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CLINICAL TRIAL

Randomized, placebo-controlled, double-blind glycemic control trial of novel sodium-dependent glucose cotransporter 2 inhibitor ipragliflozin in Japanese patients with type 2 diabetes mellitus

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ABSTRACT

Aims/Introduction: In the present dose–response study, we evaluated the efficacy and safety of ipragliflozin (ASP1941), a novel and selective inhibitor of sodium-dependent glucose cotransporter 2, in Japanese patients with type 2 diabetes mellitus.

Materials and Methods: A total of 361 patients from 39 Japanese centers were randomized to receive either once-daily oral ipragliflozin (12.5, 25, 50 or 100 mg) or a placebo for 12 weeks.

Results: All ipragliflozin-treated groups had clinically significant, dose-dependent decreases in glycated hemoglobin (HbA1c) and fasting plasma glucose levels compared with placebo-treated groups. The adjusted mean difference in HbA1c change from baseline to the end of treatment between the placebo and 12.5, 25, 50, and 100 mg ipragliflozin groups were −0.61%, −0.97%, −1.29%, and −1.31%, respectively ($P < 0.001$). Reductions in HbA1c levels were similar between obese and non-obese patients, and were larger in patients with baseline HbA1c ≥8.4% than in those with HbA1c <8.4%. Furthermore, bodyweight significantly ($P < 0.001$) and dose-dependently decreased among ipragliflozin-treated groups compared with the placebo group. The incidence of adverse events was similar across all groups. However, mild increases in hematocrit and blood urea nitrogen were found in ipragliflozin treated groups.

Conclusions: Once-daily administration of ipragliflozin was dose-dependently effective in glycemic control without major adverse effects. Ipragliflozin was equally effective between obese and non-obese patients, and led to weight loss in both groups. Ipragliflozin was safe and well-tolerated in Japanese patients with type 2 diabetes mellitus. This trial was registered with ClinicalTrials.gov (no. NCT00621868).

INTRODUCTION

The worldwide prevalence of diabetes mellitus has been estimated at 285 million in 2010, and is projected to reach 439 million by 2030[1]. A Japanese National Health and Nutrition survey in the year 2007 estimated that 8.9 million people suffer from type 2 diabetes in Japan[2]. Although oral antihyperglycemic drugs with various mechanisms of action are currently available, 66% of patients still have higher post-treatment glycated hemoglobin (HbA1c) levels than those recommended by the Japan Diabetes Society[3], highlighting extant unmet needs for glycemic control.

Previous presentation: Kashiwagi A, *et al.* ASP1941, a novel, selective SGLT2 inhibitor, was effective and safe in Japanese healthy volunteers and patients with type 2 diabetes mellitus [Abstract]. American Diabetes Association 70th Scientific Sessions, 25–29 June 2010, Orlando, FL, USA. Abstract number 75-OR.
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The kidney plays an important role in maintaining glucose homeostasis in the body. Blood glucose is filtered by the glomerulus, and almost all filtered glucose molecules are reabsorbed in the proximal renal tubule. Nearly 90% of filtered glucose in the kidney is reabsorbed through sodium-dependent glucose cotransporter 2 (SGLT2) in the S1 segment of the renal proximal tubules[4–6]. Therefore, inhibiting SGLT2-mediated glucose reabsorption helps to lower blood glucose concentrations.

Ipragliflozin (ASP1941; Astellas Pharma Inc. Tokyo, Japan and Kotobuki Pharmaceutical Co., Ltd, Nagano, Japan) is a novel and selective SGLT2 inhibitor, and is one of the first published C-aryl glycoside compounds (as opposed to the labile ortho-attachment of O-glycoside molecules seen in *in vivo* conditions[7]). Previously reported to lower blood glucose levels in both insulin-deficient and insulin-resistant animal models of diabetes mellitus, the compound is currently under consideration for use in treating patients with diabetes[8,9]. Ipragliflozin is generally safe and well-tolerated after both single and repeated dosing, and shows a dose-dependent increase in urinary glucose excretion in healthy volunteers[10,11]. Similar results were reported by another SGLT2 inhibitor, dapagliflozin, in healthy volunteers[12].

Here, we carried out a double-blind, randomized, placebo-controlled study to assess the dose–response relationship for the efficacy and safety of ipragliflozin administered for 12 weeks in Japanese patients with type 2 diabetes mellitus.

MATERIALS AND METHODS

The study was carried out in accordance with the Declaration of Helsinki, Good Clinical Practice and the International Conference on Harmonization guidelines. The study protocol was reviewed and approved by the institutional review board of each institution, and all patients provided written informed consent. All measured HbA1c values, which were originally reported according to the requirements of the Japan Diabetes Society, were converted to the corresponding National Glycohemoglobin Standardization Program (NGSP) values, using the equation established in Japan[13].

Study Design

The present multicenter, placebo-controlled, double-blind, parallel-group, dose–response study assessed the efficacy and safety of ipragliflozin in Japanese patients with type 2 diabetes mellitus. The study was carried out between March 2008 and March 2009 at 39 sites in Japan. Patients were randomized to receive either a placebo or once-daily doses of ipragliflozin (12.5, 25, 50 or 100 mg) before breakfast. All patients underwent an initial 4-week screening period, where previously administered antidiabetic drugs were washed out, followed by a 2-week run-in period with a placebo. Patients were then randomized to receive 12 weeks of treatment, and were followed for an additional 1–6 weeks after study drug treatment completion.

Patients

Eligible patients were aged 20–75 years, had been diagnosed with type 2 diabetes for at least 12 weeks, had baseline body mass indices (BMIs) of 20.0–45.0 kg/m^2, and had fasting serum C-peptide levels of >0.6 ng/mL. Patients were instructed to continue with their recommended diets and exercise habits. If patients were previously treated with antidiabetes drugs, they underwent a washout period of at least 6 weeks between a 4-week screening period and a 2-week run-in period before the start of the randomized treatment. Use of other medications, except for antidiabetes drugs, was permitted during the study period.

Patients with HbA1c levels of 7.4–10.5%, with variability between measurements of 1.0% or less, were recruited during a screening phase. We excluded patients with advanced diabetes complications, type 1 diabetes, history of clinically significant renal disease, dysuria caused by a neurogenic bladder or benign prostatic hypertrophy, repeated urinary tract infections (UTIs) or a UTI at screening, chronic disease requiring the continuous use of steroids or immunosuppressants, cardiac events within the preceding 24 weeks, uncontrolled severe hypertension (systolic blood pressure >170 mmHg or diastolic blood pressure >95 mmHg), abnormal deviation from normal ranges of serum creatinine (Cr) levels, or macroalbuminuria (albumin/creatinine ratio >300 mg/g Cr in urinalysis). Pregnant or breast-feeding women were also excluded from the study.

Clinical Evaluations

During the treatment period, blood and urine samples were collected at weeks 0, 2, 4, 8, and 12. Follow-up examinations were carried out between 1 and 6 weeks after treatment completion. The primary efficacy outcome was change in HbA1c levels from baseline to the end of treatment. Secondary efficacy variables included fasting plasma glucose (FPG) levels, bodyweight and blood pressure. Safety evaluations included the monitoring of the nature, frequency and severity of adverse events (AEs). Laboratory tests, including routine blood and urine chemistries, were also carried out.

Statistical Analysis

Efficacy and safety analyses were carried out in patients who received at least one dose of the study drug and who underwent at least one post-treatment assessment.

For the primary variable, pair-wise comparisons by analysis of covariance with baseline value as a covariate were carried out between the placebo group and each ipragliflozin group as a primary analysis. To adjust the type I error rate, a hierarchical testing procedure was used at an overall two-sided significance level at 0.05. Additionally, Tukey's multiple comparison tests were carried out to compare among all treatment groups. Post-hoc subgroup analyses were carried out to compare outcomes between drug-naïve patients and patients who had been previously treated with an antidiabetes medication (drug-trea-

ted), and between obese (BMI ≥25 kg/m^2) and non-obese (BMI <25 kg/m^2) patients classified as such using the Japanese definition of obesity[14]. Subgroup analyses were also carried out in patients with different baseline HbA1c levels (≥8.4% or <8.4%: corresponding to 8.0% before converting to the NGSP value). Analysis of covariance with the baseline value as a covariate was carried out for secondary variables. For the secondary variables, no adjustments for the multiplicity were made. AEs were categorized according to the Medical Dictionary for Regulatory Activities System Organ Class and by symptoms, and AE rates were then determined for each treatment group.

RESULTS

Patient Demographics

A total of 361 patients were randomized to either the ipragliflozin or placebo groups, and 360 patients had at least one efficacy variable measured after randomization (Figure 1). A total of 52% of patients were drug-naïve, whereas 48% had received antidiabetes medication in the past. Patient demographics and baseline characteristics, including the previous use of antidiabetes medication, were similar across all groups (Table 1). All anti-diabetic medications in drug-treated groups were washed out for at least 6 weeks before randomization. In all treatment groups, the mean compliance rate was ≥97%.

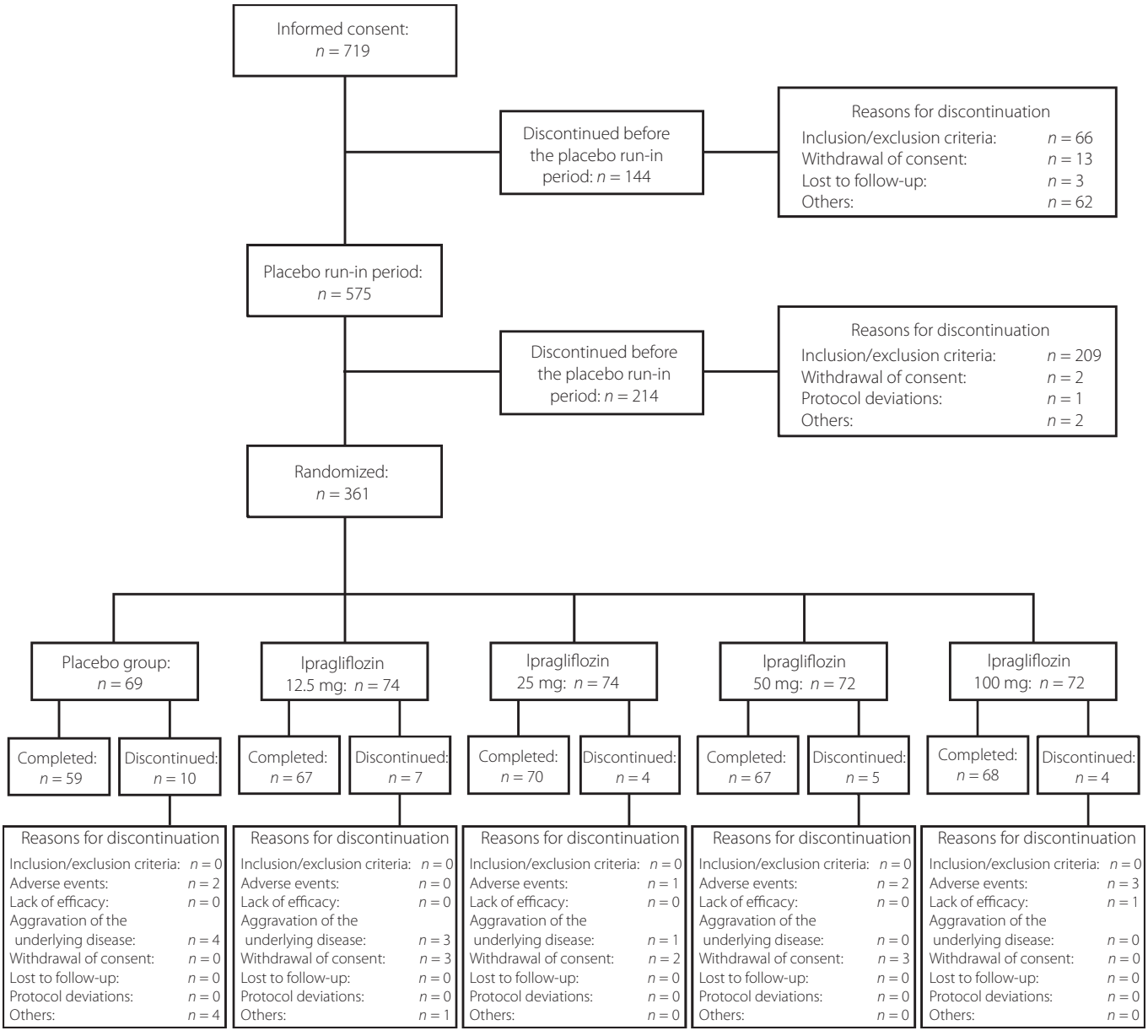


Figure 1 | Study diagram of patient enrolment and treatment protocol.

Table 1 | Demographic and baseline characteristics of patients†

	Placebo (n = 69)	Ipragliflozin			
		12.5 mg (n = 73)	25 mg (n = 74)	50 mg (n = 72)	100 mg (n = 72)
Sex, n (male/female)	49/20	43/30	49/25	43/29	49/23
Age (years)	55.2 ± 9.7	55.3 ± 10.2	57.0 ± 10.4	55.9 ± 11.4	56.0 ± 10.4
Duration of diabetes (months)	75.7 ± 66.5	75.8 ± 62.2	76.9 ± 59.7	79.7 ± 81.3	93.6 ± 87.9
Previous medication for diabetes, n (%)					
Drug-naïve	39 (56.5)	32 (43.8)	40 (54.1)	43 (59.7)	34 (47.2)
Drug-treated‡	30 (43.5)	41 (56.2)	34 (45.9)	29 (40.3)	38 (52.8)
Sulfonylurea	20 (29.0)	21 (28.8)	17 (23.0)	14 (19.4)	15 (20.8)
Metformin	4 (5.8)	12 (16.4)	8 (10.8)	7 (9.7)	7 (9.7)
Alpha-glucosidase inhibitor	8 (11.6)	6 (8.2)	8 (10.8)	8 (11.1)	9 (12.5)
Glinide	1 (1.4)	4 (5.5)	3 (4.1)	2 (2.8)	4 (5.6)
Thiazolidinedione	7 (10.1)	7 (9.6)	9 (12.2)	10 (13.9)	5 (6.9)
BMI (kg/m^2)	25.1 ± 3.4	25.6 ± 3.5	26.2 ± 4.0	25.8 ± 3.5	25.9 ± 3.8
Bodyweight (kg)	66.6 ± 10.6	67.4 ± 12.8	69.0 ± 14.5	67.8 ± 11.9	68.3 ± 12.4
HbA1c (%)	8.36 ± 0.79	8.39 ± 0.90	8.32 ± 0.83	8.33 ± 0.80	8.25 ± 0.76
Fasting plasma glucose (mg/dL)	186.4 ± 39.5	185.4 ± 40.0	178.0 ± 38.8	173.4 ± 34.9	177.5 ± 32.1
Systolic blood pressure (mmHg)	126.5 ± 12.7	128.5 ± 13.6§	127.7 ± 13.6	127.5 ± 14.3	126.1 ± 12.7
Diastolic blood pressure (mmHg)	77.8 ± 10.5	77.2 ± 9.1§	77.1 ± 9.9	77.9 ± 11.1	76.5 ± 9.2

Each value represents the mean ± standard deviation, unless stated otherwise. †All patients who received at least one dose of study drug and had at least one efficacy variable measured after the start of treatment (n = 360). ‡Drug-treated patients could be on more than one oral antidiabetes medication before screening. §n = 74; one patient did not have efficacy data, but did have blood pressure data and safety data. BMI, body mass index; HbA1c, glycated hemoglobin.

Glycemic Control Using Ipragliflozin

At the end of the treatment period, mean HbA1c levels in the 12.5, 25, 50, and 100 mg ipragliflozin groups were dose-dependently decreased by 0.11%, 0.47%, 0.79%, and 0.81% from baseline value, respectively (Table 2). Because of an increase in HbA1c levels of 0.50% above the basal value in the placebo group, the adjusted mean difference in HbA1c change from baseline to the end of treatment between the placebo and 12.5, 25, 50, and 100 mg ipragliflozin groups were −0.61%, −0.97%, −1.29%, and −1.31%, respectively (Table 2). HbA1c levels decreased significantly in the ipragliflozin groups at all tested doses compared with the placebo ($P < 0.001$). Using the Tukey's multiple comparison tests, the differences between all treatment groups were statistically significant except between 25 and 50 mg, and between 50 and 100 mg (Table 2). The maximum effect was obtained at a dose of 50 mg.

As the wash-out period was 6 weeks, the analysis was additionally carried out excluding the patients washed out of thiazolidinediones. The results showed an increase in HbA1c levels of 0.37% above the basal value in the placebo group, the adjusted mean difference in HbA1c change from baseline to the end of treatment between the placebo and 12.5, 25, 50, and 100 mg ipragliflozin groups were −0.55%, −0.89%, −1.20%, and −1.18%, respectively.

At the end of treatment, HbA1c levels <7.0% were achieved in 4.1%, 8.1%, 21.1%, and 23.6% of patients in the 12.5, 25, 50, and 100 mg ipragliflozin groups, respectively, compared with 2.9% of patients in the placebo group. Subgroup analyses on differences in drug effects were carried out by the drug-naïve and drug-treated patients, obese (BMI ≥25 kg/m^2) and non-obese (BMI <25 kg/m^2) patients, and patients with baseline HbA1c levels <8.4% and ≥8.4% (Figure 2). After the treatment with ipragliflozin, HbA1c levels significantly decreased at all tested doses except the 12.5 mg group in obese patients, compared with the placebo. The interactions between the treatment group and these subgroup factors for the change in HbA1c were assessed using analysis of variance to detect differential patterns. Interactions between the treatment group and drug naïve/non-naïve, and obese/non-obese patients were not significant ($P = 0.106$ and $P = 0.228$, respectively). However, the interaction between the treatment group and baseline HbA1c levels <8.4% and ≥8.4% was significant ($P < 0.001$).

Fasting Plasma Glucose

In response to ipragliflozin administration, FPG levels decreased dose-dependently over the 12-week treatment period. In all four ipragliflozin groups, mean FPG levels decreased from the start of treatment, and remained almost constantly in the lowest levels from week 2 until week 12 in both the 50 and 100 mg ipragliflozin groups (Table 2). Adjusted mean changes in FPG from baseline to the end of treatment were +12.0 mg/dL in the placebo group, and −15.6, −23.7, −34.1, and −46.9 mg/dL in the 12.5, 25, 50, and 100 mg ipragliflozin groups, respectively ($P < 0.001$ for all ipragliflozin groups vs placebo). The differ-

Table 2 | Dose dependent reduction of glycated hemoglobin concentrations and fasting plasma glucose levels by Ipragliflozin treatment

	Placebo (n = 69)	Ipragliflozin			
		12.5 mg (n = 73)	25 mg (n = 74)	50 mg (n = 72)	100 mg (n = 72)
HbA1c (%)					
Week 0†	8.36 ± 0.79	8.39 ± 0.90	8.32 ± 0.83	8.33 ± 0.80	8.25 ± 0.76
Week 4†	8.58 ± 1.10*	8.34 ± 1.05	8.05 ± 0.86*	7.93 ± 0.78*	7.85 ± 0.73*
Week 8†	8.62 ± 1.24*	8.23 ± 1.15	7.81 ± 0.76*	7.57 ± 0.71*	7.57 ± 0.72*
Week 12†	8.62 ± 1.19*	8.10 ± 0.91*	7.78 ± 0.75*	7.49 ± 0.70*	7.40 ± 0.68*
Change from baseline at EOT‡	0.50 ± 0.090	−0.11 ± 0.09	−0.47 ± 0.09	−0.79 ± 0.09	−0.81 ± 0.09
Difference vs placebo [95% CI]		−0.61 [−0.85, −0.36]	−0.97 [−1.21, −0.72]	−1.29 [−1.54, −1.04]	−1.31 [−1.55, −1.06]
P-value		<0.001	<0.001	<0.001	<0.001
P-value comparison between each dose groups			$P < 0.05$ (vs 12.5 mg)	$P < 0.001$ (vs 12.5 mg)	$P < 0.001$ (vs 12.5 mg) $P < 0.05$ (vs 25 mg)
FPG (mg/dL)					
Week 0†	186.4 ± 39.5	185.4 ± 40.0	178.0 ± 38.8	173.4 ± 34.9	177.5 ± 32.1
Week 2†	184.3 ± 39.9	172.8 ± 37.2*	159.8 ± 34.2*	142.6 ± 24.3*	141.4 ± 18.8*
Week 4†	189.8 ± 43.3	166.6 ± 34.7*	151.4 ± 28.0*	144.1 ± 29.1*	136.5 ± 20.3*
Week 8†	190.3 ± 42.9*	168.1 ± 32.8*	155.3 ± 29.9*	137.9 ± 19.6*	135.6 ± 19.6*
Week 12†	189.7 ± 36.7*	163.0 ± 30.7*	151.7 ± 31.9*	140.1 ± 24.1*	130.6 ± 17.6*
Change from baseline at EOT‡	12.0 ± 3.0	−15.6 ± 3.0	−23.7 ± 3.0	−34.1 ± 3.0	−46.9 ± 3.1
Difference vs placebo [95% CI]		−27.6 [−36.0, −19.2]	−35.7 [−44.1, −27.3]	−46.0 [−54.5, −37.6]	−58.9 [−67.4, −50.4]
P-value		<0.001	<0.001	<0.001	<0.001
P-value comparison between each dose groups				$P < 0.001$ (vs 12.5 mg) $P < 0.05$ (vs 25 mg)	$P < 0.001$ (vs 12.5, 25 mg) $P < 0.05$ (*vs* 50 mg)

Each value represents †The mean ± standard deviation, ‡The adjusted mean ± standard error. *$P < 0.05$ (compared with baseline by t-test). CI, confidence interval; EOT, end of treatment; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin.

ences between all treatment groups were statistically significant except between 12.5 and 25 mg, and between 25 and 50 mg by analysis of covariance.

Bodyweight and Blood Pressure

Adjusted mean changes in bodyweight from baseline at the end of treatment were –0.39 kg for patients receiving the placebo, and −1.46, −1.69, −1.81, and −2.10 kg in the 12.5, 25, 50, and 100 mg ipragliflozin groups, respectively (Figure 3a; $P < 0.001$ for all ipragliflozin groups vs placebo). After termination of ipragliflozin treatment, bodyweight was regained during the follow-up period, but the reduction was still significantly below the baseline values. Although the effects of ipragliflozin on bodyweight were variable, the reduction in bodyweight was found in both drug-treated and drug-naïve patients by the subgroup analyses (Figure 3b). The mean change in bodyweight from baseline values to the end of the treatment in drug-naïve patients was +0.06 kg in the placebo group and −1.70 kg in the 100 mg ipragliflozin group. In addition, reduction in bodyweight with ipragliflozin was observed in both obese (BMI ≥25 kg/m^2) and non-obese (BMI <25 kg/m^2) patients.

The changes in systolic blood pressure from baseline to the end of treatment tended to decrease in the ipragliflozin-treated groups compared with the placebo group. However, these differences were not significant (data not shown).

Safety and Laboratory Values

Adverse events occurred at similar frequencies across the placebo and ipragliflozin-treated groups. AEs and drug-related AEs were not dose-dependent ($P = 0.451$ and $P = 0.417$, respectively). Rates of discontinuation because of drug-related AEs were low at 0–3% across the treatment groups. Serious AEs occurred in four patients: three patients (4.3%) in the placebo group and one patient (1.4%) in the ipragliflozin 12.5 mg group. No cases of cancer and no deaths were reported in this small scale and short duration study using ipragliflozin. A single mild symptomatic hypoglycemic event occurred in a patient in the 100 mg ipragliflozin group, which was not confirmed by

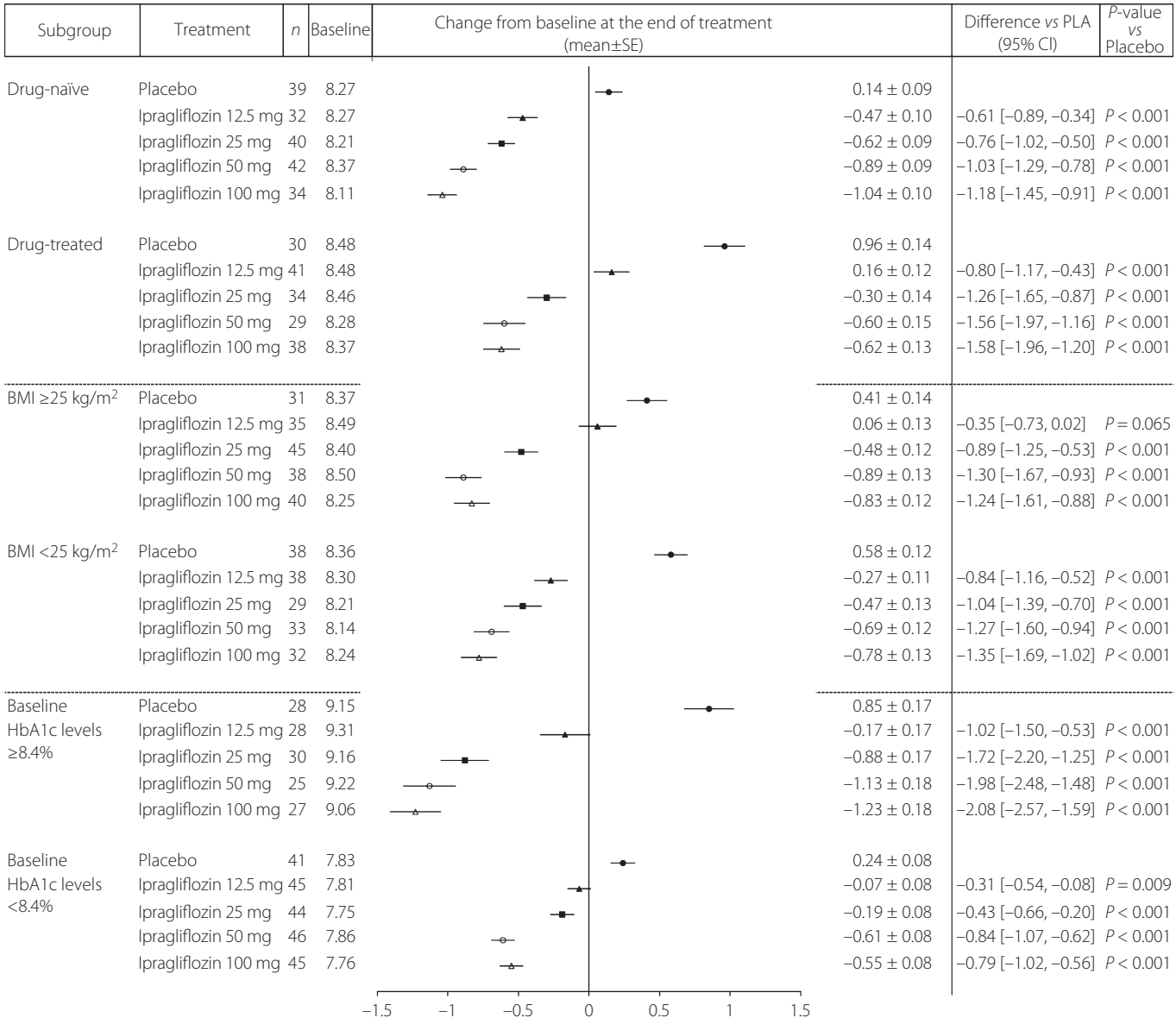
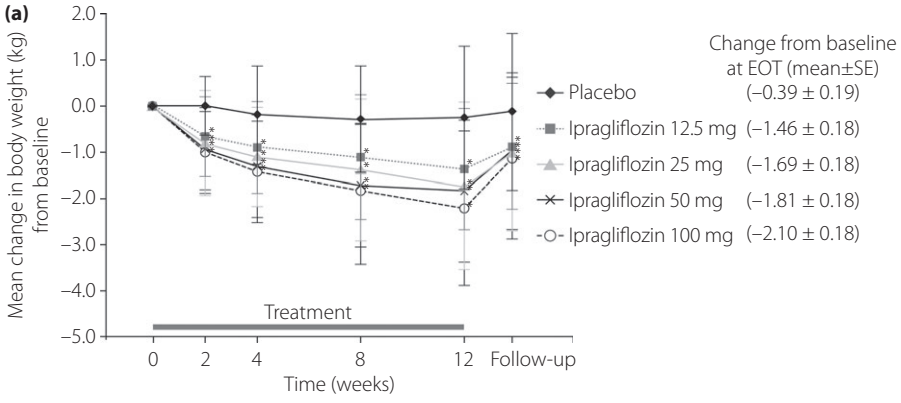
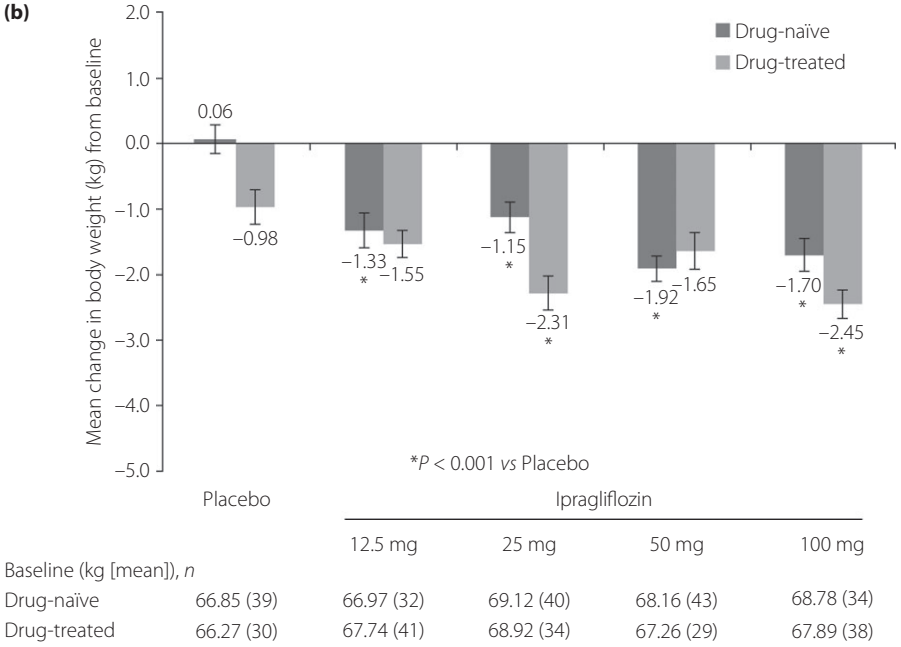


Figure 2 | Subgroup analyses by treatment experience, body mass index (BMI) level and baseline glycated hemoglobin (HbA1c) levels. Effects did not differ between drug-naïve and drug-treated patients, or between patients with BMI of ≥25 kg/m^2 and BMI <25 kg/m^2 (P = 0.106 and P = 0.228, respectively). Reductions in HbA1c values were greater in patients with HbA1c levels ≥8.4% than in those with HbA1c levels <8.4% (P < 0.001). CI, confidence interval; PLA, placebo; SE, standard error.

plasma glucose measurement. Pollakiuria and polyuria occurred in two patients (2.9%) in the placebo group, and in two (2.7%), five (6.8%), six (8.3%), and six (6.8%) patients in the 12.5, 25, 50, and 100 mg ipragliflozin groups, respectively. UTIs were observed in one patient in the placebo group, three patients in the 50 mg ipragliflozin group and one patient in the 100 mg ipragliflozin group. All cases of UTIs involved mild cystitis, were found in female patients and were resolved by antibiotic treatment. Mild vaginal candidiasis in one patient in each of the 12.5 mg and 50 mg ipragliflozin groups improved sufficiently with oxiconazole nitrate treatment. The patient with vaginal candidiasis in the 50 mg ipragliflozin group also had bacterial vaginitis. Genital pruritus occurred in one patient in each of the 12.5, 50 and 100 mg ipragliflozin groups.

In the ipragliflozin-treated groups, hematocrit was mildly increased by 1.5–2.0% at every dose. Similarly, blood urea nitrogen (BUN) and urinary osmolality were also mildly increased compared with placebo. Conversely, alanine amino transferase (ALT) levels were significantly decreased at the 25, 50 and 100 mg dose. Furthermore, serum phosphorus and





Baseline (kg [mean]), *n*					
Drug-naïve	66.85 (39)	66.97 (32)	69.12 (40)	68.16 (43)	68.78 (34)
Drug-treated	66.27 (30)	67.74 (41)	68.92 (34)	67.26 (29)	67.89 (38)

Figure 3 | (a) Dose-dependent effects of ipragliflozin on mean changes in bodyweight levels from baseline over the study period. The values (means ± standard deviation) at each point are described in the figure. *$P < 0.001$ (compared with baseline by *t*-test). (b) Changes in body weight from baseline to the end of treatment in drug-naïve ($n = 188$) and drug-treated patients ($n = 172$). Data are expressed as means ± standard error (SE). *$P < 0.001$ (compared with placebo by analysis of covariance). EOT, end of treatment.

magnesium concentrations, and urinary excretion of magnesium also increased, and urinary pH slightly decreased ($P < 0.001$; Table 3).

DISCUSSION

The present study found that HbA1c levels significantly decreased by more than 1% compared with the placebo after 12 weeks of treatment with once daily 50 or 100 mg doses of ipragliflozin. These results might be clinically meaningful if the levels could be maintained long term, as it has been reported that a reduction of HbA1c by 1% has been associated with a 21% reduction in the relative risk of death, 37% reduction in risk of microvascular complications and 14% reduction in risk of myocardial infarction[15] in patients with type 2 diabetes mellitus.

In the present study, the 6-week washout period might be insufficient to stabilize the pretreatment HbA1c levels, as HbA1c levels in the placebo group showed a 0.5% increase above basal levels during the follow-up period. However, the change in HbA1c levels from baseline to the end of treatment dose-dependently decreased by a maximum of 1.29% below placebo levels in the 50 mg ipragliflozin group and 1.31% below placebo levels in the 100 mg ipragliflozin dose group. The evidence is further supported by the results showing a similar reduction in HbA1c levels at 50 and 100 mg ipragliflozin doses (by 1.03% and 1.18%, respectively) in drug-naïve patients, whereas HbA1c levels in the placebo group showed a 0.14% increase between baseline and the end of treatment. In addition, the effect of thiazolidinediones might remain for at least 2 or

Table 3 | Mean changes in laboratory values from baseline to the end of ipragliflozin treatment

	Placebo	Ipragliflozin			
		12.5 mg	25 mg	50 mg	100 mg
Hematocrit (%)	−0.08 ± 2.61	1.47 ± 1.95**	1.49 ± 2.09**	1.98 ± 2.09**	1.98 ± 1.90**
AST (IU/L)	1.6 ± 12.8	−0.6 ± 6.3	−1.3 ± 11.1	−1.1 ± 5.2	−1.8 ± 11.0
ALT (IU/L)	0.0 ± 7.3	−1.9 ± 8.5	−5.2 ± 11.3*	−3.9 ± 9.8*	−5.8 ± 10.8**
BUN (mg/dL)	−0.3 ± 3.5	1.3 ± 2.8*	1.0 ± 3.3*	2.2 ± 3.3**	1.8 ± 3.5**
sCr (mg/dL)	−0.02 ± 0.07	−0.01 ± 0.06	−0.01 ± 0.05	0.00 ± 0.05*	0.01 ± 0.06*
Uric acid (mg/dL)	−0.04 ± 0.64	−0.05 ± 0.63	−0.39 ± 0.73	−0.30 ± 0.87	−0.13 ± 0.76
uOsm (mOsm/L)	−4 ± 303	123 ± 269	51 ± 250	146 ± 242*	165 ± 273**
Urinary pH	0.04 ± 0.67	−0.23 ± 0.67	−0.34 ± 0.58**	−0.32 ± 0.55**	−0.39 ± 0.65**
Serum electrolytes					
P (mg/dL)	−0.03 ± 0.37	0.05 ± 0.32	0.10 ± 0.39*	0.13 ± 0.39*	0.18 ± 0.41*
Mg (mg/dL)	−0.03 ± 0.14	0.04 ± 0.13*	0.08 ± 0.13**	0.09 ± 0.13**	0.12 ± 0.13**
Urinary electrolytes					
Mg (mg/g Cr)	1.4 ± 27.4	13.5 ± 24.0*	14.9 ± 27.9*	12.9 ± 20.7*	11.9 ± 30.4*

Each value represents the mean ± standard deviation. *$P < 0.05$ and **$P < 0.001$ (compared with placebo by *t*-test). ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cr, creatinine; Mg, magnesium; P, phosphorus; sCr, serum creatinine; uOsm, urinary osmolarity.

3 months after discontinuing the treatment. In order to confirm its effect, further analysis was carried out excluding the patient treated with thiazolidinediones; however, HbA1c, FPG and bodyweight showed almost the same results as in the previous analysis (data not shown).

Furthermore, ipragliflozin treatment also resulted in similar HbA1c reductions among the obese and non-obese Japanese patients. Although other SGLT2 inhibitors also reduce glycemic parameters in patients with type 2 diabetes[16–18], these are the first data showing equal efficacy in both obese and non-obese Japanese type 2 diabetes patients.

More patients receiving ipragliflozin monotherapy achieved an HbA1c level <7.0% (21.1% of the 50 mg group and 23.6% of the 100 mg group) than did with the placebo (2.9%). Ipragliflozin was also associated with a significant reduction in FPG levels. Interestingly, the reduction was found at 2 weeks after the start of treatment, and was maintained until the end of treatment in both the 50 and 100 mg groups.

Several classes of oral antidiabetes medications cause weight gain[19,20]. In the present study, ipragliflozin induced significant dose-dependent reductions in bodyweight compared with the placebo, likely caused by ipragliflozin-induced dose-dependent increases in glucosuria, as recent phase 1[10,11] and phase 2[21] studies have shown that ipragliflozin administration leads to increased excretion of urinary glucose (approximately 50–100 g/day). SGLT2 inhibitors have been reported to only inhibit 30–50% of renal glucose reabsorption in humans, resulting in energy loss that might contribute to reductions in bodyweight[22]. Furthermore, ipragliflozin might also exert a mild osmotic diuretic effect, reflected by the mild increases in hematocrit and BUN levels, which could contribute to the weight reduction and explain the rapid partial regain of weight after discontinuation of the drug.

Hypertension is a risk factor for cardiovascular complications in type 2 diabetes patients[23], and drugs including a low dose of diuretics are often effective in reducing blood pressure, because they mitigate the volume overload seen in these patients. A mild reduction in systolic blood pressure was observed with the ipragliflozin treatment, which is consistent with the results reported for dapagliflozin[16,17,24]. The clinical meaning of these mild effects of ipragliflozin on bodyweight and blood pressure will be further evaluated in ongoing clinical trials. The clinical significance of mild changes in electrolytes, such as serum phosphorus and magnesium concentrations, remains unclear in the present study.

Although ipragliflozin was generally safe and well tolerated in the present study, pollakiuria tended to occur more frequently in ipragliflozin-treated groups than in the placebo group. UTIs and genital infections are prevalent in women with diabetes mellitus[25], and increased incidences of both conditions have been reported in placebo-controlled studies using another SGLT2 inhibitor, dapagliflozin[16,22,24,26]. However, in the present study, both UTIs and genital infections were similarly prevalent between the placebo and ipragliflozin groups. Long-term and large-scale studies of ipragliflozin are required to further assess the frequency and clinical significance of these AEs. However, the present data support the safety of ipragliflozin reported in other studies[10,11,21], and show that SGLT2 inhibitors have a favorable safety profile[16,24,26].

Although the relationship between antidiabetes drugs and cancer risk has been a concern in recent years, no cancer events were reported in our study of ipragliflozin. Much larger patient groups and extended exposure time are likely required to determine whether or not treatment with ipragliflozin presents a similar cancer risk.

In summary, ipragliflozin efficiently improved glycemic control and bodyweight in a dose-dependent manner on adminis-

tration to Japanese patients with type 2 diabetes mellitus. Notably, decreases in HbA1c levels were similar between obese and non-obese patients. Ipragliflozin at once-daily doses up to 100 mg for 12 weeks appears to be safe, as no clinically significant AEs were observed. Given this ostensibly favorable safety profile, the potential therapeutic benefits of ipragliflozin on reductions in bodyweight and blood pressure warrant further investigation in Japanese patients with type 2 diabetes.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1 | Primary investigators list.