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ORIGINAL ARTICLE

Linagliptin as add-on to empagliflozin in a fixed-dose combination in Japanese patients with type 2 diabetes: Glycaemic efficacy and safety profile in a two-part, randomized, placebo-controlled trial

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Aims: This two-part, double-blind, double-dummy, randomized, placebo-controlled trial (83 sites) evaluated the efficacy and safety of empagliflozin (Empa) 10 or 25 mg and linagliptin (Lina) 5 mg fixed-dose combinations (FDCs) in Japanese patients with type 2 diabetes mellitus (T2DM) who were poorly controlled with Empa.

Materials and methods: Patients (previously drug-naive or using one oral antidiabetic drug for ≥ 12 weeks) entered an open-label stabilization period (16 weeks, Empa 10 mg [Part A] or Empa 25 mg [Part B]). Subsequently, they received Empa 10 mg plus placebo (Plc) for Empa/Lina10/5 (Empa/Plc 10/5; Part A) or Empa 25 mg plus Plc for Empa/Lina 25/5 (Empa/Plc 25/5; Part B) for 2 weeks. Patients with HbA1c 7.5–10.0% were randomized (1:1) to a 24-week regimen of once-daily Empa/Lina 10/5 (n = 107) or Empa/Plc 10/5 (n = 108) in Part A, or to Empa/Lina 25/5 (n = 116) or Empa/Plc 25/5 (n = 116) in Part B, with a 28-week extension period in Part B.

Results: Change from baseline in HbA1c at Week 24 was greater (P < 0.0001) with Empa/Lina than with Empa/Plc (primary outcome, Empa/Lina 10/5: −0.94 vs −0.12%; adjusted mean difference, −0.82%; Empa/Lina 25/5: −0.91 vs −0.33%; adjusted mean difference, −0.59%). Over 24- and 52-week periods, higher proportions of patients achieved HbA1c < 7.0% and greater decreases in fasting plasma glucose were observed with Empa/Lina compared with Empa/Plc. Empa/Lina was well tolerated, with no unexpected adverse events or diabetic ketoacidosis. One case of confirmed hypoglycaemia with Empa/Plc 25/5 was reported.

Conclusions: These results support Empa/Lina FDC as a potential option for Japanese patients with T2DM who require combination therapy. ClinicalTrials.gov NCT02489968.

KEYWORDS

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

1 | INTRODUCTION

Sodium-glucose cotransporter 2 (SGLT2) inhibitors, such as empagliflozin, and dipeptidyl peptidase-4 (DPP-4) inhibitors, such as linagliptin, exert antidiabetic effects via different mechanisms of action. SGLT2 inhibitors

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inhibit renal glucose reabsorption, resulting in increased urinary excretion of glucose and thereby reducing plasma glucose levels in an insulin-independent manner.[1] SGLT2 inhibitors also reduce body weight and blood pressure.[1] Empagliflozin, in particular, also reduces the risk of cardiovascular mortality and is associated with slower progression of kidney disease, based on surrogate markers, that is, progression to macroalbuminuria and doubling of serum creatinine level, and lower rates of renal events compared with placebo in patients with type 2 diabetes mellitus (T2DM) and established cardiovascular disease.[2,3] DPP-4 inhibitors augment the glucose-stimulated secretion of insulin[4] and are associated with low incidence of hypoglycaemia and weight neutrality.[5] Linagliptin is one of the few DDP-4 inhibitors that does not require dose adjustment in patients with hepatic/renal impairment.[6] Because of the complementary mechanisms of action of SGLT2 and DPP-4 inhibitors, dual therapy improves glycaemic control in patients with T2DM without increasing the risk of hypoglycaemia or weight gain,[4] and fixed-dose combinations (FDC) have been developed.

Empagliflozin/linagliptin FDC (Empa/Lina) is the first SGLT2 inhibitor/DPP-4 inhibitor combination approved in the United States and Europe for the treatment of T2DM. Empa/Lina FDC tablets (Empa 10 mg/Lina 5 mg [Empa/Lina 10/5] and Empa 25 mg/Lina 5 mg [Empa/Lina 25/5]) are bioequivalent to the combination of empagliflozin and linagliptin administered separately, and can be administered with or without food.[7] Phase III randomized controlled trials conducted outside Japan have demonstrated the safety and efficacy of Empa/Lina FDC for the treatment of T2DM in patients who had not received antidiabetic therapy for approximately 12 weeks and in patients using metformin.[8–10] The objective of this two-part study was to evaluate the efficacy and safety of Empa/Lina FDC in Japanese patients with T2DM who switched from empagliflozin monotherapy.

2 | MATERIALS AND METHODS

2.1 | Study details

This was a 2-part, multicentre, phase III, randomized, double-blind, double-dummy, placebo-controlled trial of once-daily Empa/Lina 10/5 (Part A) or Empa/Lina 25/5 (Part B) compared with empagliflozin plus placebo for FDC in Japanese patients with T2DM and insufficient glycaemic control after 16 weeks of treatment with empagliflozin 10 or 25 mg. The trial (ClinicalTrials.gov [NCT02489968]) was conducted at 83 study sites in Japan between May 2015 and June 2017. The protocol was approved by the institutional review board of each study site and was conducted in compliance with the Japanese Ethical Guideline for Clinical Studies and the Declaration of Helsinki. All patients provided written informed consent prior to participation.

2.2 | Study population

Male and female adults (≥ 20 years) with a diagnosis of T2DM were eligible if they were on a diet and exercise regimen for ≥ 12 weeks and were either drug-naive (ie, no antidiabetic drug ≥ 12 weeks) or were using a stable dosage of one oral antidiabetic drug (OAD) (sulfonylurea up to half the maximum approved dosage) for ≥ 12 weeks (≥ 18 weeks for thiazolidinedione) but discontinued the OAD at screening, had a body mass index ≤ 40.0 kg/m^2, had glycated haemoglobin (HbA1c) ≥ 8.0 to ≤ 10.5% (National Glycohemoglobin Standardization Programme % units; mmol/mol = [10.93 × %] − 23.5) for drug-naive patients or ≥ 7.5 to ≤ 10.5% for OAD-pre-treated patients.

Patients were excluded if they had uncontrolled hyperglycaemia, defined as fasting plasma glucose (FPG) > 270 mg/dL (> 15 mmol/L; mmol/L = [mg/dL]/18; confirmed by second measurement) during the open-label stabilization period, if they had acute coronary syndrome, if they had experienced a stroke or transient ischemic attack, if they were undergoing insulin or glucagon-like peptide-1 (GLP-1) agonist treatment, anti-obesity or any other treatment leading to unstable body weight within 12 weeks, if they had an indication of liver disease, or if they had an estimated glomerular filtration rate (eGFR; Modification of Diet in Renal Disease formula) < 45 mL/min/1.73 m^2.

2.3 | Study design

All Empa and Empa/Lina FDC tablets were provided by Boehringer Ingelheim Pharma GmbH & Co. KG (Germany) and were taken orally once daily in the morning. Patients were randomized by a computer-generated random sequence using a phone/web-based interactive response system. Randomization was stratified by HbA1c (< 8.5 or ≥ 8.5%), eGFR (≥ 45 and < 60, ≥ 60 and < 90, or ≥ 90 mL/min/1.73 m^2) and prior OAD use (yes, no).

2.3.1 | Open-label stabilization period

Patients who met inclusion criteria after screening were randomized 1:1 to receive Empa 10 mg (Part A) or 25 mg (Part B) for 16 weeks (Figure S1 in Supporting information).

2.3.2 | Placebo run-in period

Patients who completed the stabilization period entered a 2-week run-in period and received Empa 10 mg plus placebo for Empa/Lina 10/5 (Part A) or Empa 25 mg plus placebo for Empa/Lina 25/5 (Part B).

2.3.3 | Double-blind treatment period

A double-dummy design (two tablets/d) was used to maintain blinding. At the end of the run-in period, patients with HbA1c ≥ 7.5 to ≤ 10.0%, who still satisfied inclusion/exclusion criteria were randomized 1:1 to receive Empa/Lina 10/5 plus placebo for Empa 10 mg or Empa 10 mg plus placebo for Empa/Lina 10/5 (Empa/Plc 10/5) for 24 weeks (Part A), or to receive Empa/Lina 25/5 plus placebo for Empa 25 mg or Empa 25 mg plus placebo for Empa/Lina 25/5 (Empa/Plc 25/5) for 52 weeks (Part B).

Rescue medication could be initiated for patients with confirmed (≥ 2 measurements) 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). 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 discretion of the investigator.

2.4 | Efficacy outcome measures

For all endpoints, Parts A and B were evaluated independently. Treatment comparisons were made for Empa/Lina 10/5 vs Empa/Plc 10/5 and for Empa/Lina 25/5 vs Empa/Plc 25/5. The primary endpoint was change in HbA1c from baseline (at second randomization) to Week 24. Other endpoints included change in HbA1c from baseline to Week 52, proportion of patients who achieved HbA1c < 7.0% at Weeks 24 and 52, change in FPG, body weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting plasma insulin and glucagon from baseline to Weeks 24 and 52, and use of rescue therapy at Weeks 24 and 52. Additional analyses for the 16-week open-label treatment period were conducted for body weight, SBP and DBP.

2.5 | Safety outcome measures

Adverse events (AEs) (Medical Dictionary for Regulatory Activities, version 19.1 [24-week analysis] and version 20.0 [52-week analysis]), serious AEs (SAEs) and AEs of special interest (AESIs) were assessed continuously. AESIs were based on the mechanisms of action or previous safety concerns of SGLT2 and DPP-4 inhibitors: arthralgia, bone fracture, cardiac failure, confirmed hypoglycaemia (plasma glucose levels ≤ 70 mg/dL [≤ 3.9 mmol/L] or requirement of assistance), acute kidney injury, embolic/thrombotic events, genital infection, hepatic injury, hypersensitivity reactions, increased urination, infections, unsafe decrease in weight, intestinal obstruction, lower limb amputation, malignancies, increased ketogenesis, metabolic acidosis or diabetic ketoacidosis (DKA), pancreatitis, pancreatic cancer, skin lesions, urinary tract infection, including acute pyelonephritis, asymptomatic bacteriuria and sepsis, and volume depletion. Laboratory parameters were measured at Weeks 0, 4, 8, 12, 16, 20, 24, 32, 40, 48 and 52. Cardiovascular, pancreatic, hepatic and DKA events were adjudicated by independent external committees.

2.6 | Statistical analysis

Based on previous experience, the between-group difference in change in HbA1c from baseline at Week 24 was assumed to be 0.5%, with a standard deviation (SD) of 1.1%. Assuming 3% of patients would be ineligible for the full analysis set (FAS, defined as all randomized patients who received ≥ 1 dose of study drug and underwent both baseline and ≥ 1 on-treatment HbA1c assessment), 106 randomized patients per study arm would provide 90% power for the primary endpoint for each part. Assuming 12% of randomized patients in Part B discontinued during the 52-week treatment period, 114 patients per study arm would ensure that at least 100 patients were treated for the full year, as required by the Japanese Pharmaceuticals and Medical Devices Agency.

The primary endpoint was analysed using a restricted maximum likelihood-based mixed model repeated measures (MMRM) approach in the FAS. 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, and was used to estimate the differences in means between treatment groups and their 95% confidence intervals (CI). Missing data were handled implicitly by the model (observed cases), and not by imputation. Further endpoints in the double-blind periods were analysed separately for Weeks 24 and 52. 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. Efficacy endpoints in the open-label stabilization periods were analysed separately for patients who received ≥ 1 dose of study drug and underwent both pre-treatment and ≥1 on-treatment HbA1c assessment during the stabilization period and are presented using descriptive statistics. Safety in the double-blind periods was analysed separately for Week 24 (Part A) and Week 52 (Part B) in patients who received ≥ 1 dose of study drug and are presented using descriptive statistics. All AEs between the first intake and 7 days after the last intake of study drug were analysed. Two-sided *P* values < 0.05 were considered significant. Statistical analyses were performed using SAS Version 9.4 (SAS Institute Inc., Cary, North Carolina).

3 | RESULTS

3.1 | Patient disposition

Of the 1032 patients screened, 880 were randomized to the open-label stabilization period (Part A, Empa 10, *n* = 439; Part B, Empa 25, *n* = 441); one patient in Part B withdrew before study drug administration (Figure S2). After the stabilization and run-in periods, 107 patients were randomized to Empa/Lina 10/5, 108 to Empa/Plc 10/5, 116 to Empa/Lina 25/5 and 116 to Empa/Plc 25/5; 224 patients in Part A and 208 patients in Part B discontinued before randomization, primarily because they no longer met the HbA1c inclusion criterion. Completion rates were high (92.6-98.1%) in all treatment groups in both parts at Weeks 24 and 52.

3.2 | Demographic and baseline clinical characteristics

In Parts A and B, demographic and baseline clinical characteristics were generally balanced between groups (Table 1). Most patients were men, with a mean (Part A/Part B) age of 57.2/57.6 years, and a mean (Part A/Part B) of 8.0/8.4 years since being diagnosed with T2DM. Mean (Part A/Part B) baseline values were: HbA1c, 8.37%/8.27%; body weight, 69.6/68.3 kg; SBP, 126.4/125.4 mm Hg; DBP, 78.1/76.5 mm Hg; eGFR, 96.7/95.6 mL/min/1.73 m^2. Mean (Part A/Part B) FPG values were 159.1/150.4 mg/dL and 76.3%/81.0% (Part A/Part B) of patients had been pre-treated with an OAD.

3.3 | Change in HbA1c

Compared with Empa/Plc, Empa/Lina treatment resulted in significantly greater decreases in HbA1c at Weeks 24 (primary endpoint) and 52. In Part A, at Week 24, the adjusted mean (standard error [SE]) change from baseline in HbA1c was significantly greater with Empa/Lina 10/5 (–0.94%, [0.05%]) than with Empa/Plc 10/5 (–0.12%, [0.06%]; adjusted mean difference [95% CI], –0.82% [–0.97%, –0.67%]; *P* < 0.0001) (Figure 1A). In Part B, at Week 24, the adjusted mean (SE) change from baseline in HbA1c was significantly greater with Empa/Lina 25/5 (–0.91% [0.05%]) than with Empa/Plc 25/5 (–0.33%, [0.05%]); adjusted mean difference [95% CI], –0.59% [–0.73%, –0.45%]; *P* < 0.0001) (Figure 1C). This

TABLE 1 Patient demographics and baseline characteristics

	Part A (24 weeks with FDC)		Part B (52 weeks with FDC)	
	Empa/Plc 10/5 (*n* = 108)	Empa/Lina 10/5 (*n* = 107)	Empa/Plc 25/5 (*n* = 116)	Empa/Lina 25/5 (*n* = 116)
Male	85 (78.7)	85 (79.4)	79 (68.1)	87 (75.0)
Age, y	56.3 ± 9.9	58.0 ± 9.3	58.4 ± 9.2	56.8 ± 10.6
Weight, kg	70.2 ± 12.0	69.0 ± 13.0	67.5 ± 13.8	69.1 ± 14.2
Body mass index, kg/m^2	25.1 ±3.6	24.9 ± 4.0	24.7 ± 3.7	25.0 ± 4.3
HbA1c, %[a]	8.40 ± 0.68	8.34 ± 0.54	8.26 ± 0.68	8.27 ± 0.59
FPG, mg/dL[b]	159.0 ± 24.0	159.3 ± 26.1	149.1 ± 21.0	151.8 ± 22.5
SBP, mm Hg[c]	127.1 ± 15.1	125.7 ± 12.1	126.0 ± 15.1	124.8 ± 14.0
DBP, mm Hg[c]	78.5 ± 9.5	77.8 ± 10.3	76.6 ± 10.1	76.3 ± 8.8
eGFR, mL/min/1.73 m^2	96.4 ± 21.4	97.0 ± 17.6	94.7 ± 19.8	96.4 ± 19.7
Time since diagnosis of T2DM				
Mean years	7.6 ± 5.0	8.4 ± 5.6	8.3 ± 5.7	8.5 ± 5.5
≤ 1 y	9 (8.3)	6 (5.6)	5 (4.3)	3 (2.6)
> 1 to 5 y	29 (26.9)	28 (26.2)	36 (31.0)	32 (27.6)
> 5 to 10 y	39 (36.1)	37 (34.6)	40 (34.5)	41 (35.3)
> 10 y	31 (28.7)	36 (33.6)	35 (30.2)	40 (34.5)
Prior use of OADs				
No treatment	25 (23.1)	26 (24.3)	21 (18.1)	23 (19.8)
Monotherapy	83 (76.9)	81 (75.7)	95 (81.9)	93 (80.2)

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; Empa/Plc 10/5, empagliflozin 10 mg/placebo for linagliptin 5 mg fixed-dose combination; Empa/Lina 25/5, empagliflozin 25 mg/linagliptin 5 mg fixed-dose combination; Empa/Plc 25/5, empagliflozin 25 mg/placebo for linagliptin 5 mg fixed-dose combination; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; OAD, oral antidiabetic drug; SBP, systolic blood pressure; SD, standard deviation; T2DM, type 2 diabetes mellitus.
Data are given as n (%) or mean ± SD in patients who received ≥ 1 dose of study drug.
Baseline was defined as the last observation before the first intake of double-blind randomized trial medication.
[a] Conversion factor: mmol/mol = (10.93 × %) – 23.5.
[b] Conversion factor: mmol/L = mg/dL/18.
[c] Empa/Lina 10/5 (*n* = 99); Empa/Plc 10/5 (*n* = 99); Empa/Lina 25/5 (*n* = 114); Empa/Plc 25/5 (*n* = 112).

difference was maintained at Week 52 (adjusted mean difference [95% CI], −0.59% [−0.75%, −0.42%]; $P < 0.0001$). The greater decrease in HbA1c with Empa/Lina compared with Empa/Plc was evident from Week 4 (Figure 1B and D). A significantly greater proportion of patients treated with Empa/Lina achieved HbA1c levels < 7.0% at Week 24 (Empa/Lina 10/5, 27.1 vs 1.9%; Empa/Lina 25/5, 29.3 vs 6.9%; $P < 0.0001$) and at Week 52 (Empa/Lina 25/5, 28.4 vs 9.5%; $P < 0.0001$) compared with the matching Empa/Plc group (Figure 2A and B).

3.4 | Fasting plasma glucose

Consistent with decreases in HbA1c, treatment with Empa/Lina resulted in significantly greater decreases in FPG at Week 24 (adjusted mean difference: Empa/Lina 10/5, −12.29 mg/dL; $P < 0.0001$ and Empa/Lina 25/5, −5.41 mg/dL; $P = 0.0261$) (Figure 3A and C) and at Week 52 (adjusted mean difference: Empa/Lina 25/5, −6.53 mg/dL; $P = 0.0217$) compared with the matching Empa/Plc group. The greater decrease in FPG with Empa/Lina compared with Empa/Plc occurred early and was sustained (Figure 3B and D).

3.5 | Other efficacy outcomes

3.5.1 | Open-label empagliflozin monotherapy period

Body weight, SBP and DBP decreased during open-label empagliflozin monotherapy. Mean (SD) change in body weight was −2.67 kg (1.83) with Empa 10 mg and −2.82 kg (1.97) with Empa 25 mg (Figure S3). Mean (SD) change in SBP was −5.4 (13.1) mm Hg with Empa 10 mg and − 5.5 (13.1) mm Hg with Empa 25 mg (Figure S4). Mean (SD) change in DBP was −3.0 (8.4) mm Hg with Empa 10 mg and − 2.3 (7.1) mm Hg with Empa 25 mg (Figure S5).

3.5.2 | Double-blind treatment period

Body weight increased moderately with Empa/Lina treatment compared with Empa/Plc, starting from Week 8 in Part A and from Week 12 in Part B (Figure S3). The adjusted mean difference between groups in change in body weight was 0.48 kg at Week 24 ($P = 0.0231$) in Part A, and 1.02 kg at Week 24 ($P < 0.0001$) and 1.17 kg at Week 52 ($P = 0.0004$) in Part B. There were no major changes in SBP or DBP with Empa/Lina treatment compared with Empa/Plc (Figures S4, S5). The adjusted mean difference between groups in change in SBP was −1.5 mm Hg at Week 24 ($P = 0.3145$) in Part A, and 0.7 mm Hg at Week 24 ($P = 0.6485$) and −0.1 mm Hg at Week 52 ($P = 0.9261$) in Part B. Compared with Empa/Plc 10/5, treatment with Empa/Lina 10/5 significantly decreased DBP at Week 24; however, no difference in DBP was seen between Empa/Lina 25/5 and Empa/Plc 25/5 at Week 52. The adjusted mean difference between groups in change in DBP was −1.9 mm Hg at Week 24 ($P = 0.0442$) in Part A and 2.2 mm Hg at Week 24 ($P = 0.0085$) and 1.4 mm Hg at Week 52 ($P = 0.1613$) in Part B. Mean fasting plasma insulin and glucagon concentrations were numerically higher in the Empa/Lina groups than in the Empa/Plc groups throughout

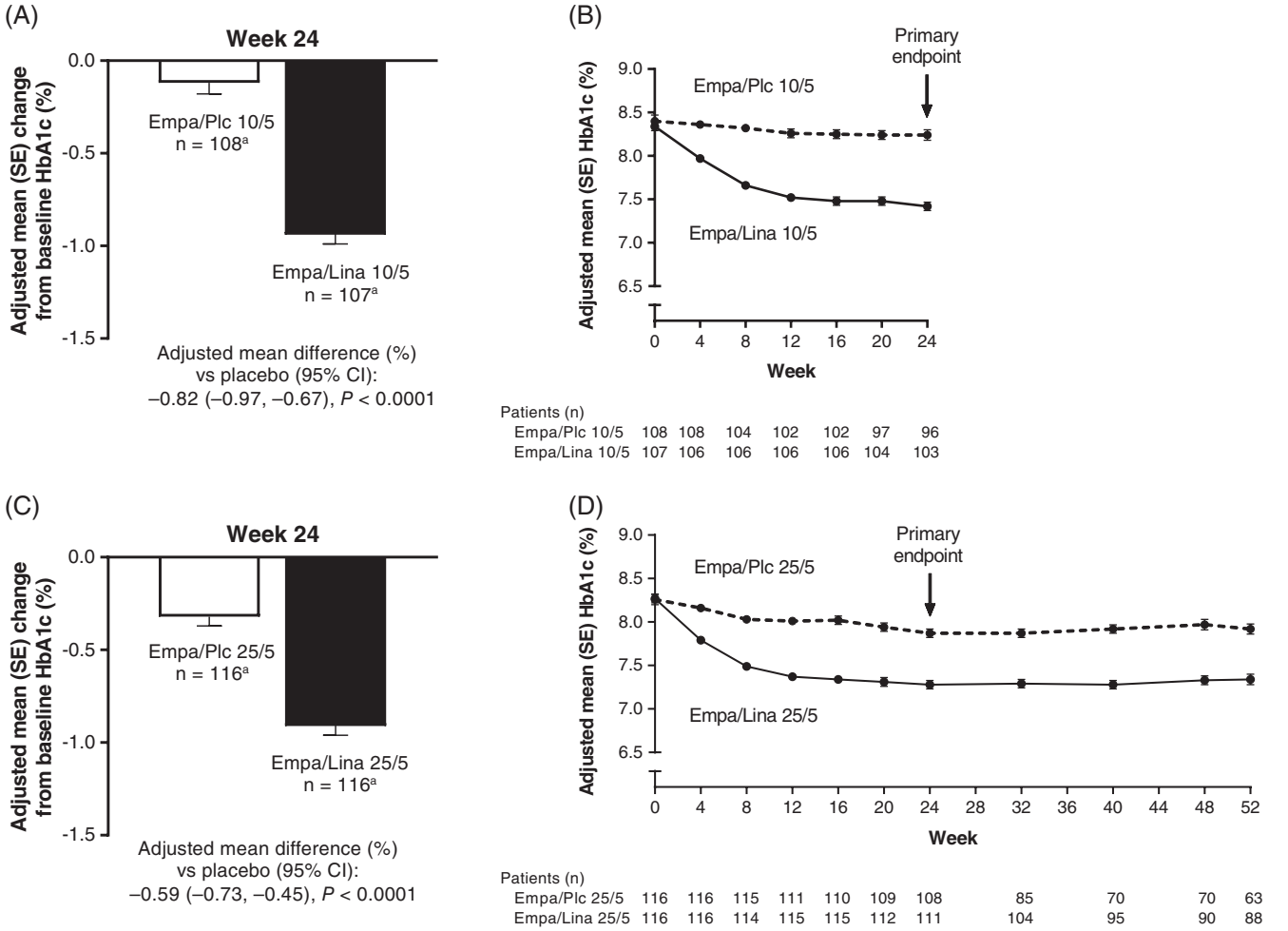

FIGURE 1 Change in HbA1c. A, Change from baseline in HbA1c at Week 24 in patients receiving Empa/Plc 10/5 or Empa/Lina 10/5. B, Change in HbA1c over time during double-blind period in patients receiving Empa/Plc 10/5 or Empa/Lina 10/5. C, Change from baseline in HbA1c at Week 24 in patients receiving Empa/Plc 25/5 or Empa/Lina 25/5. D, Change in HbA1c over time during double-blind period in patients receiving Empa/Plc 25/5 or Empa/Lina 25/5. Baseline was defined as the last observation before the first intake of double-blind randomized trial medication. Data are given as adjusted mean (±SE) from MMRM analyses in the full analysis set using observed cases. Abbreviations: CI, confidence intervals; Empa/Lina 10/5, empagliflozin 10 mg/linagliptin 5 mg fixed-dose combination; Empa/Plc 10/5, empagliflozin 10 mg/placebo for linagliptin 5 mg fixed-dose combination; Empa/Lina 25/5, empagliflozin 25 mg/linagliptin 5 mg fixed-dose combination; Empa/Plc 25/5, empagliflozin 25 mg/placebo for linagliptin 5 mg fixed-dose combination; HbA1c, glycated haemoglobin; MMRM, mixed model repeated measures; SE, standard error. [a]Number of patients analysed during the 24-week double-blind treatment period

the double-blind treatment period (Figures S6, S7). Fewer patients receiving Empa/Lina, compared with those receiving Empa/Plc, required rescue medication at Weeks 24 and 52 (Figure S8).

3.6 | Safety and tolerability measures

The overall incidence of AEs, as well as the incidence of drug-related AEs and AEs leading to discontinuation, was lower with Empa/Lina 10/5 than with Empa/Plc 10/5 over 24 weeks, but was higher with Empa/Lina 25/5 than with Empa/Plc 25/5 over 52 weeks (Table 2). Most AEs were mild or moderate in intensity. During the double-blind treatment periods, the rate of SAEs was slightly higher in the Empa/Plc groups than in the Empa/Lina groups. No SAEs were assessed as drug-related, with the exception of one event (drug-induced liver injury in the Empa/Lina 25/5 group) (Table S1 in Supporting information) and no deaths were reported. There were no DKA events confirmed by an independent central adjudication committee.

Apart from infections, the most common AESIs in all groups were increased ketogenesis, metabolic acidosis or DKA. Most events were blood ketone body increased, with the exception of one event of acetonemia (Empa/Plc 10/5), two events of ketosis (with Empa/Lina 25/5) and two events of urine ketone body present (Empa/Lina 25/5); all events were mild and non-serious. Of two (1.7%) patients with symptomatic hypoglycaemia in the Empa/Plc 25/5 group, one had confirmed hypoglycaemia. There were no reports of acute kidney injury, cardiac failure, embolic/thrombotic events, lower limb amputation or pancreatitis.

Cardiovascular events were confirmed as non-fatal acute myocardial infarction and coronary revascularization procedures (one patient, Empa/Plc 10/5) and non-fatal coronary revascularization procedures (one patient, Empa/Lina 25/5). Pancreatic events were confirmed as asymptomatic pancreatic hyperenzymemia (two patients, Empa/Lina 25/5; one patient each, Empa/Lina 10/5 and Empa/Plc 25/5). Hepatic events were confirmed as other significant hepatic injury (two

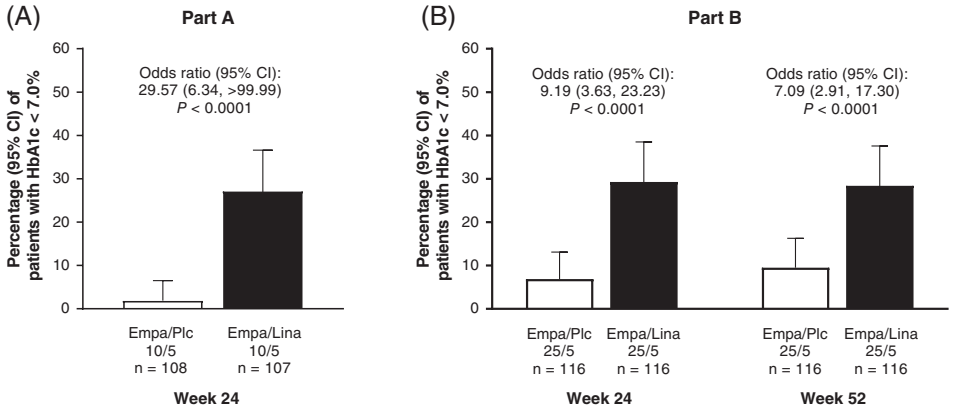

FIGURE 2 Patients who reached HbA1c < 7.0%. A, Percentage (95% CI) of patients receiving Empa/Plc 10/5 or Empa/Lina 10/5 who reached HbA1c < 7.0% at Week 24. B, Percentage (95% CI) of patients receiving Empa/Plc 25/5 or Empa/Lina 25/5 who reached HbA1c < 7.0% at Weeks 24 and 52. Odds ratios, 95% CIs and *P* values were determined by logistic regression in the full analysis set with non-completers considered failures. Abbreviations: CI, confidence intervals; Empa/Lina 10/5, empagliflozin 10 mg/linagliptin 5 mg fixed-dose combination; Empa/Plc 10/5, empagliflozin 10 mg/placebo for linagliptin 5 mg fixed-dose combination; Empa/Lina 25/5, empagliflozin 25 mg/linagliptin 5 mg fixed-dose combination; Empa/Plc 25/5, empagliflozin 25 mg/placebo for linagliptin 5 mg fixed-dose combination; HbA1c, glycated haemoglobin

patients, Empa/Plc 10/5; unlikely causal relationship) and as mild-moderate hepatic injury (two patients, Empa/Lina 25/5; one possible and one unlikely causal relationship).

4 | DISCUSSION

In this randomized, placebo-controlled trial in Japanese patients with T2DM, addition of linagliptin 5 mg to empagliflozin 10 or 25 mg in FDC formulation resulted in significantly greater decreases in HbA1c after 24 weeks compared with empagliflozin monotherapy, and this reduction was sustained for 52 weeks in the Empa/Lina 25/5 group. Moreover, the switch from empagliflozin monotherapy to Empa/Lina FDC resulted in a higher proportion of patients achieving glycaemic targets and significantly greater reductions in FPG. The safety profile was consistent with the known profiles of the monocomponents, with no increased risk of AEs.

Consistent with previous studies in non-Japanese patients,[8,9,11] reductions in HbA1c with Empa/Lina FDC in our study were superior to those with empagliflozin monotherapy. Although study differences preclude direct comparison, reductions in HbA1c with Empa/Lina FDC vs empagliflozin monotherapy in our Japanese study population appear to be more pronounced than those in non-Japanese patients.[8,11] This may reflect the increased HbA1c-lowering efficacy of DPP-4 inhibitors in Asian patients compared with non-Asian patients.[12,13] Decreases in FPG concentrations were consistent with the observed reductions in HbA1c.

As patients were pre-treated with empagliflozin monotherapy before the double-blind treatment period, other efficacy endpoints (SBP, DBP and body weight) were not substantially different with Empa/Lina FDC compared with empagliflozin monotherapy. Linagliptin is known to be neutral for these variables,[5] and changes were not expected by adding linagliptin to empagliflozin.[8,9,11] Modest increases in body weight were observed with Empa/Lina FDC compared with empagliflozin monotherapy; however, body weight in the Empa/Lina FDC group remained lower than that at initiation of open-label empagliflozin monotherapy.

Our findings indicate that Empa/Lina FDC is generally well tolerated in Japanese patients with T2DM, similar to findings concerning patients from other countries.[8–11] There were no new AEs or overall increased risk of AEs in Japanese patients with T2DM who received linagliptin as add-on to empagliflozin and no notable trend in the frequency of AEs with long-term treatment at the higher empagliflozin dose. Urinary and genital infection events, known to be associated with SGLT2 inhibitors,[14] were similar in both groups. No patients treated with Empa/Lina FDC experienced any confirmed hypoglycaemic episodes, indicating that better glycaemic control was achieved by the addition of linagliptin without increased risk of hypoglycaemia, consistent with the low risk of hypoglycaemia observed previously.[8–11]

Metabolic acidosis and ketoacidosis events were not reported in trials with Empa/Lina FDC in non-Japanese patients with T2DM.[8–11] In the current study, mild, non-serious events, categorized as increased ketogenesis, metabolic acidosis or DKA were observed in all treatment groups; most events were blood ketone body increased. However, none of these events was adjudicated as DKA by the independent adjudication committee, consistent with previous results concerning the use of combined SGLT2 inhibitors and DPP-4 inhibitors in Japanese patients.[15–17]

Although no cardiac failure events were reported, two adjudicated cardiovascular events occurred in one patient each in the Empa/Plc 10/5 and Empa/Lina 25/5 groups. Empagliflozin is associated with reduced cardiovascular mortality, all-cause mortality and hospitalization for heart failure in patients with T2DM.[2,18] The effects of linagliptin on cardiovascular outcomes in high-risk patients is currently under investigation in two large randomized clinical trials (CARMELINA [NCT01897532]; CAROLINA [NCT01243424]).[19]

Linagliptin increases insulin and reduces glucagon in patients with T2DM, in line with the mechanisms of action of DPP-4 inhibitors.[20] Addition of canagliflozin to teneligliptin in Japanese patients with T2DM showed small and statistically nonsignificant reductions in postprandial and/or fasting glucagon.[15,16] Addition of linagliptin to

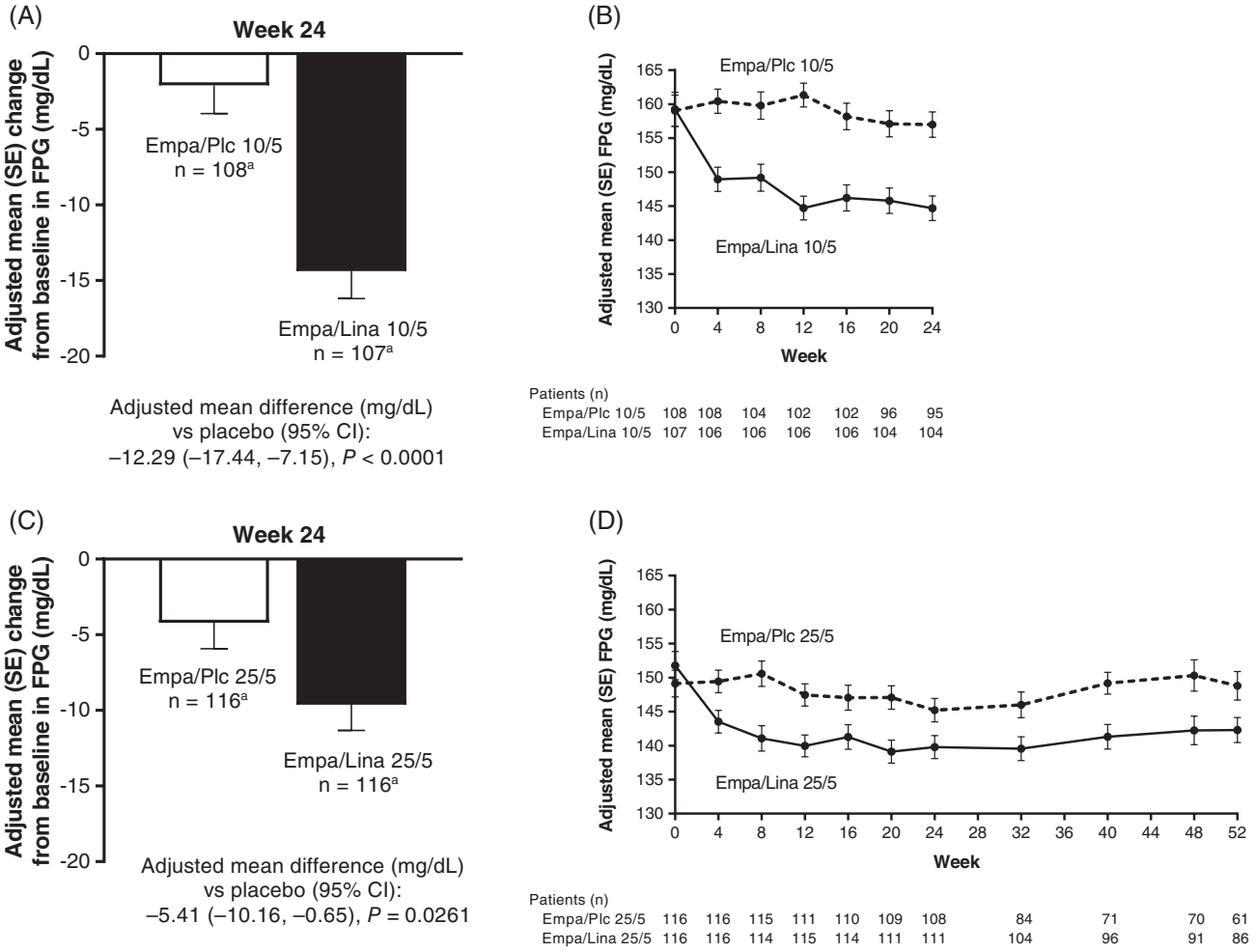

FIGURE 3 Change in FPG. A, Change from baseline in FPG at Week 24 in patients receiving Empa/Plc 10/5 or Empa/Lina 10/5. B, Change in FPG over time during double-blind period in patients receiving Empa/Plc 10/5 or Empa/Lina 10/5. C, Change from baseline in FPG at Week 24 in patients receiving Empa/Plc 25/5 or Empa/Lina 25/5. D, Change in FPG over time during double-blind period in patients receiving Empa/Plc 25/5 or Empa/Lina 25/5. Baseline was defined as the last observation before the first intake of double-blind randomized trial medication. Data are given as adjusted mean (±SE) from MMRM analyses in the full analysis set using observed cases. Abbreviations: CI, confidence intervals; Empa/Lina 10/5, empagliflozin 10 mg/linagliptin 5 mg fixed-dose combination; Empa/Plc 10/5, empagliflozin 10 mg/placebo for linagliptin 5 mg fixed-dose combination; Empa/Lina 25/5, empagliflozin 25 mg/linagliptin 5 mg fixed-dose combination; Empa/Plc 25/5, empagliflozin 25 mg/placebo for linagliptin 5 mg fixed-dose combination; MMRM, mixed model repeated measures; SE, standard error. [a]Number of patients analysed during the 24-week double-blind treatment period

empagliflozin treatment in German patients with T2DM who were insufficiently controlled with metformin monotherapy significantly lowered postprandial glucagon levels and reduced the glucagon/insulin ratio.[21] In the current study, although fasting plasma glucagon levels were slightly increased in the FDC groups, these minimal increases were considered not to be clinically significant because of the wide individual variations. Moreover, postprandial glucagon suppression has been suggested to be more important than fasting glucagon suppression for glycaemic control with DPP-4 inhibitors.[22] Further evaluations of insulin/glucagon ratios, amino acid metabolism and endogenous glucose production are needed.

This study is strengthened by the use of both low (10 mg) and high (25 mg) empagliflozin FDCs, and by a 52-week extension period with the high dose. In addition, the stabilization period allowed patients with adequate glycaemic control with empagliflozin monotherapy to be excluded. The completion rate was high (> 90%), and the results in this Japanese population were consistent with those from multinational studies. However, this study did not evaluate levels of postprandial glucose or other biomarkers. Further, although its design does not reflect usual practice in Japan, that is, initiating treatment directly with empagliflozin 25 mg monotherapy and switching to FDC, the design was approved by the Japanese health authority as the optimal way to assess the efficacy and safety of the FDC. Our results support those of another complementary study in which Japanese patients with T2DM were switched from linagliptin monotherapy to treatment with Empa/Lina FDC.[23]

In conclusion, linagliptin as add-on to empagliflozin in an FDC formulation led to significant and clinically relevant reductions in HbA1c and FPG, and higher proportions of patients achieved HbA1c target levels. Further, FDCs of empagliflozin 10 or 25 mg and linagliptin were well tolerated. These results support the clinical usefulness of Empa/Lina FDC for glycaemic control in Japanese patients with

TABLE 2 Adverse events during the double-blind treatment period

Adverse event	Part A (24 weeks with FDC)		Part B (52 weeks with FDC)	
	Empa/Plc 10/5 (*n* = 108)	Empa/Lina 10/5 (*n* = 107)	Empa/Plc 25/5 (*n* = 116)	Empa/Lina 25/5 (*n* = 116)
≥ 1 AE	64 (59.3)	53 (49.5)	86 (74.1)	94 (81.0)
≥ 1 Severe AE	3 (2.8)	1 (0.9)	1 (0.9)	2 (1.7)
≥ 1 Drug-related AE	16 (14.8)	13 (12.1)	23 (19.8)	33 (28.4)
≥ 1 AE leading to discontinuation	5 (4.6)	2 (1.9)	3 (2.6)	4 (3.4)
≥ 1 Serious AE	4 (3.7)	1 (0.9)	8 (6.9)	6 (5.2)
Death	0 (0)	0 (0)	0 (0)	0 (0)
AE of special interest categories				
Acute kidney injury (19 PTs)	0 (0)	0 (0)	0 (0)	0 (0)
Arthralgia (98 PTs)	0 (0)	1 (0.9)	7 (6.0)	3 (2.6)
Bone fracture (80 PTs)	2 (1.9)	1 (0.9)	0 (0)	3 (2.6)
Cardiac failure (30 PTs)	0 (0)	0 (0)	0 (0)	0 (0)
Confirmed hypoglycaemia[a]	0 (0)	0 (0)	1 (0.9)	0 (0)
Embolic and thrombotic events (85 PTs)	0 (0)	0 (0)	0 (0)	0 (0)
Genital infection (88 PTs)	1 (0.9)	2 (1.9)	2 (1.7)	3 (2.6)
Hepatic injury (166 PTs)	0 (0)	1 (0.9)	0 (0)	3 (2.6)
Protocol-specified[b]	0 (0)	0 (0)	0 (0)	1 (0.9)
Hypersensitivity (270 PTs)	2 (1.9)	1 (0.9)	6 (5.2)	5 (4.3)
Increased urination (3 PTs)[c]	1 (0.9)	0 (0)	0 (0)	0 (0)
Infection (1887 PTs)	37 (34.3)	28 (26.2)	NA	NA
Influence on safety caused by weight decrease (9 PTs)	1 (0.9)	0 (0)	NA	NA
Intestinal obstruction (32 PTs)	0 (0)	0 (0)	NA	NA
Lower limb amputation	0 (0)	0 (0)	0 (0)	0 (0)
Malignancies (1689 PTs)[d]	0 (0)	1 (0.9)	1 (0.9)	2 (1.7)
Increased ketogenesis, metabolic acidosis, or DKA (17 PTs)[e]	12 (11.1)	2 (1.9)	9 (7.8)	19 (16.4)
DKA (3 PTs)[f]	0 (0)	0 (0)	0 (0)	0 (0)
Pancreatitis (19 PTs)	0 (0)	0 (0)	0 (0)	0 (0)
Skin lesions (56 PTs)	1 (0.9)	2 (1.9)	NA	NA
Urinary tract infection (75 PTs)	1 (0.9)	1 (0.9)	4 (3.4)	5 (4.3)
Acute pyelonephritis	0 (0)	0 (0)	0 (0)	0 (0)
Asymptomatic bacteriuria	1 (0.9)	1 (0.9)	4 (3.4)	5 (4.3)
Sepsis	0 (0)	0 (0)	0 (0)	0 (0)
Volume depletion (8 PTs)	0 (0)	0 (0)	0 (0)	1 (0.9)

Abbreviations: AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DKA, diabetic ketoacidosis; Empa/Lina 10/5, empagliflozin 10 mg/linagliptin 5 mg fixed-dose combination; Empa/Plc 10/5, empagliflozin 10 mg/placebo for linagliptin 5 mg fixed-dose combination; Empa/Lina 25/5, empagliflozin 25 mg/linagliptin 5 mg fixed-dose combination; Empa/Plc 25/5, empagliflozin 25 mg/placebo for linagliptin 5 mg fixed-dose combination; MedDRA, Medical Dictionary for Regulatory Activities; NA, not available; PT, MedDRA preferred term; ULN, upper limit of normal.

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 of assistance.

[b] AST and/or ALT ≥ 3-fold ULN combined with total bilirubin ≥ 2-fold ULN, or AST and/or ALT ≥ 5-fold ULN. One patient in the Empa/Plc 10/5 group met the definition of protocol-specified hepatic injury, but was not included because the liver function disorder was considered to be associated with concurrent pancreatic carcinoma and not an additional event. An additional patient in the Empa/Plc 10/5 group had investigator-defined "cholangitis". One patient in the Empa/Lina 25/5 group met the definition of protocol-specified hepatic injury, however, was later diagnosed with hepatitis E, which was considered to be the cause of the elevated liver enzymes and unrelated to study drug.

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

[d] One patient in the Empa/Plc 10/5 group had pancreatic carcinoma during the post-treatment period.

[e] Preferred terms included "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". Most observed events were "blood ketone body increased"; there was one event of "acetonemia" in the Empa/Plc 10/5 group, 2 events of "ketosis" in the Empa/Lina 25/5 group, and two events of "urine ketone body present" in the Empa/Lina 25/5 group. All events were mild and non-serious.

[f] Preferred terms included "diabetic ketoacidosis", "diabetic ketoacidotic hyperglycaemic coma", and "ketoacidosis".

T2DM. In countries such as Japan, where metformin is not the first choice for T2DM management, Empa/Lina combination therapy may provide better efficacy than monotherapy with empagliflozin or linagliptin, with an expected improvement in patient adherence to treatment.

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Conflict of interest

Boehringer Ingelheim International GmbH and Nippon Boehringer Ingelheim Co. Ltd. were involved in the study design, data collection, data analysis and preparation of the manuscript. Y. T., G. L., K. S. and Y.M. are employees of Nippon Boehringer Ingelheim Co. Ltd. F. S., J. L. and J. G. are employees of Boehringer Ingelheim GmbH & Co. KG. C. L. is a former employee of Boehringer Ingelheim GmbH & Co. KG. K. K. has received research funding and/or honoraria for lectures from Astellas Pharma Inc., AstraZeneca, Daiichi Sankyo Co. Ltd., Eli Lilly Japan K.K., Kowa Pharmaceutical Co. Ltd., Mitsubishi Tanabe Pharma Corporation, MSD, Nippon Boehringer Ingelheim Co. Ltd., Novo Nordisk Pharma, Ono Pharmaceutical Co. Ltd., Sumitomo Dainippon Pharma Co. Ltd., Sanwa Kagaku Kenkyusho Co. Ltd., Taisho Toyama Pharmaceutical Co. Ltd. and Takeda Pharmaceutical Co. Ltd. M. H. has received research funding and/or honoraria for lectures from Astellas Pharma Inc., Daiichi Sankyo Co. Ltd., Eli Lilly Japan K.K., Johnson & Johnson, Kissei Pharmaceutical Co. Ltd., Kowa Pharmaceutical Co. Ltd., Kyowa Hakko Kirin Co. Ltd., Mitsubishi Tanabe Pharma Corporation, MSD, Nippon Boehringer Ingelheim Co. Ltd., Novartis Pharma, Novo Nordisk Pharma, Ono Pharmaceutical Co. Ltd., Otsuka Pharmaceutical Co. Ltd., Sanofi, Shionogi & Co. Ltd., Taisho Pharmaceutical Co. Ltd., Taisho Toyama Pharmaceutical Co. Ltd. and Takeda Pharmaceutical Company Ltd.

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. Y. T., G. L. and F. S. were involved in the study design and data analyses. K. K. was an investigator in the study and M. H. was a medical expert for the study.

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