events were "blood ketone body increased" and were mild and non-serious.

[e] Preferred terms were "diabetic ketoacidosis", "diabetic ketoacidotic hyperglycaemic coma" and "ketoacidosis".

similarly designed trial of empagliflozin as add-on to linagliptin and metformin (−0.79%).[19] This difference may be related to the higher baseline HbA1c and FPG, and the lower BMI and weight, in the current trial, as well as to racial/ethnic differences.[19] Approximately 25% of patients in the previous trial self-identified as Asian and there were no Japanese study sites.[19] Reduction in HbA1c was also

apparently larger in our trial than that seen with canagliflozin as add-on to teneligliptin in Japanese patients (least squares mean difference between groups, −0.88%).[23] Although both trials were conducted in Japan and had similar designs, baseline HbA1c and FPG levels were higher in our trial, possibly contributing to the greater response. Reflecting the higher baseline HbA1c, 71% of Empa/Lina 10/5 patients did not reach HbA1c < 7.0% after 24 weeks; however, up-titration to Empa/Lina 25/5 resulted in a further, albeit modest, reduction in HbA1c, and 43.4% of All Empa/Lina 5 patients reached HbA1c < 7.0% after 52 weeks. Although the trial was not designed to detect differences between doses, the results suggest that increasing the dose of empagliflozin could improve glycaemic control in patients who do not reach HbA1c targets with Empa/Lina 10/5.

Empagliflozin/linagliptin FDC treatment significantly decreased FPG, body weight and SBP, all of which are characteristic of SGLT2 inhibitors.[12–14] Weight loss is related to loss of calories as the result of increased glucose excretion,[24] whereas reduction in blood pressure is related primarily to osmotic diuresis, although other mechanisms contribute.[24] In the EMPA-REG OUTCOME study, patients with T2DM who were at high cardiovascular risk and were undergoing treatment with empagliflozin had a significantly lower risk of cardiovascular mortality (hazard ratio, 0.62), of all-cause mortality (0.68) and of hospitalization for heart failure (0.65) than placebo-treated patients, with potentially beneficial renal effects.[15,25] The precise mechanisms underlying empagliflozin's effects on cardiovascular and renal outcomes are not fully known, but may involve multiple cardio-renal factors, including weight and blood pressure, which were favourably modified in this trial.[15] Ongoing trials concerning the impact of linagliptin on cardiovascular outcomes in patients at high cardiovascular risk (CAROLINA [NCT01243424][26]) and/or renovascular risk (CARMELINA [NCT01897532]) could provide further insights.

The combination of empagliflozin and linagliptin was well tolerated, and observed AEs were as expected for the monocomponents.[7,27] No cases of confirmed hypoglycaemia were seen, consistent with the mechanisms of action of these drugs. Indeed, several studies have reported that DPP-4/SGLT2 inhibitor combinations do not increase the incidence of hypoglycaemia above the low rate seen with either monocomponent, unless combined with insulin and/or sulfonylureas.[16–18,23,28,29] Although drug-related AEs were more frequent with empagliflozin/linagliptin than with linagliptin, these were primarily AEs known to be associated with SGLT2 inhibitors (increased blood ketone bodies, cystitis, pollakiuria).[20,27] No cases of lower limb amputations (which were also not reported in the Japanese canagliflozin-teneligliptin study[23]), non-traumatic bone fracture, volume depletion (except 1 case of mild orthostatic hypotension) or DKA occurred in patients treated with empagliflozin/linagliptin in this trial. Notably, Japanese guidelines recommend avoiding multi-drug combination therapy in elderly patients, as these patients are more vulnerable to potential adverse effects.[30] Although 37.5% of patients in this trial were ≥ 65 years of age, our results should be interpreted cautiously when considering treatment of elderly patients with empagliflozin/linagliptin FDC.

Fasting plasma insulin was significantly reduced by empagliflozin/linagliptin therapy as compared with linagliptin alone, accompanied by reduced plasma glucose. Further, empagliflozin/linagliptin therapy improved metabolic control without an increase in glucagon. Previous studies have suggested that empagliflozin and other SGLT2 inhibitors lower fasting and postprandial insulin, but increase glucagon.[31–34] In contrast, DPP-4 inhibitors, including linagliptin, have been shown to reduce glucagon levels, and to either increase or have no effect on fasting insulin levels.[35,36]

These study results are strengthened by the randomized, double-blind, double-dummy, placebo-controlled design and the 16-week linagliptin pre-treatment period. This design reflects the clinical setting in which empagliflozin is added to treatment in patients who are inadequately controlled with linagliptin by switching to the FDC formulation. The extended up-titration period, required for regulatory purposes, demonstrated the long-term efficacy and safety of both lower and higher doses of empagliflozin, as occurs in clinical practice. Completion rates through 52 weeks were high (>90%), as was statistical power for the primary endpoint, and a broad range of outcome measures, with the exception of postprandial glucose levels, were assessed. Although the enrolment of Japanese patients only limits generalizability to other populations, the results are consistent with other multinational studies. Finally, the use of rescue medication in more than half of the patients in the placebo group reflects the need for multiple therapeutic agents in the study population.

In conclusion, switching from linagliptin monotherapy to empagliflozin/linagliptin FDC was well tolerated and resulted in clinically significant reductions in HbA1c, FPG, body weight and SBP in Japanese patients with T2DM. Thus, an empagliflozin/linagliptin fixed-dose combination represents an attractive therapeutic option for these patients, with potentially additive cardio-renal benefits from empagliflozin as well as a formulation expected to improve adherence.

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Conflict of interest

K. Su., K. Sh. and Y. M. are employees of Nippon Boehringer Ingelheim Co. Ltd. G. C. is an employee of Boehringer Ingelheim (China) Investment Co. Ltd. F. S. and J. G. are employees of Boehringer Ingelheim GmbH & Co. KG. C. L. is a former employee of Boehringer Ingelheim GmbH & Co. KG. R. K. has received honoraria for lectures from MSD, Sanofi, Sanwa Kagaku, Takeda, Sumitomo Dainippon Pharma and Novartis. M. H. has received research funding and/or honoraria for lectures from Astellas Pharma Inc., Taisho Toyama Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Nippon Boehringer Ingelheim Co., Ltd., Taisho Pharmaceutical Co., Ltd., Kowa Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., MSD, Novartis Pharma, Novo Nordisk Pharma, Sanofi, Daiichi Sankyo Company, Ltd., Takeda

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Author contributions

All authors participated in the interpretation of study results and in the drafting, critical revision and approval of the final version of the manuscript. K. Su., G. C. and F. S. were involved in the study design and/or data analyses. R. K. was an investigator in the study. M. H. was a medical expert for the study and G. C. conducted the statistical analysis.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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