ORIGINAL ARTICLE

Efficacy and safety of empagliflozin as add-on to insulin in Japanese patients with type 2 diabetes: A randomized, double-blind, placebo-controlled trial

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Aim: To assess the efficacy and safety of empagliflozin as add-on to insulin in Japanese patients with type 2 diabetes (T2D).

Materials and methods: This multicentre, double-blind, parallel-group study randomized Japanese patients with T2D insufficiently controlled with insulin (1:1:1) to empagliflozin 10 mg (n=89), empagliflozin 25 mg (n=90) or placebo (n=90) for 52 weeks. The primary endpoint was change from baseline in glycated haemoglobin (HbA1c) at 16 weeks.

Results: At 16 weeks, empagliflozin 10 mg and 25 mg significantly decreased HbA1c: adjusted mean difference −0.92% (95% confidence interval [CI] −1.11, −0.73) and −1.00% (95% CI −1.18, −0.82; both $P<0.0001$) compared with placebo. This difference was maintained up to 52 weeks: adjusted mean difference at 52 weeks −0.90% (95% CI −1.09, −0.70) and −0.96% (95% CI −1.15, −0.77; both $P<0.0001$). At 52 weeks, significant improvements in fasting plasma glucose (adjusted mean difference −27.62 mg/dL [95% CI −36.15, −19.08] and −31.99 mg/dL [95% CI −40.35, −23.62]) and in body weight (−1.78 kg [95% CI −2.46, −1.10] and −1.92 kg [95% CI −2.58, −1.25]) were also seen with empagliflozin 10 mg and 25 mg compared with placebo (all $P<0.0001$). At 52 weeks, the frequency of adverse events (AEs) and serious AEs was similar in the three treatment groups; confirmed hypoglycaemia was reported slightly more in participants in the empagliflozin 10 mg and 25 mg groups (23.3% and 22.2% vs 14.4%). All hypoglycaemic events were mild in severity; no episodes required assistance.

Conclusions: In Japanese patients with insufficiently controlled T2D, adding empagliflozin 10 mg or 25 mg to insulin treatment was associated with clinically meaningful reductions in HbA1c at 16 weeks and was generally well tolerated.

KEYWORDS

empagliflozin, insulin, Japanese, sodium-glucose co-transporter-2 inhibitor, type 2 diabetes

1 | INTRODUCTION

As a result of an ageing population, the prevalence of type 2 diabetes (T2D) in Japan is expected to increase.[1] Japan Diabetes Society guidelines recommend treating T2D with glucose-lowering drugs, including insulin, after lifestyle modifications.[2] However, while intensive glycaemic control with insulin therapy prevents diabetic complications,[3-5] it is often associated with a high risk of hypoglycaemia and weight gain.[6-8]

Among the newer oral antidiabetic drugs (OADs), sodium-glucose co-transporter-2 (SGLT2) inhibitors reduce plasma glucose independently of insulin secretion by increasing the renal excretion of glucose.[9,10] SGLT2 inhibitors are a promising class of agents for combination with exogenous insulin, as, in addition to improving glucose control, they may reduce insulin dose requirements and mitigate insulin-induced weight gain.[11]

Empagliflozin is a potent SGLT2 inhibitor that reduces glycated haemoglobin (HbA1c), body weight and blood pressure in patients with T2D when given as monotherapy, or as add-on to one or more OADs[12-16]; it also reduces the risk of cardiovascular events or death in patients with T2D at high risk for these events.[17] Empagliflozin was well tolerated in phase 3 trials, with a low risk of hypoglycaemia but an increased frequency of mild genitourinary infections typical of the class.[12-17] Empagliflozin has also shown efficacy when used in combination with insulin[18,19]; however, to date the efficacy and safety of combining empagliflozin and insulin in Japanese people has not been investigated.

The use of insulin and the pathological features of T2D in Japanese people differ from those in Caucasian people[20-22]; therefore, it is important to determine the clinical benefit of such a combination therapy in this population. Additionally, as per the revised draft of the Japanese guideline "Guideline for Clinical Evaluation of Oral Hypoglycemic Agents", new antidiabetic treatments that are co-administered with insulin must be evaluated specifically in Japanese people; that is, efficacy cannot be extrapolated from other ethnic groups. The aim of the present study, therefore, was to evaluate the efficacy and safety of empagliflozin in combination with insulin in Japanese people with T2D who had insufficient glycaemic control with insulin treatment alone.

2 | MATERIALS AND METHODS

2.1 | Study design and patients

This 52-week, randomized, double-blind, parallel group, phase 4 study was conducted at 51 sites in Japan between November 2, 2015 and January 5, 2018 (ClinicalTrials.gov Identifier: NCT02589639). The study comprised a screening visit, a 10-week OAD wash-out period, a 2-week open-label placebo run-in period and a 52-week double-blind treatment period (Figure 1). Participants who were pre-treated with insulin alone directly entered the placebo run-in period. The double-blind treatment period had two sub-periods. During treatment period 1 (first 16 weeks), background insulin dose adjustments were not allowed for any reason other than for a participant's safety or if the participant met the criteria for rescue therapy. During treatment period 2 (the following 36 weeks), the dose of background insulin could be adjusted at the investigator's discretion.

Japanese adults (aged ≥20 to <75 years) with T2D who had insufficient glycaemic control despite receiving insulin with or without an OAD for ≥12 weeks prior to screening were eligible for inclusion. Participants also had to have an HbA1c of ≥7.5% to ≤10.0% (for participants pre-treated with insulin alone) or an HbA1c of ≥7.0% to ≤9.5% at screening and ≥7.5% to ≤10.0% after the 10-week wash-out period (for participants pre-treated with insulin and an OAD), a fasting C-peptide >0.5 ng/mL and a body mass index (BMI) of >22 kg/m^2 and ≤40 kg/m^2. Individuals were excluded from the study if they were receiving a sulphonylurea at a dose that was more than half of the maximum approved daily dose (because a higher sulphonylurea dose would place participants at risk of hyperglycaemia during the wash-out period), a glucagon-like peptide-1 receptor antagonist, a thiazolidinedione or an SGLT2 inhibitor, if they had an estimated glomerular filtration rate (eGFR) <45 mL/min/1.73m^2 during screening or the run-in period, or if they had experienced a cardiovascular and/or stroke event in the last 12 weeks. The main inclusion and exclusion criteria are summarized in Table S1.

All participants provided written informed consent. The study protocol was approved by the institutional review boards at each study site and was conducted in accordance with the ethical principles of the Japanese and International Conference on Harmonization Good
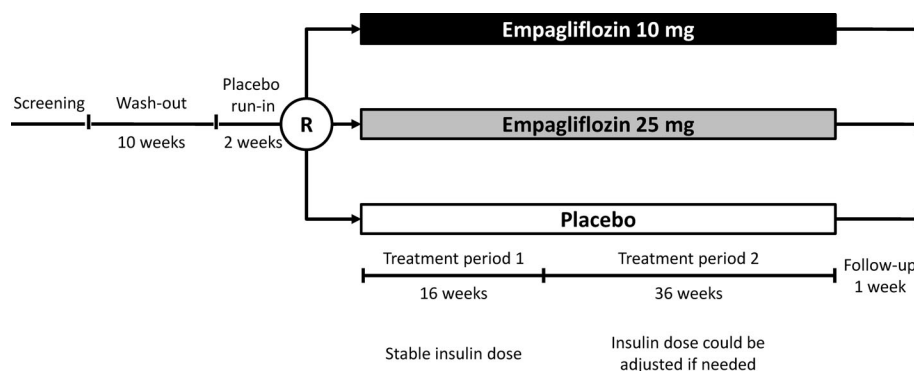

FIGURE 1 Study design. R, randomization

Clinical Practice Regulations, the Japanese Good Post-marketing Study Practice guidelines and the Declaration of Helsinki.

2.2 | Treatment and randomization

Participants were randomly assigned (1:1:1) to once-daily empagliflozin 10 mg, empagliflozin 25 mg or placebo, in addition to background insulin. Treatments were allocated via an interactive response system using a computer-generated random sequence, with randomization stratified according to baseline HbA1c (<8.5% or ≥8.5%), renal function (eGFR <60 mL/min/1.73m^2 vs ≥60 mL/min/1.73m^2) and type of pretreatment insulin therapy (basal vs other insulin therapy). During treatment period 1, the dose and usage of insulin could only be adjusted as rescue therapy if a participant had a confirmed glucose level after an overnight fast >270 mg/dL in weeks 1 to 12 or >240 mg/dL in weeks 12 to 16. The dosage of rescue medication was at the discretion of the investigator; however, any changes had to follow the Japanese label of the insulin used.

2.3 | Outcomes

The primary endpoint was the change in HbA1c from baseline at 16 weeks. Other efficacy endpoints included the change in HbA1c from baseline at 52 weeks, the proportion of participants achieving an HbA1c <7.0% at 16 and 52 weeks, the proportion of participants with a ≥0.5% reduction in HbA1c at 16 and 52 weeks, the change in fasting plasma glucose (FPG), body weight, waist circumference, systolic blood pressure and diastolic blood pressure from baseline at 16 and 52 weeks, and the change in insulin dose from baseline at 52 weeks.

The key secondary endpoint was the proportion of participants experiencing drug-related adverse events (AEs) over the 52-week treatment period (all AEs were recorded throughout the study). Other safety endpoints included the frequency and severity of AEs, as well as the frequency of AEs of special interest, hypoglycaemia, urinary tract infections (UTIs), genital tract infections and volume depletion events. All AEs were coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA version 20.1) coding dictionary; those of special interest were identified using a prespecified list of MedDRA preferred terms. AEs of special interest were events causing hepatic injury, decreased renal function, metabolic acidosis, ketoacidosis or diabetic ketoacidosis, or events involving lower limb amputation. Every confirmed episode of plasma glucose ≤70 mg/dL was documented; AEs involving hypoglycaemic episodes included episodes in which plasma glucose was ≤54 mg/dL (irrespective of symptoms), all symptomatic hypoglycaemic episodes, and any investigator-defined hypoglycaemic episodes. Safety and tolerability were also assessed by standard laboratory tests, physical examinations, ECG, and vital signs. Laboratory tests were undertaken at weeks 2 and 4, and then every 4 weeks thereafter; ketone bodies were measured at weeks 4, 8, 16, 24, 32, 40, 48 and 52.

2.4 | Statistical analyses

Sample size calculations were based on a previous study of empagliflozin with insulin, which suggested that empagliflozin would result in an HbA1c reduction of ~0.5% versus placebo after 16 weeks of treatment, and a standard deviation (SD) of 1.0%. To detect this difference, 86 evaluable participants per treatment group were required for 90% power at a 0.05 two-sided significance level. Allowing for a 3% drop-out rate, 89 participants per treatment arm were required. In addition, as per the revised draft of the Japanese guideline "Guideline for Clinical Evaluation of Oral Hypoglycemic Agents", Japanese clinical trials of OADs should include ≥100 patients receiving treatment with the OAD for ≥1 year. Allowing for a 20% loss of randomized participants during the 52 weeks, at least 63 participants had to be randomized per arm. Therefore, a total of 267 participants (89 per arm) needed to be randomized.

Efficacy variables were analysed in the full analysis set, defined as all randomized participants who received at least one dose of study drug and had a baseline HbA1c assessment. Safety data were assessed in the safety analysis set, which included all randomized participants who received at least one dose of study drug.

Demographic and clinical characteristics were summarized using descriptive statistics (frequency and percentage for categorical variables, mean and SD for continuous variables). The primary endpoint was estimated using an analysis of covariance with baseline HbA1c as a linear covariate and treatment, renal function and type of pretreatment insulin therapy as fixed effects. A last-observation-carried-forward approach was used to impute missing values. Hypothesis testing on the efficacy endpoints followed a hierarchical testing procedure to control the family-wise type I error rate. Superiority of empagliflozin 10 mg versus placebo for change from baseline in HbA1c after 16 weeks had to be established at a two-sided significance level of $P<0.05$ before testing for superiority of empagliflozin 25 mg versus placebo for change from baseline in HbA1c after 16 weeks. For the other efficacy endpoints, continuous endpoints were analysed using a statistical model similar to the primary analysis model with the respective baseline parameter as an additional covariate. Binary endpoints were analysed using logistic regression. The respective model included treatment, baseline renal function, type of insulin therapies, and continuous baseline HbA1c. Descriptive statistics (frequency and percentage) were used to analyse the safety endpoints.

All statistical analyses were performed using SAS (version 9.4).

3 | RESULTS

3.1 | Participants

Of the 444 people screened, 269 were randomized to empagliflozin 10 mg (n=89), 25 mg (n=90) or placebo (n=90; Figure S1). Three participants randomized to 10 mg were not treated and were excluded from the safety analysis set and full analysis set (n=266 each). The majority of participants (92.1%) completed the study; the most common reasons for study discontinuation were AEs.

Demographic and baseline characteristics were comparable across treatment groups (Table 1). At baseline, participants had a mean age of 58.7 years (1.1% were aged ≥75 years), a body weight of 73.2 kg, a BMI of 26.9 kg/m^2, a duration of T2D of 13.8 years, an HbA1c concentration of 8.8%, an FPG level of 161.3 mg/dL and were receiving a mean daily dose of insulin of 31.4 IU. The majority of participants were receiving basal insulin as their background medication (45.5%), followed by basal + prandial insulin (32.3%) and premixed insulin (21.4%). Before entering the study, the majority of participants were receiving insulin only, while 27.4% were receiving insulin with an OAD. The most common clinically relevant comorbidity was hypertension, 56.4% of participants had an eGFR of 60 to <90 mL/min/1.73 m^2 and 9.0% had an eGFR of 45 to <60 mL/min/1.73 m^2.

3.2 | Efficacy

At baseline, mean (standard error (SE)) HbA1c values were 8.83 (0.07)% and 8.74 (0.08)% in the empagliflozin 10 mg and 25 mg groups, and 8.70 (0.07)% in the placebo group. The adjusted mean (SE) values after 16 weeks were 7.83 (0.07)%, 7.75 (0.07)% and 8.75 (0.07)%, respectively. There was a significant reduction in HbA1c from baseline at 16 weeks with empagliflozin 10 mg or 25 mg compared with placebo (placebo-corrected adjusted mean change from baseline −0.92% [95% confidence interval {CI} −1.11, −0.73] and −1.00% [95% CI −1.18, −0.82], respectively; both P<0.0001 [Table 2]). The effect was apparent from 8 weeks and was maintained up to 52 weeks (Figure 2A). Furthermore, at weeks 16 and 52, more participants in the empagliflozin 10 mg and 25 mg groups achieved an HbA1c <7% or had a reduction in their HbA1c of ≥0.5% (Table S2). Responder rates appeared to be higher in participants receiving empagliflozin 25 mg versus those receiving 10 mg (Table S2). Subgroup analyses by age, baseline HbA1c, baseline BMI, baseline sex, baseline renal impairment, and baseline insulin use showed a consistent improvement with empagliflozin 10 mg and 25 mg in HbA1c at 16 weeks compared with placebo (Figure S2). The treatment-by-subgroup tests for changes in HbA1c at 16 weeks indicated greater effects in participants with a baseline HbA1c ≥8.5% versus <8.5% (subgroup interaction P=0.0195), in those with a higher baseline BMI (P=0.0196) and in those with a higher eGFR (P=0.0324). The interaction test did not indicate that baseline insulin was an effect modifier (Figure S2).

The addition of empagliflozin 10 mg and 25 mg also significantly reduced body weight at 16 weeks (placebo-corrected adjusted mean change from baseline −1.79 kg [95% CI −2.30, −1.29] and −1.74 kg [95% CI −2.24, −1.25], respectively; both P<0.0001) and 52 weeks (placebo-corrected adjusted mean change from baseline −1.78 kg [95% CI −2.46, −1.10] and −1.92 kg [95% CI −2.58, −1.25], respectively; both P<0.0001 [Table 2]) compared with placebo (Figure 2B). Furthermore, the placebo-corrected adjusted mean change from baseline at 52 weeks in total daily doses of insulin was −4.15 IU/d (95% CI −5.69, −2.61; P<0.0001) and −4.16 IU/d (95% CI −5.67, −2.64; P<0.0001) in participants receiving empagliflozin 10 mg and 25 mg, respectively (Table 2; Figure 2C).

Finally, participants receiving empagliflozin 10 mg and 25 mg had significantly greater improvements from baseline in FPG at weeks 16 and 52 compared with placebo (all P<0.0001), as well as significantly greater reductions from baseline in waist circumference (Table 2). No significant changes in systolic or diastolic blood pressures were observed between treatment groups (Table 2).

3.3 | Tolerability

Empagliflozin 10 mg and 25 mg were generally well tolerated; the frequency of AEs and serious AEs during the 52-week treatment period was similar between treatment groups (Table 3). Most of the AEs reported during the treatment period were mild or moderate in severity. One participant in the empagliflozin 10 mg treatment group died from prostate cancer and disseminated intravascular coagulation, which were considered not related to treatment.

More participants receiving empagliflozin 10 mg or 25 mg (43.0% and 43.3%, respectively) experienced AEs that were considered drug-related compared with those receiving placebo (25.6%; Table 3). The most common drug-related AEs were hypoglycaemia (20.9% and 24.4% vs 15.6% of the empagliflozin 10 mg or 25 mg vs placebo groups, respectively), pollakiuria (10.5% and 10.0% vs 1.1%, respectively), and asymptomatic bacteriuria (2.3% and 4.4% vs 6.7%, respectively). Two drug-related AEs were considered serious: one case of acute pyelonephritis with empagliflozin 10 mg and one case of unstable angina with placebo.

There were no protocol-specified AEs of special interest reported in any treatment group over the 52-week treatment period (Table 3).

Confirmed hypoglycaemia was reported in slightly more patients receiving empagliflozin 10 mg and 25 mg than placebo (23.3% and 22.2% vs 14.4% of participants, respectively; Table S3). Most of these hypoglycaemic events were symptomatic, but they were all mild and no participant experienced a hypoglycaemic event that required assistance.

Urinary tract infections were reported in 5.8%, 6.7% and 8.9% of participants in the empagliflozin 10 mg, 25 mg and placebo groups, respectively (Table 3). One participant receiving empagliflozin 10 mg experienced a severe and serious case of acute pyelonephritis, which was considered related to treatment and led to empagliflozin discontinuation. Most of the other UTIs were asymptomatic bacteriuria and were mild in severity.

Genital tract infections were reported in 3.5%, 3.3% and 0% of participants in the empagliflozin 10 mg, 25 mg and placebo groups, respectively (Table 3). Three women in the empagliflozin 10 mg group and one woman in the empagliflozin 25 mg group had vulvovaginal candidiasis, one woman in the empagliflozin 25 mg group had vulvitis, and one man in the empagliflozin 25 mg group had balanoposthitis. All events were mild in intensity, non-serious, and did not lead to treatment discontinuation.

Volume depletion events were reported in 2.3%, 1.1% and 1.1% of participants in the empagliflozin 10 mg, 25 mg and placebo groups,

TABLE 1 Baseline demographics

Characteristic	Empagliflozin 10 mg (n=86)	25 mg (n=90)	Placebo (n=90)	Total (n=266)
Age, years	58.3 ± 10.0	58.6 ± 9.5	59.1 ± 10.7	58.7 ± 10.0
<65 years, n(%)	56 (65.1)	62 (68.9)	60 (66.7)	178 (66.9)
≥65 years, n(%)	30 (34.9)	28 (31.1)	30 (33.3)	88 (33.1)
Men, n (%)	63 (73.3)	61 (67.8)	69 (76.7)	193 (72.6)
Time since diagnosis, years	14.4 ± 8.5	14.6 ± 8.2	12.4 ± 7.3	13.8 ± 8.0
≤5 years, n (%)	12 (14.0)	11 (12.2)	13 (14.4)	36 (13.5)
>5 to 10 years, n (%)	18 (20.9)	17 (18.9)	28 (31.1)	63 (23.7)
>10 years, n (%)	56 (65.1)	62 (68.9)	49 (54.4)	167 (62.8)
Body weight, kg	73.3 ± 11.5	72.2 ± 11.4	74.0 ± 11.3	73.2 ± 11.4
Waist circumference, cm	93.3 ± 8.8	93.1 ± 8.3	93.8 ± 9.6	93.4 ± 8.9
BMI, kg/m^2	27.0 ± 3.0	26.8 ± 3.3	26.9 ± 3.4	26.9 ± 3.2
<25 kg/m^2, n (%)	21 (24.4)	28 (31.1)	31 (34.4)	80 (30.1)
25 to <30 kg/m^2, n (%)	50 (58.1)	47 (52.2)	47 (52.2)	144 (54.1)
≥30 kg/m^2, n (%)	15 (17.4)	15 (16.7)	12 (13.3)	42 (15.8)
HbA1c, %	8.8 ± 0.7	8.7 ± 0.7	8.7 ± 0.7	8.8 ± 0.7
<8.0%, n (%)	9 (10.5)	16 (17.8)	11 (12.2)	36 (13.5)
8.0 to <9.0%, n (%)	39 (45.3)	38 (42.2)	45 (50.0)	122 (45.9)
≥9.0%, n (%)	38 (44.2)	36 (40.0)	34 (37.8)	108 (40.6)
FPG, mg/dL	168.8 ± 43.1	156.1 ± 37.7	159.1 ± 38.5	161.3 ± 40.0
SBP, mmHg	134.2 ± 14.6	136.3 ± 14.3	135.7 ± 14.0	135.4 ± 14.3
DBP, mmHg	80.1 ± 10.2	80.0 ± 10.6	79.6 ± 8.7	79.9 ± 9.8
eGFR, mL/min/1.73m^2	85.1 ± 17.8	84.3 ± 18.8	83.4 ± 23.7	84.2 ± 20.2
≥90 mL/min/1.73m^2, n (%)	30 (34.9)	31 (34.4)	29 (32.2)	90 (33.8)
60 to <90 mL/min/1.73m^2, n (%)	51 (59.3)	49 (54.4)	50 (55.6)	150 (56.4)
45 to <60 mL/min/1.73m^2, n (%)	5 (5.8)	9 (10.0)	10 (11.1)	24 (9.0)
<45 mL/min/1.73 m^2, n (%)	0	1 (1.1)	1 (1.1)	2 (0.8)
Background insulin medication, n (%)				
Basal	41 (47.7)	39 (43.3)	41 (45.6)	121 (45.5)
Prandial insulin	0	1 (1.1)	0	1 (0.4)
Premixed insulin	16 (18.6)	19 (21.1)	22 (24.4)	57 (21.4)
Other	1 (1.2)	0	0	1 (0.4)
Basal + prandial insulin	28 (32.6)	31 (34.4)	27 (30.0)	86 (32.3)
Daily insulin dose, IU	32.1 ± 16.3	30.9 ± 16.0	31.2 ± 14.8	31.4 ± 15.6
Prior glucose-lowering therapy, n (%)				
Insulin monotherapy	54 (62.8)	62 (68.9)	77 (85.6)	193 (72.6)
Insulin plus one OAD	32 (37.2)	28 (31.1)	13 (14.4)	73 (27.4)
Clinically relevant comorbidities[a], n (%)				
Diabetic retinopathy	33 (38.4)	43 (47.8)	31 (34.4)	107 (40.2)
Diabetic nephropathy	31 (36.0)	34 (37.8)	34 (37.8)	99 (37.2)
Diabetic neuropathy	16 (18.6)	27 (30.0)	16 (17.8)	59 (22.2)
Hypertension	52 (60.5)	56 (62.2)	62 (68.9)	170 (63.9)

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular rate; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; OAD, oral antidiabetic drug; SBP, systolic blood pressure.

[a]Based on participant's medical history

All values presented as mean ± SD, unless stated otherwise

TABLE 2 Change in efficacy variables

Change from baseline	At 16 weeks			At 52 weeks		
	Empagliflozin		Placebo	Empagliflozin		Placebo
	10 mg (n=86)	25 mg (n=90)	(n=90)	10 mg (n=86)	25 mg (n=90)	(n=90)
HbA1c, %	−0.92 ± 0.07	−1.00 ± 0.07	0.00 ± 0.07	−0.89 ± 0.07	−0.95 ± 0.07	0.01 ± 0.07
Mean (95% CI) vs placebo	−0.92 (−1.11, −0.73)***	−1.00 (−1.18, −0.82)***		−0.90 (−1.09, −0.70)***	−0.96 (−1.15, −0.77)***	
FPG, mg/dL	−36.87 ± 3.28	−38.07 ± 3.19	−0.85 ± 3.19	−34.39 ± 3.10	−38.76 ± 3.01	−6.77 ± 3.01
Mean (95% CI) vs placebo	−36.02 (−45.07, −26.97)***	−37.21 (−46.08, −28.34)***		−27.62 (−36.15, −19.08)***	−31.99 (−40.35, −23.62)***	
Body weight, kg	−1.67 ± 0.18	−1.62 ± 0.18	0.12 ± 0.18	−1.56 ± 0.25	−1.70 ± 0.24	0.22 ± 0.24
Mean (95% CI) vs placebo	−1.79 (−2.30, −1.29)***	−1.74 (−2.24, −1.25)***		−1.78 (−2.46, −1.10)***	−1.92 (−2.58, −1.25)***	
Waist circumference, cm	−1.16 ± 0.33	−1.63 ± 0.32	0.28 ± 0.32	−1.06 ± 0.35	−1.81 ± 0.34	0.22 ± 0.34
Mean (95% CI) vs placebo	−1.44 (−2.35, −0.53)**	−1.91 (−2.81, −1.02)***		−1.28 (−2.26, −0.31)*	−2.03 (−2.99, −1.07)***	
SBP, mmHg	−3.96 ± 1.19	−5.48 ± 1.16	−2.87 ± 1.16	−2.25 ± 1.26	−4.82 ± 1.22	−2.09 ± 1.23
Mean (95% CI) vs placebo	−1.09 (−4.38, 2.19)	−2.61 (−5.84, 0.62)		−0.16 (−3.63, 3.31)	−2.73 (−6.14, 0.68)	
DBP, mmHg	−1.00 ± 0.77	−2.65 ± 0.74	−1.20 ± 0.75	−1.17 ± 0.74	−2.81 ± 0.72	−2.32 ± 0.73
Mean (95% CI) vs placebo	0.20 (−1.91, 2.31)	−1.45 (−3.52, 0.63)		1.15 (−0.91, 3.20)	−0.50 (−2.52, 1.52)	
Daily insulin dose, IU/day	–	–	–	−0.74 ± 0.56	−0.75 ± 0.55	3.41 ± 0.54
Mean (95% CI) vs placebo	–	–		−4.15 (−5.69, −2.61)***	−4.16 (−5.67, −2.64)***	

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; SBP, systolic blood pressure.

All values presented as adjusted mean (adjusted by baseline HbA1c, renal function and pre-treatment insulin therapy) ± SE, unless stated otherwise.
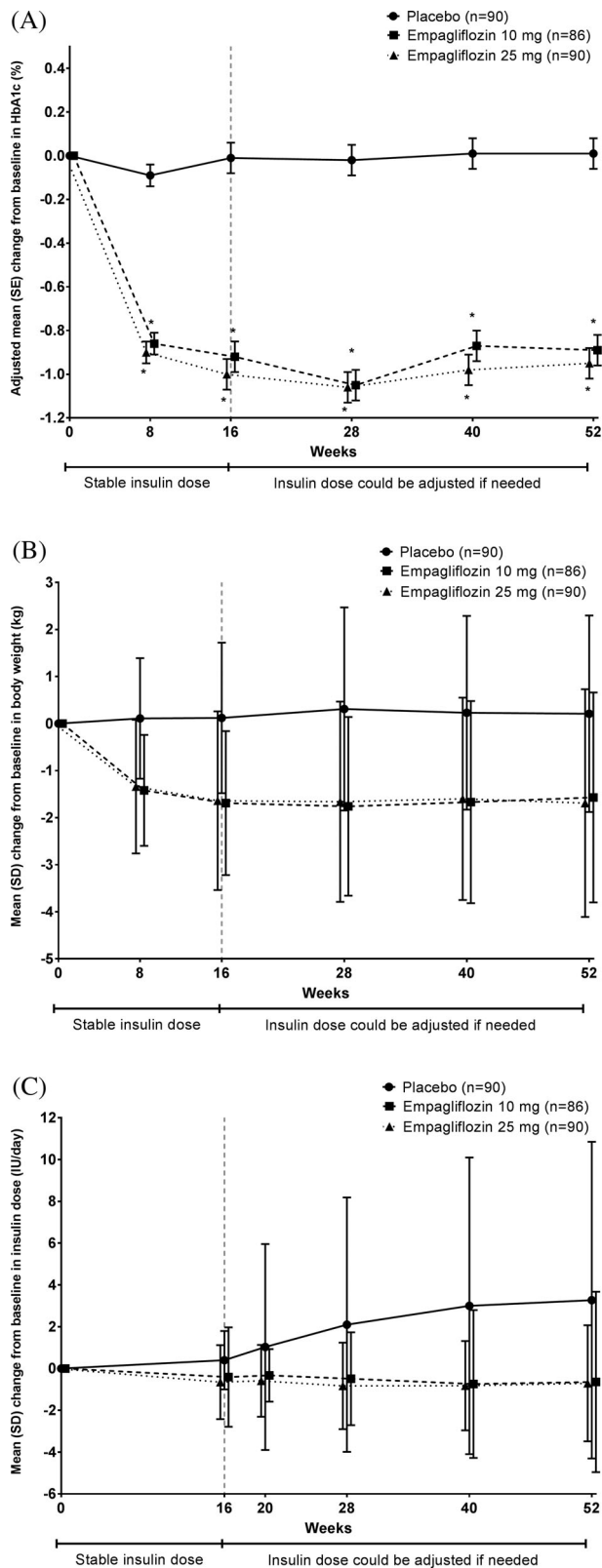
*$P < 0.05$

**$P < 0.01$

***$P < 0.001$.

FIGURE 2 Change from baseline in efficacy variables over 52 weeks. **A,** Adjusted mean (SE) glycated haemoglobin (HbA1c), **B,** mean (SD) bodyweight and **C,** mean (SD) total daily insulin dose. *P<0.0001 vs placebo

respectively (Table 3). All events were mild or moderate in severity; none was serious or required treatment discontinuation.

Some changes in laboratory variables were observed during the 52-week treatment period (Table S4). In both empagliflozin groups, mean haematocrit and total ketone body levels were slightly increased, while no change was observed with placebo. Slightly larger increases in serum creatinine and decreases in eGFR were observed with empagliflozin compared with placebo. In all treatment groups, slight increases in total cholesterol, HDL cholesterol and LDL cholesterol levels were observed, while a slight decrease in triglycerides was also seen. Finally, slight increases in vitamin D, parathyroid hormone levels, and the urine N-terminal telopeptide to creatinine ratio were also observed in all treatment groups.

4 | DISCUSSION

In this randomized, double-blind, multicentre, parallel-group study, once-daily add-on empagliflozin 10 mg or 25 mg led to significant and clinically meaningful improvements in HbA1c compared with placebo at 16 weeks in Japanese participants with T2D insufficiently controlled with insulin, along with modest decreases in FPG and body weight. Furthermore, after 16 weeks of treatment, 3.5% of participants receiving empagliflozin 10 mg and 17.8% of those receiving empagliflozin 25 mg reached the goal HbA1c level of <7%, but only 1.1% of participants receiving placebo had met the target. Empagliflozin resulted in a reduction of HbA1c ≥0.5% in 80.2% and 76.7% of participants receiving 10 mg and 25 mg, respectively, but in only 23.3% of participants receiving placebo. All of these improvements were maintained for 52 weeks.

Treatment with empagliflozin 10 mg or 25 mg for 16 weeks led to adjusted mean placebo-corrected reductions from baseline in HbA1c of −0.92% and −1.00%. The add-on effect of empagliflozin has been previously investigated in Caucasian patients with T2D receiving insulin; in those studies, the placebo-corrected decreases from baseline in HbA1c at 18 weeks with add-on empagliflozin 10 mg and 25 mg were −0.6% and −0.7%, respectively, in patients receiving basal insulin[19] or −0.44% and −0.52%, respectively, in patients receiving multiple daily doses of insulin.[18] The results of the present study are also comparable with the two studies in Caucasian patients in terms of the reductions in FPG and body weight, suggesting that adding empagliflozin to insulin is as efficacious in Japanese people as it is in Caucasian people.[18,19]

While some treatment-by-subgroup interactions were observed for the change in HbA1c at 16 weeks (P=0.0195 for baseline HbA1c, P=0.0196 for BMI and P=0.0324 for renal function), the treatment effects of empagliflozin 10 mg or 25 mg versus placebo were generally consistent across subgroups. Both the baseline HbA1c and renal function subgroup interactions are in-line with previous findings from studies of empagliflozin,[19,23] which have shown a more pronounced effect in patients with higher baseline HbA1c and those with normal renal function. By contrast, the subgroup interaction observed for

TABLE 3 Summary of adverse events over the 52-week treatment period

AEs, n (%)	Empagliflozin		Placebo
	10 mg (n=86)	25 mg (n=90)	(n=90)
Any AE	69 (80.2)	70 (77.8)	69 (76.7)
Drug-related AEs[a]	37 (43.0)	39 (43.3)	23 (25.6)
AEs leading to discontinuation	5 (5.8)	3 (3.3)	4 (4.4)
Serious AEs	9 (10.5)	8 (8.9)	6 (6.7)
Deaths	1 (1.2)	0	0
Patients with AEs of special interest[b]	0	0	0
AEs with frequency ≥5% in any group			
Nasopharyngitis	30 (34.9)	24 (26.7)	28 (31.1)
Hypoglycaemia	24 (27.9)	25 (27.8)	19 (21.1)
Pollakiuria	9 (10.5)	9 (10.0)	2 (2.2)
Back pain	5 (5.8)	6 (6.7)	3 (3.3)
Asymptomatic bacteriuria	3 (3.5)	5 (5.6)	8 (8.9)
Eczema	5 (5.8)	2 (2.2)	5 (5.6)
Blood ketone body increased	5 (5.8)	2 (2.2)	1 (1.1)
Urinary tract infection	5 (5.8)	6 (6.7)	8 (8.9)
Men	2 (3.2)	2 (3.3)	3 (4.3)
Women	3 (13.0)	4 (13.8)	5 (23.8)
Genital tract infection	3 (3.5)	3 (3.3)	0
Men	0	1 (1.6)	0
Women	3 (13.0)	2 (6.9)	0
Volume depletion	2 (2.3)	1 (1.1)	1 (1.1)

Abbreviation: AE, adverse event.
[a]Drug-related was defined by the investigator. [b]Special interest AEs were metabolic acidosis, ketoacidosis, diabetic ketoacidosis, hepatic injury, decrease renal function and events involving lower limb amputation.

BMI was not expected but is probably attributable to the unexpectedly marked effect on HbA1c at 16 weeks observed with placebo in participants in the lowest BMI group (<25 kg/m^2). Given the small number of participants per treatment arm, this is probably a chance finding. No interaction between subgroups of participants receiving different baseline insulin therapies was observed.

Body weight gain is a typical issue associated with insulin.[6-8] The results of this study suggest that adding empagliflozin to insulin treatment mitigates this issue, as body weight and waist circumference were both significantly decreased with empagliflozin 10 mg or 25 mg after 16 weeks of treatment and these improvements were maintained until the end of the study.

No unexpected safety concerns were raised in this study and empagliflozin was well tolerated when used as add-on to insulin. The proportion of participants with confirmed hypoglycaemia was somewhat higher with empagliflozin than with placebo; however, no severe hypoglycaemic events requiring assistance were reported. Participants with T2D are at an increased risk of UTIs and genital infections,[24,25] and some studies have indicated that SGLT2 inhibitors may be

associated with events consistent with UTIs, genital infections and volume depletion.[26-28] In this trial, the frequency of events consistent with UTIs did not differ between empagliflozin and placebo, whereas the proportion of participants with events consistent with genital tract infections was higher with empagliflozin than placebo. Finally, there may be an increased risk of developing diabetic or euglycaemic ketoacidosis with SGLT2 inhibitor treatment,[29,30] as SGLT2 inhibitors increase glucagon levels and ketone body formation, while clearing glucose via renal excretion.[30] Furthermore, as insulin suppresses lipolysis, it is thought that lowering the dose of insulin (as seen in the present study) when adding treatment with an SGLT2 inhibitor could increase the production of ketone bodies, which also increases the risk of diabetic ketoacidosis.[31] However, while a slight increase in total ketone bodies was observed in participants receiving empagliflozin 10 mg or 25 mg, no diabetic ketoacidosis was reported.

There have been several studies of other SGLT2 inhibitors (canagliflozin, tofogliflozin, dapagliflozin and ipragliflozin) in combination with insulin conducted in Japanese people with T2D.[32-37] These studies have shown that adding an SGLT2 inhibitor to an insulin regimen provides clinically meaningful improvements in glycaemic control and body weight, but could be associated with a slightly increased risk of hypoglycaemia and increased frequency of genital tract infections.[32-37] Taken together with the results from the present study, these studies highlight that adding an SGLT2 inhibitor (eg, empagliflozin) to insulin is an effective and safe treatment option for Japanese patients.

Prior evidence has demonstrated that insulin doses typically need to be increased to maintain glycaemic control over time.[38,39] In the present study, two distinct treatment phases were employed: a 16-week period during which the insulin dose was fixed, to directly assess the drug effect, followed by a 36-week period in which the insulin dose could be adjusted at the discretion of the investigator. During the second period, few insulin adjustments were made suggesting that combining empagliflozin with insulin allowed for long-term glycaemic control without having to increase insulin doses. These results are consistent with the two randomized controlled trials of add-on empagliflozin conducted in Caucasian patients,[18,19] both of which also employed different insulin dosing periods.

The present study has some limitations. Firstly, there was no treat-to-target strategy for insulin dosing in the second part of the double-blind treatment period, and the lack of this may mean that insulin doses were not optimized by investigators; however, while the results of this study cannot be generalized to patients who are undergoing a strict treat-to-target insulin regimen, this approach reflects routine clinical practice, where insulin algorithms are not strictly executed. Secondly, other OADs were washed out before the initial treatment period; caution is necessary when using empagliflozin in combination with insulin in patients who are also receiving an OAD. Another limitation was the relatively short follow-up period; a longer follow-up would have helped to assess whether increases in the insulin dose would be necessary to maintain glycaemic control.

In conclusion, the addition of empagliflozin 10 mg or 25 mg to insulin treatment was associated with clinically meaningful reductions

in HbA1c at 16 weeks and was generally well tolerated in Japanese patients with insufficiently controlled T2D.

CONFLICT OF INTEREST

H.S. has received consulting fees and/or speakers' bureau fees from Nippon Boehringer Ingelheim Co., Ltd., Novo Nordisk Pharma Ltd. and MSD K.K. and has received research support from Takeda Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Taisho Pharma Co., Ltd. and Novartis Pharma K.K. N.T. has received speakers' bureau fees from Nippon Boehringer Ingelheim Co., Ltd. and Takeda Pharmaceutical Co., Ltd. T.K., K.S. and Y.T. are employees of Nippon Boehringer Ingelheim Co., Ltd. E.P. and J.L. are employees of Boehringer Ingelheim Pharma GmbH & Co. KG.

AUTHOR CONTRIBUTIONS

H.S. and N.T. supervised the study and contributed to the design and protocol of the study. K.S., Y.T. and J.L. contributed to development of the protocol and the design, and prepared the data. E.P. contributed to statistical analyses. T.K. contributed to preparation of the manuscript. All authors had complete access to all the study data (including patient-level data), contributed to manuscript preparation, the interpretation and discussion of the data, and have approved the final draft.

DATA AVAILABILITY

To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors access to all relevant material, including participant-level clinical study data, and relevant material as needed by them to fulfill their role and obligations as authors under the International Committee of Medical Journal Editors criteria.

Furthermore, clinical study documents (eg, study report, study protocol, statistical analysis plan) and participant clinical study data are available to be shared after publication of the primary manuscript in a peer-reviewed journal and if regulatory activities are complete and other criteria met per the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data: https://trials.boehringer-ingelheim.com/transparency_policy.html. Prior to providing access, documents will be examined, and, if necessary, redacted and the data will be de-identified, to protect the personal data of study participants and personnel, and to respect the boundaries of the informed consent of the study participants. Clinical Study Reports and Related Clinical Documents can be requested via this link: https://trials.boehringer-ingelheim.com/trial_results/clinical_submission_documents.html.

All such requests will be governed by a Document Sharing Agreement. Bona fide, qualified scientific and medical researchers may request access to de-identified, analyzable participant clinical study data with corresponding documentation describing the structure and content of the datasets. Upon approval, and governed by a Data Sharing Agreement, data are shared in a secured data-access system for a limited period of 1 year, which may be extended upon request. Researchers should use https://vivli.org/ to request access to study data.

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SUPPORTING INFORMATION

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