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ORIGINAL ARTICLE

Clinical pharmacology study of ipragliflozin in Japanese patients with type 1 diabetes mellitus: A phase 2, randomized, placebo-controlled trial

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Aim: To evaluate the pharmacodynamics, pharmacokinetics, and safety of the novel oral sodium-glucose co-transporter-2 inhibitor, ipragliflozin, in Japanese patients with type 1 diabetes mellitus.

Materials and methods: We conducted a multicentre, double-blind, placebo-controlled, parallel-group study. Patients were randomized to receive 25, 50, or 100 mg/day ipragliflozin or placebo for 2 weeks. Key pharmacokinetic endpoints included area under the concentration-time curve 24 hours postdose (AUC_{24h}), maximum plasma concentration (C_{max}), and renal clearance. Key pharmacodynamic endpoints included 24-hour urinary glucose excretion, mean plasma glucose $AUC_{0\text{-}24h}$, and mean renal glucose clearance. Changes in total, basal, and bolus insulin dosages were recorded. Adverse events (AEs) were monitored for safety.

Results: Dose-dependent increases were observed in AUC_{24h} and C_{max} on days 1 and 14 for 25-, 50-, and 100-mg ipragliflozin. The mean plasma glucose $AUC_{0\text{-}24h}$ was lower than that of placebo and the mean renal glucose clearance increased in a dose-dependent manner from baseline, but remained unchanged in the placebo group. The mean (standard deviation) change from baseline in total daily insulin dose was greater in the ipragliflozin 25-, 50-, and 100-mg groups (−14.77 ± 14.04%, −18.40 ± 12.49% and −19.25 ± 16.77%, respectively), than placebo (−4.51 ± 16.28%). Most AEs were mild in severity; no patients discontinued the study because of treatment-emergent AEs.

Conclusions: The pharmacokinetic and pharmacodynamic properties of ipragliflozin in Japanese patients with type 1 diabetes mellitus were confirmed. Increases in urinary glucose excretion lead to dose-dependent decreases in plasma glucose. Concomitant insulin dose decreased with ipragliflozin treatment. No clinically relevant safety concerns were identified.

KEYWORDS

hyperglycaemia, ipragliflozin, plasma glucose, sodium-glucose co-transporter, type 1 diabetes mellitus

1 | INTRODUCTION

Insulin therapy is the current standard of care for patients with type 1 diabetes.[1] However, a recognized problem with this therapy is hypoglycaemia, particularly when the insulin dose is increased.[1] Moreover, the risk of severe hypoglycaemia increases in proportion to decreasing HbA1c levels in patients with type 1 diabetes.[2] The mean HbA1c level is notably higher in patients with type 1 diabetes than in patients with type 2 diabetes (7.80% and 7.00%, respectively), which highlights the difficulties of glycaemic control for patients with type 1 diabetes, even if they are treated by a specialist.[3] Therefore, novel oral antidiabetic agents are required to improve glycaemic control in patients with type 1 diabetes mellitus without increasing the risk of hypoglycaemia.

Ipragliflozin, a selective sodium-glucose co-transporter-2 (SGLT2) inhibitor jointly developed by Astellas Pharma Inc. and Kotobuki Pharmaceutical Co., Ltd., was approved for type 2 diabetes in Japan in 2014 as the first drug in its class.[4] The regular dose of ipragliflozin is 50 mg/day and doses up to 100 mg/day are approved in cases of insufficient efficacy. Ipragliflozin inhibits SGLT2-mediated glucose reabsorption in the renal proximal tubule and increases glucose excretion in the urine, thereby lowering blood glucose levels.[5,6] The safety and efficacy of ipragliflozin in type 2 diabetes mellitus patients (including elderly patients) have been confirmed in preapproval clinical trials, as well as in large-scale postmarketing surveillance studies in the real-world clinical setting in Japan.[7–10] Furthermore, in a multicentre, randomized, placebo-controlled, double-blind study in insulin-treated patients with type 2 diabetes mellitus, ipragliflozin was shown to be well tolerated and effective.[11]

Although there is a large amount of published data on the efficacy and safety of ipragliflozin for type 2 diabetes, to date, no data have been obtained on the use of ipragliflozin for the treatment of type 1 diabetes mellitus. Considering its glucose-lowering effects and insulin-independent mechanism of action, ipragliflozin is expected to be efficacious and well tolerated in patients with type 1 diabetes mellitus. The aim of the present phase 2 study was to assess the pharmacodynamics (PD), pharmacokinetics (PK), and safety of ipragliflozin 25, 50, and 100 mg administered once daily for 2 weeks in Japanese patients with type 1 diabetes mellitus who have inadequate glycaemic control with insulin therapy.

2 | MATERIALS AND METHODS

2.1 | Patients

Eligible patients for this study were male or female, aged ≥20 and <75 years, with type 1 diabetes mellitus, who had been receiving insulin therapy for at least 52 weeks (364 days) at the time of informed consent.

Patients were included if their HbA1c value at screening was between 7.5% and 10.0% (58-86 mmol/mol), and they had a body mass index of ≥20.0 and ≤35.0 kg/m^2, and a fasting blood C-peptide level of ≤0.5 ng/mL (≤0.17 nmol/L). In addition, patients were excluded if they had changed the daily dose of insulin therapy by more than ±20% during the 12 weeks (83 days) prior to screening. The complete inclusion and exclusion criteria are listed in the Supporting Information. All patients provided written informed consent.

2.2 | Ethics

The study was approved by the institutional review board of each participating site and conducted in accordance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines, applicable regulations, and the Declaration of Helsinki. This study was registered at clinicaltrials.gov: NCT02529449.

2.3 | Study design and treatments

This was a multicentre, double-blind, placebo-controlled, parallel-group comparative study conducted at 12 sites in Japan from 1 September 2015 to 19 March 2016. The study design is illustrated in Figure S1. Examinations and observations were performed on patients under hospitalization from 2 days prior to the initiation of treatment (day −2 to day 3). On day −1, the placebo was administered before breakfast under single-blind conditions to assess patient eligibility. Eligible patients were then assigned to a treatment group under double-blind conditions. Ipragliflozin and placebo were administered as three tablets once daily for 14 days.

From day 13 (the day before the end of treatment) to day 15 (the day after the end of study drug administration), the examinations and observations were again performed on patients under hospitalization. After the treatment period was completed, patients underwent a 1 to 3-week follow-up period.

Eligible patients were randomized using the block randomization technique (using a block size of four) to receive an oral dose of ipragliflozin 25, 50, or 100 mg/day or placebo once daily before breakfast for 2 weeks in a double-blind manner. Neither the investigator, the sponsor, clinical staff, nor the patient knew which agent was being administered. The randomization number was assigned based on the Interactive Response Technology (IRT) service.

Prohibited concomitant medications included glucose-lowering agents (other than insulin preparations) during the 12 weeks before the start of screening to the end of the treatment period. Glucose and glucagon (infusion/injection) from day −1 to the end of treatment were also prohibited. Conditionally allowed concomitant drugs included diuretics or antidiuretics; however, these were only permitted if they were used prior to the treatment period and if the treatment regimen and dose were not to be changed. Corticosteroids and immunosuppressants were prohibited except for topical applications.

The dose of insulin was adjusted according to the method of dose adjustment implemented by patients in typical clinical settings based on the physician's instructions during the period from the start of screening to the end of the treatment period. If the self-monitored blood glucose level was below 80 mg/dL (4.4 mmol/L), the principal investigator considered reducing the insulin dose.

2.4 | Endpoints

This study evaluated PK and PD variables following administration of ipragliflozin. PK endpoints included area under the concentration-time curve at 24 hours postdose (AUC_{24h}), maximum plasma concentration (C_{max}), time at maximum plasma concentration (t_{max}), fraction of drug excreted in urine 24 hours postdose (Ae_{24h}%), renal clearance (CL_R), oral clearance (CL/F), peak-trough ratio (PTR), and accumulation ratio (R_{ac}).

PD endpoints included plasma glucose level (daily profile and plasma glucose $AUC_{0\text{-}24h}$), fasting plasma glucose level, postprandial plasma glucose level at 1, 2, and 3 hours after breakfast, glycoalbumin, cumulative urinary glucose excretion (g/24 h; mmol/24 h), body weight, and 0 to 24 hour renal glucose clearance (mL/min).

TABLE 1 Demographic and baseline characteristics (PDAS)

	Insulin plus placebo (n = 10)	Insulin plus ipragliflozin 25 mg (n = 9)	Insulin plus ipragliflozin 50 mg (n = 12)	Insulin plus ipragliflozin 100 mg (n = 10)
Sex				
Male	3 (30.0)	3 (33.3)	2 (16.7)	4 (40.0)
Female	7 (70.0)	6 (66.7)	10 (83.3)	6 (60.0)
Age, years				
	44.8 ± 13.2	47.2 ± 15.7	43.4 ± 12.3	41.7 ± 14.0
Body weight, kg				
	63.09 ± 7.63	67.27 ± 10.20	64.88 ± 10.32	66.53 ± 6.82
BMI, kg/m^2				
	23.93 ± 2.72	26.56 ± 5.60	24.54 ± 3.77	24.25 ± 2.64
Duration of type 1 diabetes, months				
	213.9 ± 99.1	230.6 ± 182.0	180.0 ± 114.2	130.2 ± 62.5
HbA1c				
%	8.66 ± 0.74	8.51 ± 0.79	8.45 ± 0.76	8.85 ± 0.72
mmol/Mol	71.1 ± 7.9	69.4 ± 8.7	68.9 ± 8.3	73.1 ± 8.2
Fasting plasma glucose level				
mg/dL	150.9 ± 72.4	152.2 ± 68.1	128.3 ± 32.9	198.2 ± 75.4
mmol/L	8.38 ± 4.02	8.43 ± 3.79	7.11 ± 1.82	11.00 ± 4.21
Postprandial plasma glucose level, mg/dL				
1 h after breakfast	265.2 ± 100.3	230.0 ± 67.8	228.2 ± 61.9	275.4 ± 50.4
2 h after breakfast	302.7 ± 96.0	239.1 ± 76.5	234.0 ± 66.7	293.5 ± 61.1
3 h after breakfast	271.2 ± 90.5	232.1 ± 101.9	228.8 ± 51.4	275.4 ± 73.4
Postprandial plasma glucose level, mmol/L				
1 h after breakfast	14.73 ± 5.58	12.78 ± 3.77	12.66 ± 3.44	15.28 ± 2.80
2 h after breakfast	16.79 ± 5.34	13.26 ± 4.25	13.00 ± 3.71	16.30 ± 3.39
3 h after breakfast	15.06 ± 5.02	12.90 ± 5.65	12.71 ± 2.85	15.28 ± 4.06
Plasma glucose $AUC_{0\text{-}24h}$				
h·mg/dL	5048 ± 1301	4498 ± 842	4230 ± 1075	4464 ± 657
h·mmol/L	280.2 ± 72.2	249.6 ± 46.6	234.7 ± 59.8	247.8 ± 36.5
Urinary glucose excretion				
g/24 h	24.8 ± 20.4	7.9 ± 9.0	8.6 ± 9.5	11.1 ± 7.0
mmol/24 h	137.44 ± 113.36	44.01 ± 49.77	47.85 ± 52.79	61.77 ± 38.87
Renal glucose $clearance_{0\text{-}24h}$, mL/min				
	7.13 ± 5.13	2.77 ± 2.85	2.94 ± 3.09	3.98 ± 2.38
Fasting C-peptide				
ng/mL	0.05 ± 0.13	0.12 ± 0.16	0.09 ± 0.14	0.04 ± 0.07
nmol/L	0.01 ± 0.03	0.03 ± 0.05	0.03 ± 0.05	0.01 ± 0.03
Glycoalbumin, %				
	26.05 ± 3.73	25.46 ± 4.25	25.48 ± 2.76	24.59 ± 4.63
Insulin daily dose, IU				
Basal	16.70 ± 7.24	17.10 ± 8.02	16.72 ± 7.00	18.60 ± 4.88
Bolus	27.30 ± 11.69	29.64 ± 12.89	22.08 ± 6.42	33.80 ± 10.46
Total	44.00 ± 17.83	46.74 ± 19.71	38.80 ± 12.27	52.40 ± 11.05
eGFR, mL/min/1.73 m^2				
	105.98 ± 31.10	90.60 ± 27.07	93.74 ± 22.48	100.62 ± 17.20
Total serum ketones, μmol/L[a]				
	373.74 ± 322.59	148.09 ± 162.80	197.44 ± 139.87	338.79 ± 298.77

Values are presented as *n* (%) or mean ± standard deviation.
[a]Safety analysis set data (placebo n = 11, ipragliflozin 25 mg n = 10, 50 mg n = 12, and 100 mg n = 10).
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; PDAS, pharmacodynamic analysis set.

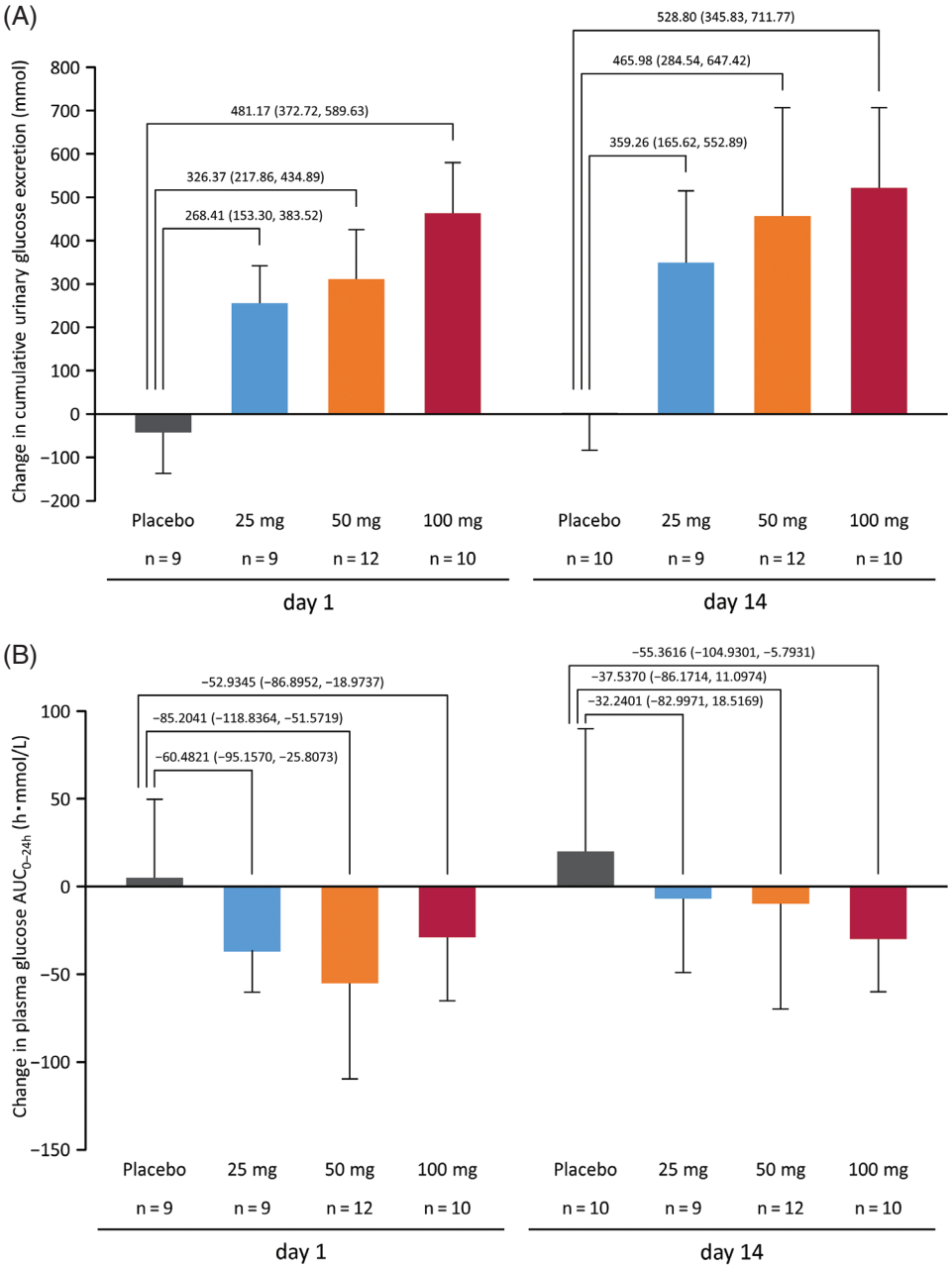

FIGURE 1 Changes in (A) cumulative urinary glucose excretion (mmol), (B) plasma glucose $AUC_{0\text{-}24h}$ (h·mmol/L), and (C) renal glucose clearance $_{0\text{-}24h}$, at days 1 and 14 in the placebo and 25-, 50-, and 100-mg ipragliflozin groups (mean ± standard deviation). Values are adjusted mean differences from placebo and 95% confidence intervals, calculated using an analysis of covariance model including baseline measurements as a covariate

Renal glucose clearance was calculated as follows: cumulative urinary glucose excretion/plasma glucose AUC.

Safety was evaluated by monitoring adverse events (AEs) (coded by MedDRA version 18.0), haematology, biochemistry, urinalysis, vital signs (supine blood pressure and pulse rate), and self-monitored blood glucose. Blood glucose was measured four times a day (before breakfast, before lunch, before dinner, and before bedtime) during the study and a level of ≤70 mg/dL (≤3.89 mmol/L) was considered an AE (hypoglycaemia). Serum ketone levels (total serum ketones, acetoacetic acid, 3-hydroxybutryic acid) were measured at the following times: during screening; before administration of study drugs on days 1 (baseline), 2, 3, 14, and 15 in the treatment period; and during the postinvestigational period.

Other endpoints included the number of units of insulin administered concomitantly (basal insulin daily dose, bolus insulin daily dose, and total insulin daily dose), and continuous glucose monitoring (CGM, Medtronic iPro2) variables [mean amplitude of glycaemic excursions (MAGE) and percentage duration]. Percentage duration refers to the percentage of time when glucose levels were below, within, and above the 70 to 180 mg/dL (3.89-9.99 mmol/L) range within a 24-hour period.

2.5 | Statistical analysis

The study planned to enroll a total of 40 patients; four groups comprising 10 patients each. PK, PD, and safety analyses were performed in the following analysis sets: the pharmacokinetic analysis set (PKAS,

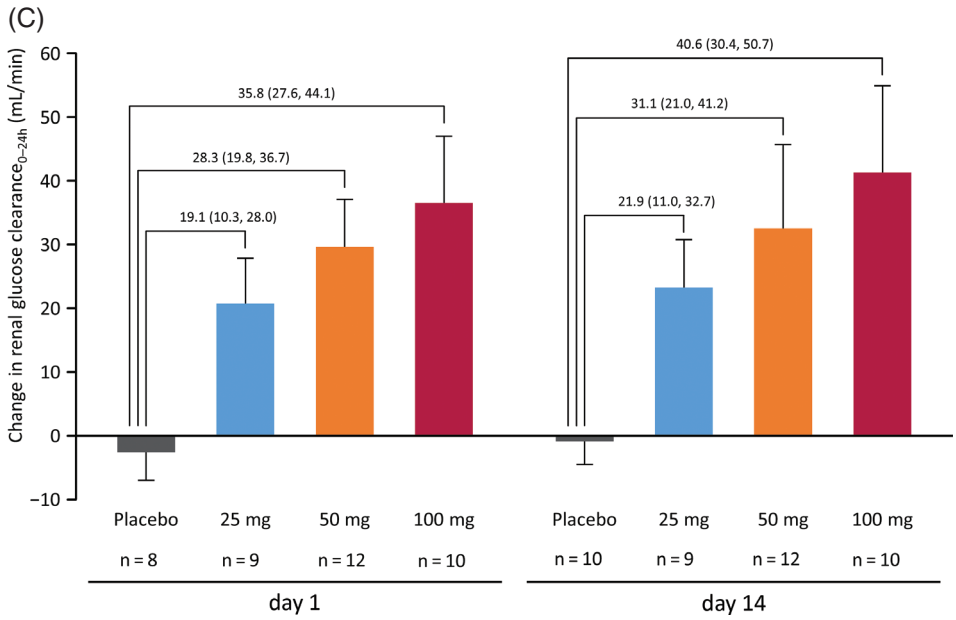

FIGURE 1 (Continued)

which included patients who received the study drug and provided at least one sample for measurement of drug concentrations), the pharmacodynamic analysis set (PDAS, which included patients who received the study drug and provided at least one sample for the measurement of PD data on day 14), and the safety analysis set (SAF, which included all patients who received at least one dose of the study drug).

For continuous data, measured values and changes from baseline (except PK variables) were summarized using descriptive statistics by treatment group for each time point. The adjusted mean differences from placebo (ipragliflozin − placebo) and 95% confidence intervals (CIs) were calculated using an analysis of covariance model, which included baseline measurement as a covariate for each variable. For categorical laboratory data, the frequency and percentage were summarized for each time point.

Data and statistical analyses were conducted using SAS Drug Development software (version 4.5 or higher; SAS Inc., Cary, North Carolina), PC-SAS software (version 9.1.3; SAS Inc.), and Phoenix WinNonlin (version 6.3; Certara USA Inc., Princeton, New Jersey).

3 | RESULTS

3.1 | Patient disposition and characteristics

After providing informed consent, 43 patients were randomized to receive placebo or ipragliflozin. One patient discontinued the study owing to an AE that began prior to randomization and therefore a total of 42 patients completed the study (Figure S2).

The PKAS included all 42 patients who completed the study. The patient who subsequently discontinued after entering the study was excluded from the PKAS because of a possibility of influence on the patient's PK data. The PDAS comprised 41 patients; reasons for exclusion included a serious protocol violation (one patient), and not providing a sample for measurement of PD data on day 14, as well as non-compliance with study drug administration (one patient). All 43 patients were included in the SAF (Figure S2).

The baseline characteristics of patients in the PDAS are summarized in Table 1. Baseline variables, including age, sex, and body weight, were similar among all treatment groups. However, the mean fasting plasma glucose level was higher in the ipragliflozin 100-mg group compared with the other treatment groups.

3.2 | Pharmacokinetics

The PK variables measured on days 1 and 14 are summarized in Table S1. The mean ± SD AUC_{24h} values on day 14 were 2510 ± 495 ng·h/mL, 5790 ± 1130 ng·h/mL, and 10 600 ± 2050 ng·h/mL in the 25-, 50-, and 100-mg ipragliflozin groups, respectively. Dose-dependent increases were observed in AUC_{24h} and C_{max} on days 1 and 14 for 25, 50, and 100 mg ipragliflozin. The mean Ae_{24h}% value was low in all ipragliflozin groups on days 1 and 14. The mean CL_R values were similar among all ipragliflozin groups.

3.3 | Pharmacodynamics

The changes from baseline in PD variables are summarized in Figure 1A-C and Table 2. There was a dose-dependent increase from baseline to day 1 and to day 14 in 0 to 24 hour urinary glucose excretion in all ipragliflozin groups (Figures 1A and S3A). In all ipragliflozin groups, the mean plasma glucose $AUC_{0\text{-}24h}$ was lower than that of placebo on days 1 and 14 (Figures 1B and S3B). The mean renal glucose clearance (0-24 h) increased in a dose-dependent manner from baseline on days 1 and 14 in the ipragliflozin groups but remained unchanged in the placebo group (Figure 1C).

Greater dose-dependent decreases from baseline in fasting plasma glucose were observed in all ipragliflozin groups compared with placebo on days 2 and 15; the dose-dependent effect was maintained at day 15 (Table 2). A similar tendency was observed in

plasma glucose levels measured at 1, 2, and 3 hours after breakfast on days 1 and 14. Compared with baseline, the mean plasma glucose level in the ipragliflozin groups showed a tendency to decrease over time on days 1 and 14 (Figures S4A-D and S5A-D, and Table 2). The mean glycoalbumin levels decreased from baseline to day 15 by an adjusted mean difference from placebo (95% CI) of −2.17% (−3.84, −0.51), −2.03% (−3.58, −0.48), and − 2.67% (−4.31, −1.04) in the 25-, 50-, and 100-mg ipragliflozin groups, respectively (Table 2). In the placebo group, the mean glycoalbumin levels remained almost unchanged from baseline. Similarly, compared with placebo, body weight decreased to a greater extent in all ipragliflozin groups from baseline to day 15 (Table 2).

3.4 | Other endpoints

The change from baseline in total, basal and bolus insulin dose on day 14 was greater in all ipragliflozin groups compared with the placebo group. The mean (±SD) percentage changes from baseline to day 14 for the total daily insulin dose were −14.77% ± 14.04%, −18.40% ± 12.49%, and −19.25% ± 16.77% in the ipragliflozin 25-, 50-, and 100-mg groups, respectively (Figure 2A). The corresponding percentage changes in basal insulin dose were −20.83% ± 22.67%, −25.38% ± 22.55%, and −14.68% ± 18.87% (Figure 2B); those for bolus insulin dose were −10.68% ± 13.39%, −13.94% ± 12.22%, and −21.25% ± 19.56% (Figure 2C).

The changes in CGM variables (MAGE and percentage duration) are shown in Table S2. MAGE and percentage duration improved (especially on day 1) in all ipragliflozin groups compared with placebo. However, this improvement decreased on day 14.

3.5 | Safety

Treatment-emergent AEs (TEAEs) are summarized in Table 3. TEAEs were reported in all patients, except in one patient in the ipragliflozin 100-mg group. Most TEAEs were mild in severity, and no deaths, other serious TEAEs, or TEAEs leading to discontinuation, were reported. One patient in the placebo group discontinued the study because of an AE with onset prior to initiation of the treatment period; therefore, this was not considered a TEAE.

Blood ketone body increases were reported as AEs in four patients: one in the ipragliflozin 25-mg group (56-year-old female, 991 μmol/L on day 15, 24 hours postdose), one in the ipragliflozin 50-mg group (28-year-old female, 968 μmol/L on day 15, 24 hours postdose), and two in the ipragliflozin 100-mg group (a 56-year-old

TABLE 2 Mean changes from baseline in pharmacodynamics parameters (PDAS)

			Insulin plus ipragliflozin		
		Insulin plus placebo (n = 10)	25 mg (n = 9)	50 mg (n = 12)	100 mg (n = 10)
Change in fasting plasma glucose, mg/dL	Day 2	15.9 ± 92.5	−37.0 ± 47.7	−42.0 ± 24.8	−75.2 ± 60.7
	AMD (95% CI)	–	−56.6 (−89.3, −23.9)	−80.1 (−111.1, −49.0)	−59.3 (−92.1, −26.6)
	Day 15	24.9 ± 68.8	−2.6 ± 70.6	−14.1 ± 42.6	−78.2 ± 57.0
	AMD (95% CI)	–	−26.6 (−69.3, 16.1)	−52.9 (−93.1, −12.8)	−73.9 (−117.1, −30.8)
Change in fasting plasma glucose, mmol/L	Day 2	0.88 ± 5.13	−2.03 ± 2.68	−2.33 ± 1.37	−4.17 ± 3.36
	AMD (95% CI)	-	−3.13 (−4.95, −1.32)	−4.45 (−6.17, −2.72)	−3.29 (−5.11, −1.48)
	Day 15	1.37 ± 3.81	−0.13 ± 3.93	−0.78 ± 2.36	−4.34 ± 3.18
	AMD (95% CI)	-	−1.47 (−3.83, 0.89)	−2.94 (−5.16, −0.72)	−4.09 (−6.48, −1.71)
Change in postprandial plasma glucose, mg/dL					
1 h after breakfast	Day 1	−12.4 ± 91.1	−21.0 ± 73.0	−27.5 ± 54.7	−26.7 ± 30.8
	Day 14	2.1 ± 104.0	−21.2 ± 70.1	−31.5 ± 53.0	−84.3 ± 36.9
2 h after breakfast	Day 1	−35.1 ± 79.1	−40.7 ± 87.2	−45.3 ± 72.4	−53.7 ± 43.8
	Day 14	−42.5 ± 91.9	−17.3 ± 67.9	−30.4 ± 61.4	−83.0 ± 55.5
3 h after breakfast	Day 1	−15.4 ± 67.1	−50.9 ± 100.7	−51.2 ± 74.3	−45.1 ± 41.6
	Day 14	−20.6 ± 78.0	−29.7 ± 76.8	−42.6 ± 60.1	−66.2 ± 53.1
Change in postprandial plasma glucose, mmol/L					
1 h after breakfast	Day 1	−0.69 ± 5.05	−1.18 ± 4.06	−1.53 ± 3.04	−1.46 ± 1.70
	Day 14	0.11 ± 5.78	−1.19 ± 3.92	−1.76 ± 2.96	−4.68 ± 2.06
2 h after breakfast	Day 1	−1.93 ± 4.39	−2.23 ± 4.84	−2.53 ± 4.04	−2.99 ± 2.44
	Day 14	−2.35 ± 5.11	−0.94 ± 3.78	−1.69 ± 3.43	−4.61 ± 3.09
3 h after breakfast	Day 1	−0.86 ± 3.72	−2.84 ± 5.62	−2.86 ± 4.16	−2.49 ± 2.30
	Day 14	−1.16 ± 4.34	−1.64 ± 4.27	−2.37 ± 3.33	−3.66 ± 2.94
Glycoalbumin, %	Day 15	−0.64 ± 1.99	−2.67 ± 2.30	−2.53 ± 1.52	−2.95 ± 2.24
	AMD (95% CI)	–	−2.17 (−3.84, −0.51)	−2.03 (−3.58, −0.48)	−2.67 (−4.31, −1.04)
Body weight, kg	Day 15	−0.25 ± 0.81	−0.83 ± 0.48	−1.18 ± 1.06	−0.94 ± 0.89

Values are presented as mean ± standard deviation.
Abbreviations: AMD, adjusted mean difference to placebo (calculated using analysis of covariance model that includes baseline measurements as covariate); CI, confidence interval; PDAS, pharmacodynamic analysis set.

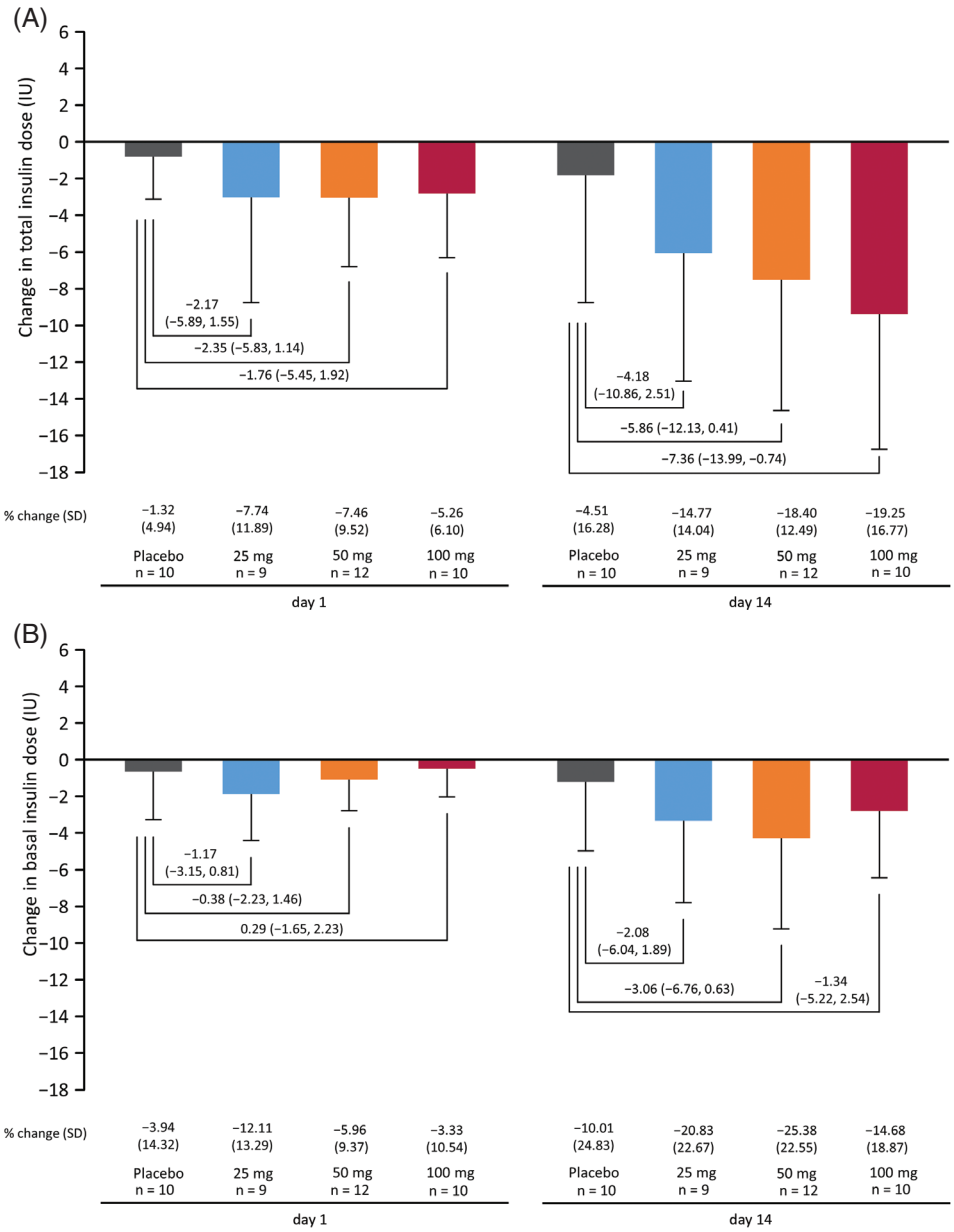

FIGURE 2 Changes in (A) total, (B) basal, and (C) bolus insulin doses at days 1 and 14 in the placebo and 25-, 50-, and 100-mg ipragliflozin groups (mean ± standard deviation). Values are adjusted mean differences from placebo and 95% confidence intervals, calculated using an analysis of covariance model including baseline measurements as a covariate

male, 1200 μmol/L on day 2, predose; and a 48-year-old female, 1770 μmol/L on day 15, 24 hours postdose). These increases were mild and did not include ketoacidosis. The mean (SD) changes in total serum ketones from baseline until the end of treatment were 173.38 (267.48) μmol/L, 357.07 (294.41) μmol/L, and 233.18 (387.35) μmol/L in the ipragliflozin 25-, 50-, and 100-mg groups, respectively. In comparison, the mean (SD) change in total serum ketones from baseline until the end of treatment was −34.98 (152.54) μmol/L in the placebo group.

Table 3 also shows details of TEAEs related to hypoglycaemia. All TEAEs related to hypoglycaemia were minor, as patients recovered from hypoglycaemia without requiring the attention or assistance of caregivers. Most of the TEAEs related to hypoglycaemia were mild in severity. All patients in the placebo group (11/11, 100%, 74 events), and all patients in the ipragliflozin 25- (10/10, 100%, 102 events) and 50-mg (12/12, 100%, 141 events) groups experienced mild hypoglycaemia. In the ipragliflozin 100-mg group, 9/10 patients (90%, 85 events) experienced mild hypoglycaemia. One patient (10%, one event) in the 25-mg ipragliflozin group and one patient (8.3%, three events) in the 50-mg ipragliflozin group experienced moderate hypoglycaemia.

Table S3 shows the onset of TEAEs related to hypoglycaemia. The incidence rate of hypoglycaemic events tended to be higher in the ipragliflozin groups compared with the placebo group from days 1 to 3.

4 | DISCUSSION

Ipragliflozin is a selective SGLT2 inhibitor shown to improve blood glucose levels in patients with type 2 diabetes by increasing urinary

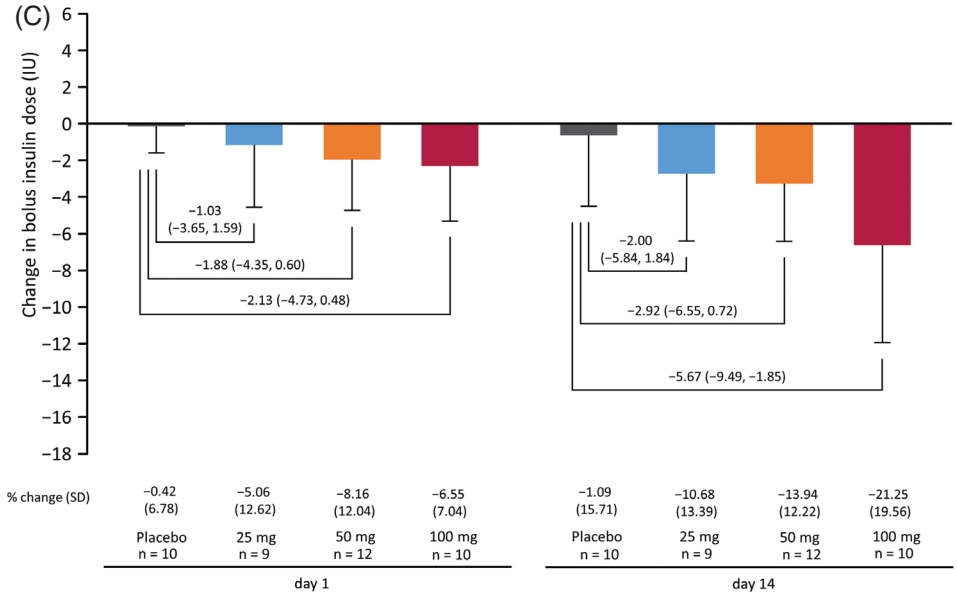

FIGURE 2 (Continued)

glucose excretion.[12] The present study is the first to analyse the pharmacodynamics of ipragliflozin in Japanese patients with type 1 diabetes. Our results showed that ipragliflozin administered at 25, 50, and 100 mg/day induced dose-dependent improvements in plasma glucose C_{max} and AUC_{24h}. Additionally, there was a concomitant dose-dependent increase in mean renal glucose clearance.

Fasting plasma glucose levels decreased in a dose-dependent manner with an accompanying dose-dependent increase in mean cumulative urinary glucose excretion. The mean changes in plasma glucose $AUC_{0\text{-}24h}$ from baseline to day 14 were greater for the ipragliflozin groups compared with placebo. Mean glycoalbumin levels decreased from baseline in all ipragliflozin groups compared with placebo at the end of treatment. The mean body weight decreased from baseline in all ipragliflozin groups, although only a modest difference in body weight was observed between the placebo and treatment groups. The mean insulin daily dose decreased for all ipragliflozin groups during the treatment period, with a 14.8% to 19.3% decrease in the total insulin daily dose in each ipragliflozin group from baseline to day 14. The reduction in bolus insulin in the 100-mg group had a greater contribution to the overall dose reduction than the reduction in basal insulin, a result that was not observed for the 25- or 50-mg groups. However, it is difficult to comment on the significance of this finding, particularly in light of the small sample size and the fact that adjustments to insulin regimens are performed on a case-by-case basis.

It should be noted that all blood glucose-related variables may have been affected by the insulin dose, which was adjusted after the start of ipragliflozin treatment. The effect was considered more pronounced on day 14 or day 15 compared with day 1 or day 2. For example, a smaller reduction from baseline in fasting plasma glucose was observed on day 15 than day 2 in the 25- and 50-mg groups, which could be explained by a decrease in insulin dose.

The PK and PD data reported in the present study confirm the results published outside of Japan for other SGLT2 inhibitors including dapagliflozin,[13] canagliflozin,[14] and empagliflozin.[15] An exploratory study of dapagliflozin in adults with type 1 diabetes showed expected PK profiles and increases in urinary glucose excretion. Additionally, dose-related reductions in 24 hour glucose, glycaemic variability, and insulin dose were suggested.[13] Results from a phase 2 study in patients with type 1 diabetes showed that canagliflozin improved indices of glycaemic variability.[14] Canagliflozin was also shown to reduce HbA1c, body weight, and insulin dose. Similarly, in patients with type 1 diabetes, empagliflozin treatment for 28 days as adjunct to insulin increased urinary glucose excretion, improved HbA1c, and reduced body weight with lower insulin doses.[15]

In addition, the results of the present study confirm the previous PK and PD results obtained for ipragliflozin in Japanese patients with type 2 diabetes mellitus.[16] In that study, ipragliflozin (50 and 100 mg/day) significantly reduced fasting plasma glucose and $AUC_{0\text{-}24h}$ for plasma glucose, compared with placebo. Furthermore, both doses of ipragliflozin reduced $AUC_{0\text{-}24h}$ for serum insulin, body weight, and glycoalbumin, while increasing urinary glucose excretion. Further analysis of the PK and PD data revealed that similar results were obtained from patients with either type 1 or type 2 diabetes (data on file).

No deaths, other SAEs, or TEAEs leading to discontinuation were reported in this study. Notably, no ketoacidosis was observed, and although there were four cases of increased serum ketone bodies, all cases were mild. Nevertheless, this finding requires further study and will be addressed in future phase 3 clinical trials. Regarding TEAEs related to hypoglycaemia, most were mild in severity, and there were no cases of major hypoglycaemia that required the assistance of caregivers for the patient to recover. No significant difference was found in the incidence of hypoglycaemia between the placebo group and the ipragliflozin groups. However, during the early stages of the treatment

TABLE 3 Treatment-emergent adverse events (SAF)

		Insulin plus ipragliflozin		
	Insulin plus placebo (n = 11)	25 mg (n = 10)	50 mg (n = 12)	100 mg (n = 10)
Overall	11 (100.0)	10 (100.0)	12 (100.0)	9 (90.0)
Hypoglycaemia	11 (100.0) 74	10 (100.0) 103	12 (100.0) 144	9 (90.0) 85
Drug-related[a]	10 (90.9) 54	10 (100.0) 83	12 (100.0) 122	9 (90.0) 77
Serious	0	0	0	0
Mild[b]	11 (100.0) 74	10 (100.0) 102	12 (100.0) 141	9 (90.0) 85
Moderate[c]	0	1 (10.0) 1	1 (8.3) 3	0
Severe[d]	0	0	0	0
Major[e]	0	0	0	0
Documented symptomatic[f]	9 (81.8) 35	8 (80.0) 58	11 (91.7) 96	7 (70.0) 25
Asymptomatic[g]	10 (90.9) 39	10 (100.0) 44	9 (75.0) 34	9 (90.0) 60
Probable symptomatic[h]	0	0	3 (25.0) 3	0
Relative[i]	0	1 (10.0) 1	4 (33.3) 11	0
Blood ketone body increased	0	1 (10.0)	1 (8.3)	2 (20.0)
Headache	2 (18.2)	0	0	0
Pyrexia	1 (9.1)	0	1 (8.3)	0
Nasopharyngitis	0	1 (10.0)	1 (8.3)	0
Urine ketone body present	0	0	1 (8.3)	1 (10.0)
Hemorrhoidal hemorrhage	1 (9.1)	0	0	0
Gastroenteritis	0	1 (10.0)	0	0
Beta 2 microglobulin increased	0	1 (10.0)	0	0
Blood bilirubin increased	0	1 (10.0)	0	0
Constipation	0	0	1 (8.3)	0
Vomiting	0	0	1 (8.3)	0
Decreased appetite	0	0	1 (8.3)	0
Hyperglycaemia	0	0	1 (8.3)	0
Pollakiuria	0	0	1 (8.3)	0
Papule	0	0	1 (8.3)	0
Upper respiratory tract infection	0	0	0	1 (10.0)

Data represent number and percentage of patients (%), and in the case of hypoglycaemia, number of events.
Sorting order: descending by number of events.
Abbreviation: SAF, safety analysis set.
[a]Relationship to ipragliflozin possible, probable, or unknown as assessed by the investigator.
[b]No disruption of normal daily activities.
[c]Affects normal daily activities.
[d]Inability to perform daily activities.
[e]Condition that requires attention and/or assistance of caregivers to recover from.
[f]Typical hypoglycaemic symptoms were present and blood glucose level was ≤70 mg/dL (≤3.89 mmol/L).
[g]Typical hypoglycaemic symptoms were absent but the blood glucose level was ≤70 mg/dL (≤3.89 mmol/L).ss
[h]Blood glucose level was not measured but hypoglycaemic symptoms that could be estimated as caused by a drop in blood glucose level to ≤70 mg/dL (≤3.89 mmol/L) were present.
[i]Typical hypoglycaemia symptoms were estimated to be present, but the blood glucose level was >70 mg/dL (≤3.89 mmol/L).

period, the incidence rate and the number of events per patient tended to be higher in the ipragliflozin group compared with placebo. Therefore, caution is advised during this period of treatment, as it is possible the initial increase in hypoglycaemic events could have been a result of an insufficient reduction in insulin dose. This result is consistent with that found in a recent meta-analysis that examined the use of SGLT2 inhibitors as adjunct to insulin therapy for type 1 diabetes.[17]

The limitations of the present study include the exploratory nature and study design; from day 3 to day 13, patients were administered ipragliflozin but not on an inpatient basis, nor were they monitored for safety under the same conditions as they had been in the hospitalization period (from day −2 to day 3, and day 13 to day 15). This could be considered a confounding factor regarding the reporting of AEs such as those related to hypoglycaemia. However, the outpatient design of this study can also be considered a strength given that under free-living conditions, no severe serum ketone body-related events were reported. Other limitations of this study are the small sample size and short duration (2 weeks).

In conclusion, the results of the present study have confirmed the PK and PD properties of ipragliflozin in Japanese patients with type 1 diabetes mellitus, with an increase in urinary glucose excretion leading to decreases in plasma glucose and glycoalbumin levels in a dose-dependent manner. The concomitant insulin dose decreased with

ipragliflozin treatment and no clinically relevant safety concerns were observed.

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Conflict of interest

K.K. has received honoraria from Astellas Pharma Inc., AstraZeneca, Boehringer-Ingelheim, Mitsubishi Tanabe, Ono, Daiichi-Sankyo, Dainippon-Sumitomo Pharma, Kowa Pharmaceutical, MSD, Novo Nordisk Pharma, Taisho Pharmaceutical, and Takeda Pharmaceutical Company; and consulting fees from Sanwa Kagaku Kenkyusho. H.I., J.T., and T.S. are employees of Astellas Pharma Inc.

Author contributions

K.K. contributed to study design and writing of the manuscript. H.I. contributed to study design, study conduct, data collection, and writing of the manuscript. J.T. and T.S. contributed to study design, data analysis, and writing of the manuscript.

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SUPPORTING INFORMATION

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

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