Received: 27 February 2018 | Revised: 27 April 2018 | Accepted: 5 May 2018

DOI: 10.1111/dom.13351

WILEY

ORIGINAL ARTICLE

Empagliflozin as adjunct to insulin in Japanese participants with type 1 diabetes: Results of a 4-week, double-blind, randomized, placebo-controlled phase 2 trial

Akira Shimada MD[1] | Toshiaki Hanafusa MD[2] | Atsutaka Yasui PhD[3] | Ganghyuck Lee MSc[3] | Yusuke Taneda MSc[3] | Akiko Sarashina MSc[4] | Kosuke Shiki MSc[3] | Jyothis George MD[5] | Nima Soleymanlou PhD[6*] | Jan Marquard MD[5*]

[1]Department of Endocrinology and Diabetes, Saitama Medical University, Saitama, Japan

[2]Sakai City Medical Center, Osaka, Japan

[3]Nippon Boehringer Ingelheim Co., Ltd., Tokyo, Japan

[4]Nippon Boehringer Ingelheim Co., Ltd., Hyogo, Japan

[5]Boehringer Ingelheim International GmbH, Ingelheim, Germany

[6]Boehringer Ingelheim Canada, Burlington, Canada

Correspondence
Nima Soleymanlou, PhD, Boehringer Ingelheim Canada, 5180 South Service Road, Burlington, ON L7L 5H4, Canada.
Email: nima.soleymanlou@boehringer-ingelheim.com; Jan Marquard, MD, Boehringer Ingelheim International GmbH, Binger Str. 173, 55216 Ingelheim am Rhein, Germany.
Email: jan.marquard@boehringer-ingelheim.com

Funding information
Boehringer Ingelheim Eli Lilly and Company

Aims: This phase 2, double-blind, randomized, placebo-controlled trial (ClinicalTrials.gov NCT02702011) with 4 sites in Japan investigated the pharmacodynamics (PD), pharmacokinetics (PK) and safety profile of empagliflozin in Japanese participants with type 1 diabetes mellitus (T1DM) as adjunctive therapy to insulin.

Materials and methods: Participants using multiple daily injections of insulin for ≥12 months, with HbA1c of 7.5%-10.0%, entered a 2-week, open-label, placebo run-in period, followed by a 4-week, double-blind period during which participants were randomized 1:1:1:1 to receive empagliflozin 2.5 mg (n = 13), empagliflozin 10 mg (n = 12), empagliflozin 25 mg (n = 12) or placebo (n = 11). The primary objective was to assess the effect of empagliflozin vs placebo on urinary glucose excretion (UGE) after 7 days of treatment.

Results: PD: Empagliflozin resulted in a dose-dependent significant increase in 24-hour UGE compared with placebo (UGE placebo-corrected mean [95% confidence interval] change from baseline: 2.5 mg, 65.10 [43.29, 86.90] g/24 h; 10 mg, 81.19 [58.80, 103.58] g/24 h; 25 mg, 98.11 [75.91, 120.31] g/24 h). After 4 weeks of treatment, UGE increase was associated with improved glycaemic control, reduced body weight and decreased insulin needs. Empagliflozin treatment also resulted in dose-dependent increases in serum ketone bodies and free fatty acids. PK: Plasma empagliflozin levels increased in a dose-dependent manner and peaked at 1.5 hours. In this short study, empagliflozin was well tolerated, with no increase in rate of hypoglycaemia and no diabetic ketoacidosis events reported.

Conclusions: Based on this short-duration phase 2 study, the PK/PD profile of empagliflozin in Japanese participants with T1DM is comparable to that of non-Japanese participants.

KEYWORDS

empagliflozin, pharmacodynamics, pharmacokinetics, randomized trial, SGLT2 inhibitor, type 1 diabetes

1 | INTRODUCTION

Life-long exogenous insulin replacement is the mainstay of therapy for patients with type 1 diabetes mellitus (T1DM); however, it still has several shortcomings. New adjunct treatment options for T1DM

*Contributed equally as senior authors

should enable patients to attain glycaemic targets (glycated haemoglobin [HbA1c] ≤ 7.0%),[1,2] to decrease the risk of hypoglycaemia,[3] to prevent weight gain[4] and to reduce glucose variability.[5]

Several antihyperglycaemic agents (ie, pramlintide, metformin and liraglutide) with low risk of hypoglycaemia and weight gain in participants with type 2 diabetes mellitus (T2DM) improve glycaemic control and/or decrease insulin dose and body weight as adjuncts to insulin therapy in participants with T1DM.[4,6–10] However, these medications have limitations in T1DM, such as increased risk of undesirable effects (ie, nausea, vomiting, anorexia and hypoglycemia),[6] absence of sustained effect on glycaemic control,[8,9] and increased rates of symptomatic hypoglycaemia, hyperglycaemic episodes with ketosis and diabetic ketoacidosis (DKA) when compared with placebo.[10] Therefore, an adjunct to insulin treatment with a more favourable benefit/risk profile would be highly desirable in patients with T1DM.

Selective sodium-glucose co-transporter 2 (SGLT2) inhibitors have a unique insulin-independent mode of action; these agents decrease renal glucose reabsorption, which leads to urinary glucose excretion (UGE), and, consequently, decreased blood glucose levels. In participants with T2DM, SGLT2 inhibitors improve glycaemic control, along with a decrease in weight and blood pressure, without increasing the risk of hypoglycaemia.[4] Sotagliflozin, canagliflozin and dapagliflozin as adjunct to insulin therapy in T1DM resulted in a higher proportion of study participants achieving glycaemic target compared with placebo, and reduced glycaemic variability, rate of hypoglycaemia, body weight and insulin dose.[11–14] Moreover, adjunct therapy with SGLT2 inhibitors may offer benefits for T1DM management in paediatric populations in the future after the benefits and risks in adults are clearly established.[15] Indeed, based on the mode of action of SGLT2 inhibitors, it is important to adequately characterize potential risks associated with these agents in terms of ketoacidosis in T1DM, particularly as suboptimal insulin usage may contribute to this acute T1DM complication. Given that the benefit/risk profiles of these agents are currently under investigation, no combination therapy with SGLT2 inhibitor is approved for use in T1DM.

Empagliflozin is a highly selective SGLT2 inhibitor that improves glycaemic control in T2DM; empagliflozin was also shown in the EMPA-REG OUTCOME trial to reduce the risk of cardiovascular death by 38% and to reduce incident or worsening nephropathy by 39% in participants with T2DM with established cardiovascular disease.[16–19] In the phase 2 EASE-1 trial in participants with T1DM, empagliflozin as adjunct to insulin improved glycaemic control, decreased glucose variability, body weight and insulin dose, and increased time spent in the glucose target range, without increasing the rate of hypoglycaemia or DKA compared with placebo.[20,21] However, given that EASE-1 was a small, short-duration study of Caucasian participants, larger studies, as well as studies in participants with different demographics (eg, Asian participants whose body mass index [BMI], body composition and diet are different), are required to investigate the potential therapeutic benefits of empagliflozin in patients with T1DM.

In this 4-week, double-blind, randomized, placebo-controlled trial, we aimed to assess the pharmacodynamics (PD) (effect of empagliflozin on UGE compared with placebo) of once-daily empagliflozin 2.5, 10 and 25 mg as adjunct therapy to insulin treatment in Japanese participants with T1DM. Additionally, we aimed to evaluate pharmacokinetic (PK) parameters, HbA1c, fasting plasma glucose (FPG), body weight, glucose exposure and variability assessed by continuous glucose monitoring (CGM), ketogenesis markers, insulin doses, carbohydrate intake, blood pressure, and overall empagliflozin safety and tolerability in these participants. We hypothesized that empagliflozin would exhibit PD, PK, and short-term efficacy and safety profiles in Japanese participants with T1DM consistent with those of non-Japanese participants as previously reported.[20,21]

2 | MATERIALS AND METHODS

2.1 | Study details

This was a phase 2, double-blind, randomized, placebo-controlled, parallel-group trial of 3 doses of empagliflozin taken once daily for 4 weeks as adjunct to insulin therapy in Japanese participants with T1DM (ClinicalTrials.gov [NCT02702011]). The trial was conducted at 4 study sites in Japan (March 21 to October 3, 2016). The protocol was approved by the institutional review board at each site and was conducted in compliance with the Japanese Ethical Guideline for Clinical Studies and the Declaration of Helsinki. All participants provided written informed consent prior to participation in the trial.

2.2 | Study population

Eligible participants included male and female adults (≥20 to ≤65 years), with T1DM who were treated for ≥12 months with multiple daily injections of insulin prior to study initiation (≥1 basal and ≥3 bolus injections, with total daily insulin dose needs of ≥0.3 to ≤1.5 U/kg), and with HbA1c of ≥7.5% to ≤10.0% (National Glycohaemoglobin Standardization Programme % units; mmol/mol = [10.93 × %] – 23.5), with a fasting C-peptide value of <0.6 ng/mL, with BMI of ≥18.5 to ≤35.0 kg/m^2, and with an estimated glomerular filtration rate (eGFR) of ≥60 to ≤150 mL/min/1.73 m^2, who could manage blood glucose monitoring, carbohydrate counting and insulin dose adjustment.

Participants were excluded if they had a history of T2DM, maturity onset diabetes of the young, pancreatic surgery or chronic pancreatitis; acute coronary syndrome, stroke, transient ischemic attack or indication of liver disease; severe hypoglycaemia, treatment with any antihyperglycaemic drug except insulin, anti-obesity drugs or other treatment leading to unstable body weight within 3 months before screening; DKA within 3 months prior to screening or occurring between screening and randomization.

2.3 | Study design

2.3.1 | Open-label run-in period

Participants who met inclusion criteria after screening entered a 2-week, open-label, placebo run-in period designed to stabilize insulin therapy before randomization and to assess therapy adherence by mimicking the dosing regimen in the double-blind treatment period (Figure S1).

2.3.2 | Double-blind treatment period

Participants who met inclusion criteria after the run-in period were randomized 1:1:1:1 to receive empagliflozin 2.5, 10 or 25 mg, or placebo (Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany) for 4 weeks. Randomization followed a permuted block design and was used by a pseudo-random number generator and supplied seed number. All study drugs were taken orally once daily in the morning. Participants, investigators and study personnel remained blinded to the randomized treatment assignments until database lock. Randomization codes were provided to bioanalysts to exclude placebo-treated participants from PK analyses. At randomization and upon initiation of trial drug administration, participants with screening HbA1c of ≥7.5% and <8% received a 10% reduction in total daily insulin dose, whereas participants with screening HbA1c of ≥8% received an adjusted insulin dose based on their needs as assessed by frequent self-monitoring of blood glucose and close follow-up to avoid hypoglycaemia and hyperglycaemia. Initial and subsequent insulin dosing adjustments (both basal and bolus insulin) were at the investigators' discretion. Strategies were set for the prevention of DKA events; these included reminders to participants concerning the signs and symptoms of DKA, instructions to perform self-measurement of blood ketone if symptoms occurred, and instructions not to reduce the insulin dose below investigator recommendations (Appendix S1). Investigators were also made aware of the potential risk of euglycaemic DKA.

2.4 | Exploratory outcome measures

2.4.1 | Pharmacodynamics

The primary endpoint was change from baseline in 24-hour UGE on Day 7 of treatment. All urine voided during 24 hours was collected at baseline and on Days 1, 7 and 28.

2.4.2 | Pharmacokinetics

Blood and urine samples were taken for PK on Days 1 and 28. Empagliflozin concentrations in plasma and urine samples were determined by a validated liquid chromatography-tandem mass spectrometry assay (Bioanalytical Systems, Inc., West Lafayette, Indiana). Steady state attainment was explored using trough concentrations on Days 2, 7, 14, 21, 27, 28 and 29. Half-life at steady state ($t_{1/2,ss}$), area under the concentration-time curve (AUC) and maximal measured concentration of empagliflozin in plasma (C_{max}) were calculated.

2.4.3 | Efficacy

Blood samples, measured at a central laboratory, were taken for HbA1c on Days 1 and 28, and for FPG on Days −1, 1, 2, 7, 8, 14, 21, 28 and 29. Body weight was measured on Day 28. Glucose exposure, defined as mean daily AUC (MDAUC) of glucose, and glucose variability, defined as interquartile range (IQR) of glucose and percentage of time spent in glucose ranges ≤70 mg/dL, >70 to ≤180 mg/dL (target range) and >180 mg/dL, were determined by CGM (iPro2-Professional Continuous Glucose Monitoring Device, Medtronic, Tolochenaz, Switzerland) from Days −6 to 28. Blood samples were taken for β-hydroxybutyrate (BHB), acetoacetic acid, total ketone bodies and free fatty acids (FFA) on Days −1, 1, 7 and 8 (measured by SRL Inc., Shinjuku-ku, Tokyo, Japan) and changes from baseline in AUC from 0 to 24 hours ($AUC_{0\text{-}24h}$) on Day 7 were calculated. BHB levels on Day 28 were measured as part of laboratory safety parameters. Changes from baseline in systolic blood pressure (SBP), diastolic blood pressure (DBP) and eGFR on Days 7 and 28 were determined. Weekly recorded total, basal and bolus insulin doses and average carbohydrate intake over 4 weeks were identified. Participants recorded their insulin dose, carbohydrate intake, blood glucose and blood ketones in a diary throughout the treatment and follow-up periods. Participants were provided with material for self-monitoring blood glucose and self-monitoring blood ketone (FreeStyle Precision Neo, Abbott, Tokyo, Japan) from initiation of the run-in period until the end of follow-up.

2.4.4 | Safety

The type and frequency of adverse events (AEs), coded using the Medical Dictionary for Regulatory Activities, version 19.1, of serious AEs (SAEs), of AEs of special interest (AESIs), of hypoglycaemic AEs and of clinical laboratory parameters were assessed during 4 weeks of treatment. Hypoglycaemic AEs were based on blood glucose (scheduled blood glucose test and/or CGM). AESIs included genital infection, urinary tract infection, sepsis, asymptomatic bacteriuria, bone fracture, malignancies and volume depletion. Severe hypoglycaemia and DKA events were adjudicated by independent external committees. Blood and urine samples were taken for laboratory safety parameters on Days 1, 7 and 28, and were measured centrally.

2.5 | Statistical analysis

A total of 48 participants (12 in each group) was generally considered sufficient for the evaluation of PD, PK, exploratory efficacy, safety and tolerability of multiple doses. This sample size would result in an overall power of >99% to test the primary endpoint (change from baseline in 24-hour UGE on Day 7) in the empagliflozin 10 and 25 mg groups compared with placebo, assuming a type I error of 5% (2-sided) and differences in mean UGE of 106.4 and 104.8 g/24 h between empagliflozin 10 mg and empagliflozin 25 mg, respectively, and placebo, with standard deviation of 27.3 g/24 h.[20] An analysis of covariance (ANCOVA) model was used to compare the primary endpoint between empagliflozin groups and placebo.

The primary analysis included all randomized participants who were treated with ≥1 dose of study drug and for whom there was 24-h UGE at baseline and on Day 1 or Day 7 (full analysis set [FAS]) with last observation carried forward imputation. PK analysis included participants who were treated with ≥1 dose of study drug (treated set) and with ≥1 PK observation and no relevant protocol violations. Missing and undetectable concentration data were ignored and were not replaced. Descriptive statistics of concentrations at specific timepoints were calculated only when ≥2/3 of the individuals had concentrations within the validated range. PK parameters were calculated using Phoenix WinNonlin (version 6.3, Princeton, New Jersey), applying a non-compartmental method. An ANCOVA model with treatment

as a fixed effect and baseline as a linear covariate was fitted to the efficacy endpoints on Days 1, 7 and 28, and was used to determine the treatment effect of different doses of empagliflozin compared with placebo. Safety was analysed in the treated set and is presented using descriptive statistics. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

3 | RESULTS

3.1 | Participant disposition

Among 71 enrolled participants, 48 were randomized and treated with ≥1 dose of placebo (n = 11), empagliflozin 2.5 mg (n = 13), empagliflozin 10 mg (n = 12) or empagliflozin 25 mg (n = 12) (Figure S2). The most frequent reason for discontinuation before randomization was failure to meet HbA1c inclusion criterion (15 participants). A total of 47 participants (97.9%) completed the 4-week trial.

3.2 | Demographic and baseline clinical characteristics

Baseline characteristics were similar across treatment groups, with the exception of a higher percentage of male participants, lower baseline mean HbA1c and longer time since T1DM diagnosis in the empagliflozin 25 mg group and a higher UGE in the empagliflozin 10 mg group (Table 1).

3.3 | Pharmacodynamics

Concerning urinary glucose excretion, all empagliflozin doses significantly increased 24-hour UGE compared with placebo in a dose-dependent manner (Figure 1A). The placebo-corrected adjusted mean (95% confidence interval [CI]) change from baseline in UGE on Day 7 was greatest in the empagliflozin 25 mg group (2.5 mg: 65.10 [43.29, 86.90] g/24 h, 10 mg: 81.19 [58.80, 103.58] g/24 h, 25 mg: 98.11 [75.91, 120.31] g/24 h).

3.4 | Pharmacokinetics

Empagliflozin was rapidly absorbed after single and multiple oral doses, reaching peak levels approximately 1.5 hours after dosing (Figure S3). Thereafter, plasma concentrations showed a decline, with a rapid distribution phase and a slower elimination phase. Steady state was reached within 7 days (data not shown). Mean elimination $t_{1/2ss}$ ranged from 12.0 to 19.3 hours. Empagliflozin exposure (AUC and C_{max}) increased proportionally with dose, after a single dose and at steady state (data not shown).

TABLE 1 Participant demographics and baseline characteristics

Variables	Placebo (n = 11)	Empa 2.5 mg (n = 13)	Empa 10 mg (n = 12)	Empa 25 mg (n = 12)
Male	5 (45.5)	5 (38.5)	4 (33.3)	8 (66.7)
Age, years	43.9 (11.7)	44.2 (12.6)	44.5 (11.8)	46.6 (10.8)
Time since diagnosis of T1DM				
Mean years	14.8 (10.0)	16.8 (11.2)	14.3 (8.4)	20.8 (13.5)
>1 to 5 years	1 (9.1)	1 (7.7)	0	0
>5 to 10 years	3 (27.3)	3 (3.1)	4 (33.3)	2 (16.7)
>10 years	7 (63.6)	9 (69.2)	8 (66.7)	10 (83.3)
Weight, kg	63.6 (7.7)	63.3 (10.5)	59.9 (10.6)	60.5 (10.2)
Body mass index, kg/m^2	23.7 (2.6)	24.4 (3.93)	22.68 (3.27)	22.6 (2.7)
HbA1c, %[a]	8.23 (0.47)	8.02 (0.36)	8.12 (0.37)	7.89 (0.91)
FPG, mg/dL[b]	194.0 (55.8)	189.1 (72.4)	187.8 (110.9)	147.8 (79.2)
MDG, mg/dL[b]	187.8 (23.4)	209.8 (56.4)	209.3 (52.9)	196.0 (54.7)
eGFR, mL/min/1.73 m^2 [c]	95.1 (16.5)	88.0 (15.9)	87.0 (12.9)	88.8 (14.1)
UGE, g/24 h	15.2 (13.3)	16.9 (18.1)	21.1 (18.3)	14.9 (14.5)
SBP, mm Hg	116.5 (18.0)	114.1 (16.9)	110.1 (17.5)	115.8 (18.2)
DBP, mm Hg	72.6 (9.7)	71.9 (11.8)	71.1 (14)	69.8 (13.6)
Daily insulin dose, U/kg				
Basal	0.30 (0.17)	0.30 (0.10)	0.31 (0.09)	0.27 (0.09)
Bolus	0.40 (0.20)	0.43 (0.12)	0.42 (0.22)	0.39 (0.13)
Total	0.71 (0.22)	0.73 (0.17)	0.73 (0.23)	0.66 (0.15)

Abbreviations: DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; Empa, empagliflozin; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; MDG, mean daily glucose; SBP, systolic blood pressure; T1DM, type 1 diabetes mellitus; UGE, urinary glucose excretion. Data are presented as n (%) or mean (standard deviation) in participants who received ≥1 dose of study drug.

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

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

[c] eGFR (mL/min/1.73 m^2) = 194 × [serum creatinine (mg/dL)]$^{-1.094}$ × [age]$^{-0.287}$ × [0.739 if participant was female].[30]

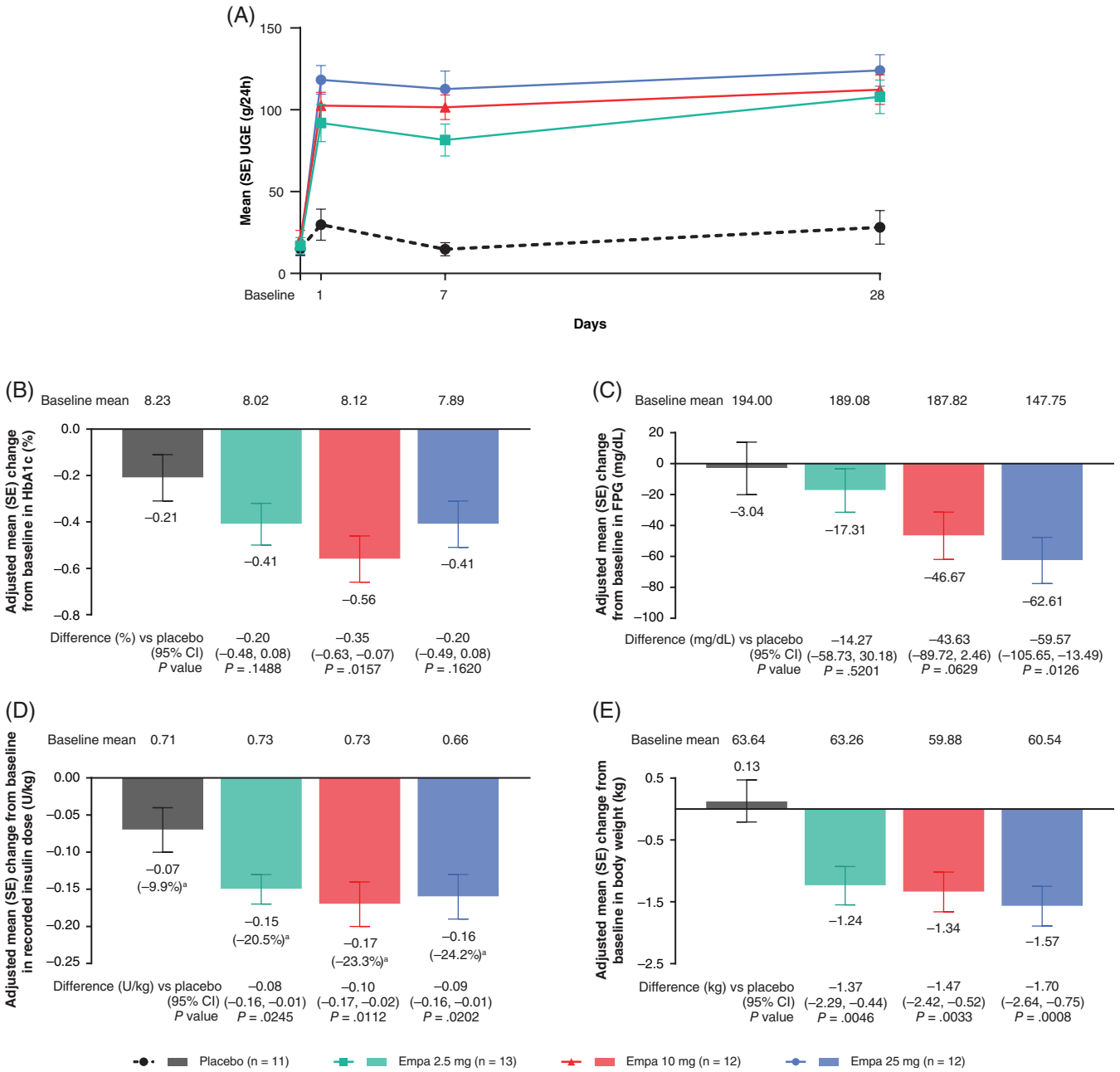

FIGURE 1 Change in UGE and efficacy parameters. A, Mean UGE (±SE) over 28 days. B, Adjusted mean (±SE) change from baseline in HbA1c on Day 28. C, Adjusted mean (±SE) change from baseline in FPG on Day 28. D, Adjusted mean (±SE) change from baseline in recorded insulin dose within Week 4. E, Adjusted mean (±SE) change from baseline in body weight on Day 28. Abbreviations: CI, confidence interval; Empa, empagliflozin; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; h, hours; SE, standard error; UGE, urinary glucose excretion. [a] % of adjusted mean change from baseline

3.5 | Efficacy

3.5.1 | HbA1c

All doses of empagliflozin reduced HbA1c on Day 28 (adjusted mean difference vs placebo: 2.5 mg, −0.20%; 10 mg, −0.35%; 25 mg, −0.20%) (Figure 1B).

3.5.2 | Fasting plasma glucose

Empagliflozin treatment led to dose-dependent reductions from baseline in FPG on Day 28 (adjusted mean difference vs placebo: 2.5 mg, −14.27 mg/dL; 10 mg, −43.63 mg/dL; 25 mg, −59.57 mg/dL) (Figure 1C).

3.5.3 | Insulin requirement and carbohydrate intake

All empagliflozin doses significantly decreased weekly mean recorded insulin dose compared with placebo at Week 4 (adjusted mean difference [reduction from baseline]: 2.5 mg, −0.08 U/kg [−20.5%]; 10 mg, −0.10 U/kg [−23.3%]; 25 mg, −0.09 U/kg [−24.2%]) (Figure 1D and Figure S4A). The reduction was equally attributable to greater decreases in both basal and bolus insulin doses in the empagliflozin groups compared with placebo (Figure S4B–S4E). Empagliflozin treatment was associated with increased carbohydrate intake compared with placebo over 4 weeks of treatment, with the exception of the empagliflozin 10 mg group

at Week 2 when carbohydrate intake returned to baseline level (Figure S5).

3.5.4 | Body weight

Empagliflozin treatment significantly decreased body weight compared with placebo on Day 28 in a dose-dependent manner (adjusted mean difference: 2.5 mg, −1.37 kg; 10 mg, −1.47 kg; 25 mg, −1.70 kg) (Figure 1E).

3.5.5 | Blood pressure

Small reductions from baseline in SBP and DBP were reported in the empagliflozin 10 mg group on Days 7 and 28 (Table S1).

3.5.6 | Continuous glucose monitoring

Within Week 4, empagliflozin 2.5 and 25 mg significantly decreased the mean change from baseline in MDAUC compared with placebo (adjusted mean difference: 2.5 mg, −558 mg/dL*h; 10 mg, −338 mg/dL*h; 25 mg, −514 mg/dL*h) (Figure 2A). Empagliflozin 2.5 and 25 mg significantly reduced the IQR of glucose compared with placebo (adjusted mean difference: 2.5 mg, −23.08 mg/dL; 10 mg, −13.08 mg/dL; 25 mg, −22.09 mg/dL) (Figure 2B). The empagliflozin groups generally had a greater increase from baseline in percentage of time spent in the target glucose range (>70 and ≤180 mg/dL) (adjusted mean difference vs placebo: 11.1%-16.7% or 2.7–4 h/d) and a decrease in time spent in the hyperglycaemic range (>180 mg/dL) compared with placebo (Figure 2C and D).

3.5.7 | Safety and tolerability

All three empagliflozin doses were generally well tolerated. All participants reported at least 1 AE and at least 1 AE of hypoglycaemia, with the exception of one participant in the empagliflozin 2.5 mg group (Table 2). Most AEs were considered drug related, and most drug-related AEs were hypoglycaemia. No deaths, serious AEs, severe AEs or AEs leading to discontinuation of trial drug were reported in any group. One participant in the placebo group experienced hepatic injury, which was not considered drug related. Two participants (1 in the empagliflozin 2.5 mg group and 1 in the empagliflozin 25 mg group) experienced a genital infection (both vulvovaginal candidiasis of mild intensity, with recovery after treatment with 1 antimicrobial for 5 days). There were no other AESIs in any group.

3.5.8 | Ketogenesis markers

Changes from baseline in $AUC_{0\text{-}24\ h}$ of BHB, acetoacetic acid, total ketone bodies and FFA were numerically greater at Day 7 in all empagliflozin groups compared with placebo and were dose dependent (Figure 3A and B and Figure S6A-S6C). Dose-dependent increases in mean BHB were observed also at Day 28 (Figure 3B).

3.5.9 | DKA

No events meeting the criteria for DKA were reported by investigators or adjudicated by the committee.

3.5.10 | Hypoglycaemia

All but one participant experienced hypoglycaemia. There were no reports of hypoglycaemia requiring assistance in any group during the 4-week treatment period (Table 2). Rates of symptomatic hypoglycaemia with plasma glucose ≥54 mg/dL and ≤70 mg/dL and with plasma glucose <54 mg/dL were generally similar among all groups. The rate of asymptomatic hypoglycaemia was numerically higher in the empagliflozin 25 mg group than in other groups.

3.5.11 | Renal function

No investigator reported decreased renal function in any participant during the randomized treatment period (Table 2).

3.5.12 | Laboratory safety parameters

Overall, no significant changes from baseline in laboratory safety parameters were observed in the empagliflozin groups on Day 28 (Table S2).

4 | DISCUSSION

This is the first randomized placebo-controlled trial investigating the PK, PD, efficacy, safety, and tolerability of empagliflozin, as adjunct therapy to insulin in Japanese participants with T1DM. In this trial, empagliflozin increased UGE, improved glycaemic control and reduced body weight and total daily insulin dose without increasing the rate of hypoglycaemia. The PK of empagliflozin in Japanese participants with T1DM was similar to its PK in Japanese participants with T2DM.[22] In addition, this is the first report of empagliflozin treatment in Japanese participants with T1DM that showed dose-dependent increases in markers of ketogenesis, which were below clinically significant ranges.

Similar to the results of a previous trial in non-Japanese participants with T1DM,[20] empagliflozin significantly increased 24-hour UGE during 4 weeks of treatment in Japanese participants. In this study, the increase in UGE was accompanied by decreases in FPG and HbA1c, although the dose effect was less apparent than that for UGE, especially for HbA1c; this is probably explained by the short duration of treatment. By Day 28, the adjusted effect of empagliflozin 2.5 mg on UGE in Japanese participants with T1DM was similar to that of empagliflozin 10 mg in Japanese participants with T2DM (91.0 g/24 h vs 80.9 g/24 h).[22] Based on CGM assessment in this study, empagliflozin decreased glucose exposure and variability, increased time spent with glucose in the target range, and decreased time spent in the hyperglycaemic range; however, again, there was no clear dose effect. Empagliflozin also significantly decreased body weight and insulin dose and increased carbohydrate intake. Because participants adjusted their insulin dose according to their blood glucose levels, the decreased blood glucose as the result of empagliflozin treatment resulted in a decline in dosage amount of insulin. Reductions in basal and bolus insulin doses contributed equally to the reduced total dose, consistent with the DEPICT-1 study in participants with T1DM receiving dapagliflozin as adjunct to insulin.[14] In contrast, in non-Japanese participants with T1DM receiving empagliflozin as adjunct to insulin, the reduced total dose was driven primarily by reduced bolus insulin.[20]

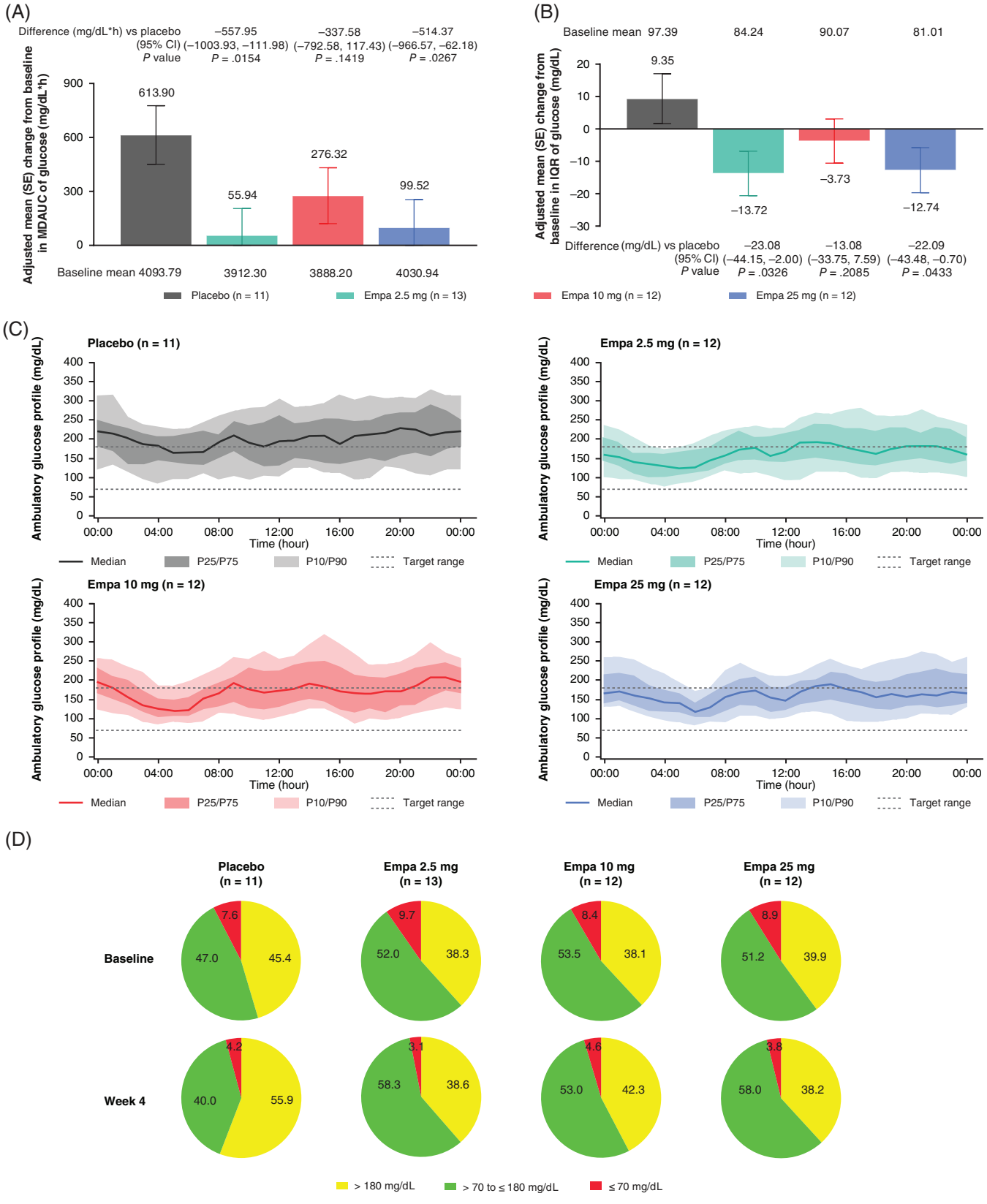

FIGURE 2 Change in glucose exposure, glucose variability and time spent with glucose in target range. A, adjusted mean (±SE) change from baseline in MDAUC of glucose within Week 4. B, Adjusted mean (±SE) change from baseline in the IQR of glucose within Week 4. C, Ambulatory glucose profiles (mg/dL) within Week 4. D, Percentage of time with glucose ≤70 mg/dL, >70 to ≤180 mg/dL, and >180 mg/dL at baseline and at Week 4. Abbreviations: P10, 10th percentile; P25, 25th percentile; P75, 75th percentile; P90, 90th percentile

TABLE 2 Summary of adverse events and rates of hypoglycaemic episodes during the 4-week, double-blind treatment period

Adverse event	Placebo (n = 11)	Empa 2.5 mg (n = 13)	Empa 10 mg (n = 12)	Empa 25 mg (n = 12)
≥1 AE	100 (11)	92.3 (12)	100 (12)	100 (12)
≥1 Severe AE	0 (0)	0 (0)	0 (0)	0 (0)
≥1 Drug-related AE	81.8 (9)	84.6 (11)	100 (12)	91.7 (11)
≥1 AE leading to discontinuation	0 (0)	0 (0)	0 (0)	0 (0)
≥1 Serious AE	0 (0)	0 (0)	0 (0)	0 (0)
Death	0 (0)	0 (0)	0 (0)	0 (0)
Events consistent with UTI	0 (0)	0 (0)	0 (0)	0 (0)
Events consistent with genital infection	0 (0)	7.7 (1)	0 (0)	8.3 (1)
Events consistent with volume depletion	0 (0)	0 (0)	0 (0)	0 (0)
Hepatic injury	9.1 (1)	0 (0)	0 (0)	0 (0)
Decreased renal function	0 (0)	0 (0)	0 (0)	0 (0)
Ketoacidosis	0 (0)	0 (0)	0 (0)	0 (0)
Hypoglycaemia	100 (11)	92.3 (12)	100 (12)	100 (12)
Protocol-defined hypoglycaemia criteria, total number of episodes (number of episodes per 30 days per participant)				
Asymptomatic hypoglycaemia with PG ≤70 mg/dL	54 (5.1)	62 (5.1)	78 (6.7)	140 (12.1)
Symptomatic hypoglycaemia with PG ≥54 and ≤70 mg/dL	37 (3.5)	22 (1.8)	45 (3.9)	12 (1.0)
Symptomatic hypoglycaemia with PG <54 mg/dL	24 (2.3)	18 (1.5)	31 (2.7)	21 (1.8)
Hypoglycaemia requiring assistance	0 (0)	0 (0)	0 (0)	0 (0)

Abbreviations: AE, adverse event; Empa, empagliflozin; PG, plasma glucose; UTI, urinary tract infection. Data are presented as % (n) of participants who received ≥1 dose of study drug, unless otherwise indicated.

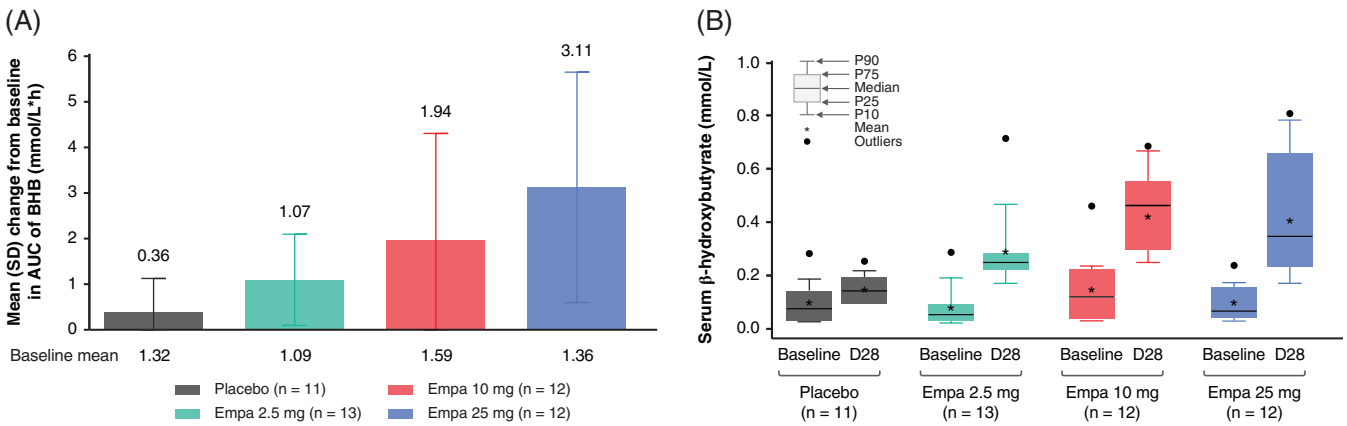

FIGURE 3 Serum β-hydroxybutyrate profile. A, Mean (±SD) change from baseline in $AUC_{0\text{-}24h}$ for serum BHB on Day 7. B, Boxplots for serum β-hydroxybutyrate at baseline and on Day 28 (descriptive statistics). Abbreviations: AUC, area under the concentration-time curve; BHB, β-hydroxybutyrate; D, Day; Empa, empagliflozin; P10, 10th percentile; P25, 25th percentile; P75, 75th percentile; P90, 90th percentile; SD, standard deviation

In previously reported T1DM studies, SGLT2 inhibition was associated with an increase in rates of DKA compared with placebo (sotagliflozin: 21 [3.0%] vs 4 [0.6%] participants; canagliflozin: 100 mg, 5 [4.3%], and 300 mg, 7 [6.0%] vs placebo: 0 participants).[11,12] DKA events (certain/potential) were reported with dapagliflozin (5 mg, 4 [1%]/16 [6%] and 10 mg, 5 [2%]/19 [6%] participants), which represented an increased risk of DKA compared with placebo (3 [1%]/6 [2%] participants) after 24 weeks of treatment.[14]

No DKA events were reported in the current study. Empagliflozin increased levels of serum ketone bodies in Japanese participants with T1DM in this study, as was previously observed in non-Japanese[23] and Japanese[24] participants with T2DM receiving empagliflozin. Mean serum BHB levels after 4 weeks of empagliflozin treatment were generally <0.5 mmol/L, with the highest individual BHB level at approximately 0.8 mmol/L, below the levels of total ketone bodies seen with physiological ketosis, such as prolonged fasting or exercise (1-2 mmol/L),[25] and well below levels seen in DKA (>3 mmol/L).[26] Importantly, special attention was paid to prevention of DKA during the study, including adoption of measures such as avoiding marked reduction in insulin dose.

Our findings from this short-term trial indicate that empagliflozin is generally well tolerated in Japanese participants with T1DM, similar to participants from other countries.[20,27] Consistent with empagliflozin's insulin-independent mechanism of action, the risk of hypoglycaemia was not increased. No decreased renal function and no events consistent with volume depletion were reported. We observed two cases of genital infection, consistent with genitourinary infection rates observed previously in Caucasian participants with T1DM[20] and consistent with the established association of these infections with SGLT2 inhibitor usage in participants with T2DM.[28]

This study has several strengths. First, it is a double-blind, randomized, placebo-controlled trial evaluating the PD/PK effects of three dose levels of empagliflozin. Second, we used the same empagliflozin doses used in previous trials in non-Japanese participants,[20,21,27] allowing us to compare the PD, PK, efficacy and safety of empagliflozin among populations. Third, by using CGM, we were able to examine glucose exposure and variability, as well as time spent in the target glucose range in a blinded, unbiased fashion. This study does, however, have some limitations, including the small number of participants and its short duration, thus preventing conclusions concerning the long-term safety and efficacy of empagliflozin in Japanese participants with T1DM, which will need to be evaluated as part of phase 3 trials. Further, blood glucose readings by CGM are less accurate in the hypoglycaemic range, and measurements taken from interstitial fluid do not necessarily match the actual glucose concentrations in capillary blood.[29]

In conclusion, in this short-term efficacy and safety study, administration of empagliflozin for 4 weeks in Japanese participants with T1DM, as adjunct to insulin therapy, increased UGE, improved glycaemic control and reduced total daily insulin needs and body weight. All three doses of empagliflozin were well tolerated, without increased risk of hypoglycaemia or DKA events. In Japanese participants with T1DM, the PK of empagliflozin was similar to that previously reported for participants with T2DM. The safety and efficacy of empagliflozin as adjunct to insulin therapy in T1DM will be further clarified when data from two large, international, phase 3 trials in non-Japanese participants with T1DM (EASE-2, NCT02414958 and EASE-3, NCT02580591) are available.

ACKNOWLEDGMENTS

The authors would like to thank all study investigators and participants. The authors would also like to thank Yuto Mizuguchi, Junichi Hamada and Kazuki Koiwai for advice on acquisition and interpretation of study data (J. H. and K. K. are former employees of Nippon Boehringer Ingelheim Co. Ltd.). Medical writing assistance was provided by Rebecca Lew, PhD, CMPP and Thao Le, MD, PhD of ProScribe – Envision Pharma Group, which was funded by Nippon Boehringer Ingelheim Co. Ltd. ProScribe's services complied with international guidelines for Good Publication Practice (GPP3).

CONFLICT OF INTEREST

Y. Taneda, A. Sarashina, G. Lee, K. Shiki, A. Yasui, J. George, N. Soleymanlou, and J. Marquard are employees of Boehringer Ingelheim Co. Ltd. T. Hanafusa has received honoraria from Novo Nordisk Pharma for lectures. A. Shimada has received honoraria from Novo Nordisk Pharma, Sanofi, Eli Lilly and Company, and Nippon Boehringer Ingelheim Co. Ltd for lectures.

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. Taneda, A. Sarashina, G. Lee, N. Soleymanlou, and J. Marquard were involved in the study design and data analyses. A. Shimada was the coordinating investigator in the study. G. Lee conducted the statistical analysis. A. Sarashina conducted the PK analysis.

REFERENCES

1. American Diabetes Association. Standards of medical care in diabetes 2017. https://professional.diabetes.org/sites/professional.diabetes.org/files/media/dc_40_s1_final.pdf. Accessed October 12, 2017.
2. Home P, Haddad J, Latif ZA, et al. Comparison of national/regional diabetes guidelines for the management of blood glucose control in non-Western countries. *Diabetes Ther*. 2013;4:91-102.
3. Gubitosi-Klug RA, Braffett BH, White NH, et al. Risk of severe hypoglycemia in type 1 diabetes over 30 years of follow-up in the DCCT/EDIC study. *Diabetes Care*. 2017;40:1010-1016.
4. Frandsen CS, Dejgaard TF, Madsbad S. Non-insulin drugs to treat hyperglycaemia in type 1 diabetes mellitus. *Lancet Diabetes Endocrinol*. 2016;4:766-780.
5. Mathieu C, Gillard P, Benhalima K. Insulin analogues in type 1 diabetes mellitus: getting better all the time. *Nat Rev Endocrinol*. 2017;13:385-399.
6. Qiao YC, Ling W, Pan YH, et al. Efficacy and safety of pramlintide injection adjunct to insulin therapy in patients with type 1 diabetes mellitus: a systematic review and meta-analysis. *Oncotarget*. 2017;8:66504-66515.
7. National Institute for Health and Care Excellence. Type 1 diabetes in adults: Diagnosis and management. https://www.nice.org.uk/guidance/ng17. Accessed December 13, 2017.
8. Al Khalifah RA, Alnhdi A, Alghar H, Alanazi M, Florez ID. The effect of adding metformin to insulin therapy for type 1 diabetes mellitus children: a systematic review and meta-analysis. *Pediatr Diabetes*. 2017;18:664-673.
9. Petrie JR, Chaturvedi N, Ford I, et al. Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2017;5:597-609.
10. Mathieu C, Zinman B, Hemmingsson JU, et al. Efficacy and safety of liraglutide added to insulin treatment in type 1 diabetes: the ADJUNCT ONE treat-to-target randomized trial. *Diabetes Care*. 2016;39:1702-1710.
11. Garg SK, Henry RR, Banks P, et al. Effects of sotagliflozin added to insulin in patients with type 1 diabetes. *N Engl J Med*. 2017;377:2337-2348.
12. Henry RR, Thakkar P, Tong C, Polidori D, Alba M. Efficacy and safety of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to insulin in patients with type 1 diabetes. *Diabetes Care*. 2015;38:2258-2265.
13. Rodbard HW, Peters AL, Slee A, Cao A, Traina SB, Alba M. The effect of canagliflozin, a sodium glucose cotransporter 2 inhibitor, on glycemic end points assessed by continuous glucose monitoring and patient-reported outcomes among people with type 1 diabetes. *Diabetes Care*. 2017;40:171-180.
14. Dandona P, Mathieu C, Phillip M, et al. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (DEPICT-1): 24 week results from a multicentre, double-blind, phase 3, randomised controlled trial. *Lancet Diabetes Endocrinol*. 2017;5:864-876.

15. Biester T, Aschemeier B, Fath M, et al. Effects of dapagliflozin on insulin-requirement, glucose excretion and beta-hydroxybutyrate levels are not related to baseline HbA1c in youth with type 1 diabetes. *Diabetes Obes Metab*. 2017;19:1635-1639.
16. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117-2128.
17. Kaku K, Lee J, Mattheus M, et al. Empagliflozin and cardiovascular outcomes in Asian patients with type 2 diabetes and established cardiovascular disease- Results from EMPA-REG OUTCOME(R). *Circ J*. 2017;81:227-234.
18. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med*. 2016;375:323-334.
19. Grempler R, Thomas L, Eckhardt M, et al. Empagliflozin, a novel selective sodium glucose cotransporter-2 (SGLT-2) inhibitor: characterisation and comparison with other SGLT-2 inhibitors. *Diabetes Obes Metab*. 2012;14:83-90.
20. Pieber TR, Famulla S, Eilbracht J, et al. Empagliflozin as adjunct to insulin in patients with type 1 diabetes: a 4-week, randomized, placebo-controlled trial (EASE-1). *Diabetes Obes Metab*. 2015;17:928-935.
21. Famulla S, Pieber TR, Eilbracht J, et al. Glucose exposure and variability with empagliflozin as adjunct to insulin in patients with type 1 diabetes: continuous glucose monitoring data from a 4-week, randomized, placebo-controlled trial (EASE-1). *Diabetes Technol Ther*. 2017;19:49-60.
22. Kanada S, Koiwai K, Taniguchi A, Sarashina A, Seman L, Woerle HJ. Pharmacokinetics, pharmacodynamics, safety and tolerability of 4 weeks' treatment with empagliflozin in Japanese patients with type 2 diabetes mellitus. *J Diabetes Investig*. 2013;4:613-617.
23. Bonora BM, Avogaro A, Fadini GP. Sodium-glucose co-transporter-2 inhibitors and diabetic ketoacidosis: an updated review of the literature. *Diabetes Obes Metab*. 2018;20:25-33.
24. Nishimura R, Tanaka Y, Koiwai K, et al. Effect of empagliflozin monotherapy on postprandial glucose and 24-hour glucose variability in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled, 4-week study. *Cardiovasc Diabetol*. 2015;14:11.
25. Kanikarla-Marie P, Jain SK. Hyperketonemia and ketosis increase the risk of complications in type 1 diabetes. *Free Radic Biol Med*. 2016;95:268-277.
26. Dhatariya KK, Vellanki P. Treatment of diabetic ketoacidosis (DKA)/hyperglycemic hyperosmolar state (HHS): novel advances in the management of hyperglycemic crises (UK versus USA). *Curr Diab Rep*. 2017;17:33.
27. Perkins BA, Cherney DZ, Partridge H, et al. Sodium-glucose cotransporter 2 inhibition and glycemic control in type 1 diabetes: results of an 8-week open-label proof-of-concept trial. *Diabetes Care*. 2014;37:1480-1483.
28. Geerlings S, Fonseca V, Castro-Diaz D, List J, Parikh S. Genital and urinary tract infections in diabetes: impact of pharmacologically-induced glucosuria. *Diabetes Res Clin Pract*. 2014;103:373-381.
29. Zijlstra E, Heise T, Nosek L, Heinemann L, Heckermann S. Continuous glucose monitoring: quality of hypoglycaemia detection. *Diabetes Obes Metab*. 2013;15:130-135.
30. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis*. 2009;53:982-992.

SUPPORTING INFORMATION

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

How to cite this article: Shimada A, Hanafusa T, Yasui A, et al. Empagliflozin as adjunct to insulin in Japanese participants with type 1 diabetes: Results of a 4-week, double-blind, randomized, placebo-controlled phase 2 trial. *Diabetes Obes Metab*. 2018;20:2190–2199. https://doi.org/10.1111/dom.13351