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Ipragliflozin in combination with metformin for the treatment of Japanese patients with type 2 diabetes: ILLUMINATE, a randomized, double-blind, placebo-controlled study

This multicenter, double-blind, placebo-controlled study examined the efficacy and safety of ipragliflozin, a sodium-glucose co-transporter 2 inhibitor, in combination with metformin in Japanese patients with type 2 diabetes mellitus (T2DM). Patients were randomized in a 2 : 1 ratio to 50 mg ipragliflozin (n = 112) or placebo (n = 56) once daily for 24 weeks, followed by a 28-week open-label extension in which all patients received 50 or 100 mg ipragliflozin, while continuing metformin. The primary outcome was the change in glycated haemoglobin (HbA1c) from baseline to week 24. HbA1c decreased significantly in the ipragliflozin group (−0.87%; adjusted mean difference from placebo: −1.30%; $p < 0.001$). The overall incidence of treatment-emergent adverse events was similar in both groups, although pollakiuria and constipation were more common in the ipragliflozin group; thus, ipragliflozin significantly improved glycaemic control and reduced body weight without major safety issues in Japanese patients with T2DM.

Keywords: ipragliflozin, Japanese, metformin, randomized controlled trial, SGLT2, type 2 diabetes

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Introduction

Ipragliflozin, a sodium-glucose co-transporter 2 inhibitor [1], improves glycaemic control by promoting urinary glucose excretion in patients with type 2 diabetes mellitus (T2DM) [2–6]. Western studies have shown that ipragliflozin in combination with metformin improves glycaemic control with a low incidence of adverse events [7,8]. We conducted a 24-week, randomized, double-blind, placebo-controlled trial with a 28-week open-label extension to confirm the efficacy and safety of adding ipragliflozin to metformin to treat Japanese patients with T2DM.

Methods

The methods are described in more detail in the Supporting Information. Patients aged ≥20 years with T2DM (≥12 weeks of duration) being treated with metformin (≥6 weeks), with a HbA1c (National Glycohemoglobin Standardization Program) level of 7.4–9.9% and a body mass index of 20.0–45.0 kg/m^2 were eligible. All the patients provided written informed consent before participating in this study.

Eligible patients entered a 4-week observation period and a 2-week run-in period in which they received placebo, after which they were randomized to either 50 mg ipragliflozin or placebo (2 : 1 ratio) for 24 weeks (treatment period 1; Figure S1, Supporting Information). Patients with HbA1c values that had declined from baseline and were <8.4% at the end of treatment period 1 were allowed to enter an open-label extension of 28 weeks (treatment period 2). In treatment period 2, the ipragliflozin dose could be increased to 100 mg, if HbA1c was ≥7.4% at week 20. Patients were followed up for 4 weeks after study completion or treatment withdrawal. The study was approved by the institutional review board at each participating site. The study was conducted in accordance with Good Clinical Practice, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, as well as local laws and regulations. The study was registered at ClinicalTrials.gov (identifier NCT01135433).

The primary efficacy variable was the change in HbA1c from baseline to week 24. The secondary efficacy variables included body weight, waist circumference, fasting plasma glucose (FPG), fasting serum insulin (FSI), plasma leptin, and adiponectin levels. Homeostasis model assessment of insulin resistance (HOMA-R) and homeostasis model assessment of β-cell function (HOMA-β) were also measured. Safety outcomes included vital signs, physical examination, 12-lead ECG, haematology, biochemistry, urine analysis and adverse events.

Results

This study was conducted between May 2010 and November 2011 across 34 sites in Japan. The disposition of patients is summarized in Figure S2. Overall, 56 patients were treated

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Table 1. Patient characteristics (full analysis set).

Characteristic	Placebo (n = 56)	Ipragliflozin (n = 112)	p-value
Sex, n (%)			
Male	33 (58.9)	66 (58.9)	1.000*
Female	23 (41.1)	46 (41.1)	
Mean age, years (s.d.)	57.7 (9.24)	56.2 (10.67)	0.379†
Mean BMI, kg/m^2 (s.d.)	25.47 (3.092)	25.96 (4.410)	0.462†
Mean duration of diabetes, months (s.d.)	96.6 (61.93)	89.9 (68.10)	0.536†
History of hypertension, n (%)	27 (48.2)	54 (48.2)	1.000*
Dyslipidaemia, n (%)	38 (67.9)	81 (72.3)	0.591*
Mean HbA1c, % (s.d.)	8.38 (0.738)	8.25 (0.719)	0.277†
Mean FPG, mmol/l [mg/dl] (s.d.)	9.70 (1.380) [174.5 (24.84)]	8.98 (1.663) [161.6 (29.93)]	0.006†
Treatment with hypoglycaemic drugs other than metformin within 12 weeks before screening, n (%)	29 (51.8)	39 (34.8)	0.045*

BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; s.d., standard deviation.
*Fisher's exact test.
†*t*-test.

with placebo and 112 with ipragliflozin, of whom 42 and 110, respectively, completed treatment period 1. The baseline characteristics of patients in both groups were generally similar (Table 1) except that patients in the ipragliflozin group had lower FPG and less frequently used hypoglycaemic agents other than metformin than patients in the placebo group before the start of the study. The mean duration of exposure in treatment period 1 was shorter in the placebo group (147.3 ± 41.79 days; mean ± standard deviation) than in the ipragliflozin group (168.3 ± 7.12 days), reflecting the higher discontinuation rate in the placebo group. Of 96 patients in the ipragliflozin group who entered treatment period 2, 90 completed this period.

The changes in HbA1c from baseline to the end of treatment period 1 are presented in Table 2 and Figure S3A. HbA1c decreased in the ipragliflozin group by 0.87% but increased in the placebo group, resulting in a statistically significant adjusted mean difference of −1.30% (95% confidence interval: −1.501, −1.095) between the two groups. At the start of treatment, HbA1c was <8.0% in 32.1% (18/56) and 40.2% (45/112) of patients in the placebo and ipragliflozin groups, respectively; none of the patients in either group had an HbA1c of <7.0%. At week 24, 17.9% (10/56) and 86.6% (97/112) of patients in the placebo and ipragliflozin groups, respectively, achieved HbA1c <8.0%; and 0% (0/56) and 21.4% (24/112) of patients in the placebo and ipragliflozin groups, respectively, achieved HbA1c <7.0%.

The decreases in FPG, body weight, and waist circumference and the increase in plasma adiponectin levels from baseline to week 24 were significantly greater in the ipragliflozin group than in the placebo group (Table 2, Figure S3B, C). The reductions in FSI and leptin levels were not significantly different between the two groups (Table 2). The increase in high-density lipoprotein cholesterol levels was significantly greater in the ipragliflozin group than in the placebo group, but the changes in the other lipid levels were not significantly different between the two groups. Systolic blood pressure decreased slightly in the ipragliflozin group but it was not significantly different between the two groups.

There was no change in HOMA-β from baseline to week 24 in the ipragliflozin group but it decreased in the placebo group (Table 2); however, these results should be interpreted with caution and re-evaluated using other methods because HOMA-β is a function of FPG and fasting insulin levels. Efficacy outcomes in treatment period 2 are presented in the Supporting Information (Appendix S2 and Figure S4).

Table S1 shows all the treatment-emergent adverse events (TEAEs) occurring in ≥2% of patients in either group in treatment period 1. The TEAEs were distributed similarly in both groups. None of the patients died during the study. TEAEs leading to discontinuation were less frequent in the ipragliflozin group than in the placebo group. Two patients in each group experienced serious TEAEs (cataract and anal abscess in the placebo group, and worsening of diabetes and carpel tunnel syndrome in the ipragliflozin group).

The incidence rates of pollakiuria and constipation, events possibly related to osmotic diuresis, were higher in the ipragliflozin group than in the placebo group (5.4 vs. 1.8% and 4.5 vs. 1.8%, respectively). Cystitis was less frequent in the ipragliflozin group than in the placebo group and genital infection was not reported. There were no episodes suggestive of hypoglycaemia in either group. Safety outcomes in treatment period 2 are presented in the Supporting Information (Table S2). The total daily dose of metformin at screening did not influence the incidence of TEAEs in either treatment period (Tables S3 and S4).

Discussion

The present study showed that ipragliflozin significantly improved glycaemic control in terms of HbA1c and FPG at 24 weeks and its efficacy was maintained over 52 weeks. Patients treated with ipragliflozin also experienced reductions in body weight and waist circumference, as well as an increase in adiponectin levels. No hypoglycaemic events were reported. The overall incidence of TEAEs was not significantly different between the two groups; however, pollakiuria and constipation were more common in the ipragliflozin group than in the placebo group. The former was probably attributable to drug-induced osmotic diuresis.

Our results support those of Western studies showing the efficacy and safety of ipragliflozin in combination with metformin [7,8]. Likewise, the addition of dapagliflozin or canagliflozin to metformin was reported to reduce HbA1c and body weight without major adverse effects [9,10].

Limitations of the present study include the open-label, non-randomized design of treatment period 2, the increase in ipragliflozin dose in some patients in treatment period 2, and the limited generalization of the study population relative to Japanese patients with T2DM in actual clinical settings.

Table 2. Changes in efficacy outcomes from baseline to week 24 (treatment period 1).

A. Efficacy variables	Placebo (n = 56)			Ipragliflozin (n = 112)				
Variable	Baseline	Week 24 (LOCF)	Change from baseline	Baseline	Week 24 (LOCF)	Change from baseline	Adjusted mean difference (95% CI)*	p-value*
HbA1c, %	8.38 ± 0.738	8.76 ± 0.912	0.38 ± 0.703	8.25 ± 0.719	7.38 ± 0.712	−0.87 ± 0.655	−1.30 (−1.501, −1.095)	<0.001
FPG, mmol/l [mg/dl]	9.70 ± 1.380 [174.5 ± 24.84]	10.29 ± 1.801 [185.2 ± 32.42]	0.59 ± 1.526 [10.7 ± 27.46]	8.98 ± 1.663 [161.6 ± 29.93]	7.75 ± 1.298 [139.5 ± 23.36]	−1.23 ± 1.484 [−22.2 ± 26.72]	−2.19 (−2.609, −1.769) [−39.4 (−46.96, −31.85)]	<0.001
Body weight, kg	67.51 ± 11.365	66.88 ± 11.469	−0.63 ± 1.679	68.52 ± 13.864	66.20 ± 13.836	−2.33 ± 1.798	−1.69 (−2.256, −1.117)	<0.001
Waist circumference, cm	88.95 ± 7.176	88.48 ± 7.833	−0.48 ± 2.723	90.70 ± 10.736	88.20 ± 10.609	−2.39 ± 3.720	−1.83 (−2.927, −0.725)	0.001
FSI, μU/ml	6.71 ± 3.826	6.10 ± 3.268	−0.61 ± 2.478	7.91 ± 5.392	6.13 ± 3.862	−1.78 ± 3.301	−0.67 (−1.412, 0.071)	0.076
HOMA-R	2.88 ± 1.718	2.79 ± 1.552	−0.08 ± 1.137	3.16 ± 2.249	2.12 ± 1.421	−1.04 ± 1.686	−0.81 (−1.156, −0.460)	<0.001
HOMA-β	23.0 ± 13.97	19.2 ± 11.10	−3.8 ± 9.83	31.2 ± 22.97	31.2 ± 21.26	0.0 ± 12.21	5.8 (2.40, 9.20)	<0.001
Adiponectin, μg/ml	6.54 ± 3.075	7.28 ± 3.909	0.75 ± 1.971	5.95 ± 2.981	7.42 ± 3.443	1.47 ± 1.224	0.77 (0.287, 1.255)	0.002
Leptin, ng/ml	7.22 ± 4.285	6.83 ± 4.439	−0.39 ± 1.822	7.15 ± 4.723	6.40 ± 4.070	−0.74 ± 2.074	−0.37 (−0.961, 0.222)	0.220

B. Other variables	Placebo (n = 56)			Ipragliflozin (n = 112)			
Variable	Baseline	Week 24 (LOCF)	Change from baseline	Baseline	Week 24 (LOCF)	Change from baseline	p-value†
Triglycerides, mmol/l [mg/dl]	1.459 ± 0.6759 [129.3 ± 59.87]	1.324 ± 0.5944 [117.3 ± 52.64]	−0.135 ± 0.5369 [−12.0 ± 47.56]	1.868 ± 1.3485 [165.4 ± 119.44]	1.529 ± 1.3320 [135.4 ± 117.98]	−0.339 ± 1.1288 [−30.0 ± 99.99]	0.203
TC, mmol/l [mg/dl]	4.920 ± 0.7161 [190.3 ± 27.69]	5.155 ± 0.7008 [199.3 ± 27.10]	0.235 ± 0.5031 [9.1 ± 19.45]	4.786 ± 0.8660 [185.1 ± 33.49]	5.074 ± 0.9245 [196.2 ± 35.75]	0.288 ± 0.6571 [11.1 ± 25.41]	0.593
HDL-C, mmol/l [mg/dl]	1.485 ± 0.3437 [57.4 ± 13.29]	1.612 ± 0.4415 [62.3 ± 17.07]	0.127 ± 0.2289 [4.9 ± 8.85]	1.385 ± 0.3481 [53.6 ± 13.46]	1.613 ± 0.4004 [62.4 ± 15.48]	0.228 ± 0.2263 [8.8 ± 8.75]	0.007
LDL-C, mmol/l [mg/dl]	2.939 ± 0.6569 [113.6 ± 25.40]	3.110 ± 0.6295 [120.3 ± 24.34]	0.171 ± 0.440 [6.6 ± 17.17]	2.792 ± 0.8163 [108.0 ± 31.56]	2.970 ± 0.8767 [114.9 ± 33.90]	0.179 ± 0.5771 [6.9 ± 22.32]	0.933
SBP, mmHg	125.8 ± 16.11	128.2 ± 12.89	2.4 ± 13.70	126.3 ± 13.56	125.1 ± 13.65	−1.2 ± 11.70	0.074
DBP, mmHg	75.4 ± 8.35	76.2 ± 9.61	0.8 ± 8.25	75.7 ± 10.13	74.7 ± 10.82	−1.0 ± 9.08	0.206

Values are means ± standard deviation except for adjusted mean differences, which are presented with confidence intervals (CIs). HbA1c, glycated haemoglobin; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FSI, fasting serum insulin; HDL-C, high-density lipoprotein cholesterol; HOMA-R, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell function; LDL-C, low-density lipoprotein cholesterol; LOCF, last observation carried forward; SBP, systolic blood pressure; TC, total cholesterol.

*Analysed using ANCOVA with treatment group as a fixed effect and the baseline value as a covariate.

†The difference in change from baseline between the two groups was analysed using Student's *t*-test.

In conclusion, adding ipragliflozin to ongoing metformin therapy significantly improved glycaemic control and reduced body weight and waist circumference in Japanese patients with T2DM. Ipragliflozin also had a good safety profile.

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Conflict of Interest

A. K. contributed to study design, data analysis, and writing of the manuscript; K. K. contributed to study design, study conduct, data collection and analysis and writing of the manuscript; K. G. contributed to study design, study conduct, data collection and writing of the manuscript; S. Y. contributed to study design, data analysis and writing of the manuscript; E. U. contributed to data analysis and writing of the manuscript; A. U. contributed to study design, data analysis and writing of the manuscript. All authors read and approved the final draft of the manuscript. A. K. serves as a consultant for Astellas Pharma Inc., Japan. K. K., K. G., S. Y., E. U. and A. U. are employees of Astellas Pharma Inc., Japan.

Supporting Information

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

Figure S1. Study design.

Figure S2. Patient disposition.

Figure S3. Time-course of HbA1c (A), FPG (B), and change in BW (C) over 24 weeks.

Figure S4. Time-course of HbA1c over 52 weeks in patients treated with ipragliflozin in both treatment periods according to the ipragliflozin dose in treatment period 2.

Table S1. Treatment-emergent adverse events occurring during the first 24 weeks of the study (treatment period 1).

Table S2. Treatment-emergent adverse events occurring over 52 weeks of treatment with ipragliflozin (treatment periods 1 and 2).

Table S3. Incidence of treatment-emergent adverse events in treatment period 1 according to treatment group and the total daily dose of metformin at screening.

Table S4. Incidence of treatment-emergent adverse events in treatment periods 1 and 2 according to the total daily dose of metformin at screening.

Appendix S1. Supplementary methods (Patients, Study design and treatments, Efficacy and safety outcomes, and Statistical analysis) and references.

Appendix S2. Supplementary results (Efficacy outcomes at week 52 and Safety outcomes at week 52).

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