

ORIGINAL ARTICLE

Efficacy and safety of ipragliflozin as an add-on therapy to sitagliptin and metformin in Korean patients with inadequately controlled type 2 diabetes mellitus: A randomized controlled trial

Kyung-Ah Han¹ | Suk Chon² | Choon Hee Chung³ | Soo Lim⁴  | Kwan-Woo Lee⁵ | SeiHyun Baik⁶ | Chang Hee Jung⁷  | Dong-Sun Kim⁸ | Kyong Soo Park⁹ | Kun-Ho Yoon¹⁰ | In-Kyu Lee¹¹ | Bong-Soo Cha¹²  | Taishi Sakatani¹³ | Sumi Park¹⁴ | Moon-Kyu Lee¹⁵ 

¹Nowon Eulji Medical Center, Eulji University, Seoul, Korea

²Kyung Hee University Hospital, Seoul, Korea

³Yonsei University Wonju Severance Christian Hospital, Gangwon, Korea

⁴Seoul National University College of Medicine and Seoul National University Bundang Hospital, Seongnam, Korea

⁵Ajou University Hospital, Suwon-si, Korea

⁶Korea University Guro Hospital, Seoul, Korea

⁷Department of Endocrinology and Metabolism, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

⁸Department of Endocrinology and Metabolism, Hanyang University Hospital, Seoul, Korea

⁹Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea

¹⁰Department of Endocrinology and Metabolism, Seoul St. Mary's Hospital, Catholic University Medical College, Seoul, Korea

¹¹Department of Internal Medicine, Kyungpook National University Hospital, Daegu, Korea

¹²Department of Internal Medicine, Yonsei University Severance Hospital, Seoul, Korea

¹³Biostatistics Group, Japan-Asia Data Science, Development, Astellas Pharma Inc., Tokyo, Japan

¹⁴Clinical Research Team, Development Department, Astellas Pharma Korea, Inc., Seoul, Korea

¹⁵Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Correspondence

Moon-Kyu Lee, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea.
Email: leemk@skku.edu

Aim: To evaluate the efficacy and safety of ipragliflozin vs placebo as add-on therapy to metformin and sitagliptin in Korean patients with type 2 diabetes mellitus (T2DM).

Methods: This double-blind, placebo-controlled, multi-centre, phase III study was conducted in Korea in 2015 to 2017. Patients were randomized to receive either ipragliflozin 50 mg/day or placebo once daily for 24 weeks in addition to metformin and sitagliptin. The primary endpoint was the change in glycosylated haemoglobin (HbA1c) from baseline to end of treatment (EOT).

Results: In total, 143 patients were randomized and 139 were included in efficacy analyses (ipragliflozin: 73, placebo: 66). Baseline mean (SD) HbA1c levels were 7.90 (0.69)% for ipragliflozin add-on and 7.92 (0.79)% for placebo. The corresponding mean (SD) changes from baseline to EOT were -0.79 (0.59)% and 0.03 (0.84)%, respectively, in favour of ipragliflozin (adjusted mean difference -0.83% [95% CI -1.07 to -0.59]; $P < .0001$). More ipragliflozin-treated patients than placebo-treated patients achieved HbA1c target levels of $<7.0\%$ (44.4% vs 12.1%) and $<6.5\%$ (12.5% vs 1.5%) at EOT ($P < .05$ for both). Fasting plasma glucose, fasting serum insulin, body weight and homeostatic model assessment of insulin resistance decreased significantly at EOT, in favour of ipragliflozin (adjusted mean difference -1.64 mmol/L, -1.50 μ U/mL, -1.72 kg, and -0.99 , respectively; $P < .05$ for all). Adverse event rates were similar between groups (ipragliflozin: 51.4%; placebo: 50.0%). No previously unreported safety concerns were noted.

Conclusions: Ipragliflozin as add-on to metformin and sitagliptin significantly improved glycaemic variables and demonstrated a good safety profile in Korean patients with inadequately controlled T2DM.

KEYWORDS

DPP-4 inhibitor, ipragliflozin, Korean, randomized controlled trial, SGLT2 inhibitor, type 2 diabetes mellitus

Funding information

This study was funded by Astellas Pharma Korea, Inc. Medical writing and editorial support was funded by Astellas.

1 | INTRODUCTION

Diabetes presents a considerable burden to patients, their families, and public health systems worldwide. In 2015, the International Diabetes Federation (IDF) estimated there were 415 million cases of diabetes and an additional 318 million adults with impaired glucose tolerance worldwide.¹ In Korea, it was estimated that ~4.8 million people aged ≥ 30 years had type 2 diabetes mellitus (T2DM) in 2014,² almost doubling the observed incidence in 2013.³

In line with the IDF guidelines, the Korean Diabetes Association guidelines recommend managing T2DM with an initial therapy of metformin, in conjunction with lifestyle modification.^{4,5} Dual therapy may be considered if patients' initial glycated haemoglobin (HbA1c) level is $\geq 7.5\%$ or if the HbA1c target is not achieved within 3 months of initiating metformin monotherapy.^{4,5} If inadequate glycaemic control persists with dual therapy, a third agent with a complementary action may be added.⁵ Because increased insulin resistance and diminishing β -cell function tend to occur with T2DM progression, antidiabetic agents that target components of the glucose metabolism pathway may become less effective over time.⁶ Agents that work via alternative biological processes will ultimately be essential for chronic disease management. Sodium-glucose co-transporter-2 (SGLT2) inhibitors act via the kidney to inhibit SGLT2, and thereby suppress renal glucose uptake, resulting in urinary glucose excretion.⁷ The unique mechanism of SGLT2 inhibitors complements the actions of other antidiabetic agents to reduce hyperglycaemia, making them suitable for use as part of combination regimens in patients with T2DM, regardless of the degree of insulin resistance and β -cell dysfunction.⁸

There is considerable interest in the combined use of SGLT2 inhibitors with dipeptidyl peptidase-4 (DPP-4) inhibitors for effective glycaemic control without an increased potential for hypoglycaemia, weight gain or cardiovascular diseases.^{8,9} Randomized studies have demonstrated the efficacy and safety of triple therapy using a SGLT2 inhibitor, a DPP-4 inhibitor, and metformin in patients who have inadequately controlled T2DM.^{10,11} Ipragliflozin has been shown to be efficacious and well tolerated both as a monotherapy^{12,13} and in dual therapy with metformin or DPP-4 inhibitors^{14–18}; however, no study has investigated the effects of ipragliflozin added to metformin and a DPP-4 inhibitor. In the present paper, we report the findings from a phase III, randomized, placebo-controlled study, which compared the efficacy and safety of ipragliflozin against placebo as an add-on therapy to metformin and sitagliptin in Korean patients with inadequately controlled T2DM.

2 | METHODS

2.1 | Study design

This was a double-blind, randomized, parallel-group, placebo-controlled, multi-centre, phase III study conducted at 22 sites in Korea

between 2015 and 2017 (ClinicalTrials.gov identifier: NCT02452632). The study comprised a 2-week single-blind placebo run-in period, followed by a 24-week double-blind treatment period, and a 4-week follow-up period. The study protocol and other relevant study documents were reviewed and approved by the institutional review board at each study site. The study was conducted in compliance with the principles of the Declaration of Helsinki, the International Conference on Harmonization Harmonized Tripartite Guideline for Good Clinical Practice, and the applicable local laws and regulations. All patients provided written informed consent prior to study enrolment.

2.2 | Study population

Inclusion criteria included: age 19 to 74 years (inclusive); confirmed T2DM diagnosis; stable diet and exercise programme ≥ 8 weeks prior to study participation; treatment with metformin at ≥ 1500 mg/day (or ≥ 1000 mg/day at the investigator's discretion) and sitagliptin at 100 mg/day for at least 8 weeks prior to study participation; HbA1c 7.0% to 10.5% (inclusive); and body mass index (BMI) 20.0 to 45.0 kg/m² (inclusive). Key exclusion criteria included: diagnosis of type 1 diabetes mellitus; proliferative diabetic retinopathy; renal disease, such as renovascular occlusive disease, nephrectomy, or renal transplant; and pregnancy or breastfeeding. Women of childbearing potential who were unwilling to use appropriate contraception during the study were also excluded.

2.3 | Treatments

Eligible patients were randomly assigned to receive ipragliflozin (50 mg/day) or placebo as an add-on therapy to metformin and sitagliptin. Randomization was stratified by study site and HbA1c level ($\geq 8.0\%$ or $< 8.0\%$) using a computer-generated randomization schedule. Assignment of study medications was blinded to all patients, investigators and the sponsor. To maintain blinding, the packaging and appearance of medications used in this study were identical and no urinary glucose measurements were permitted during the study, unless deemed necessary for safety reasons.

Patients whose fasting plasma glucose (FPG) levels were > 14.99 mmol/L between weeks 0 and 4, > 13.32 mmol/L between weeks 4 and 12, or > 11.10 mmol/L between weeks 12 and 24, or whose HbA1c levels were $> 8.0\%$ between weeks 12 and 24, received rescue therapy with glimepiride at the investigator's discretion. Apart from ipragliflozin, sitagliptin, metformin and rescue medication, other medications that may have an influence on blood glucose levels were prohibited during the study. The use of weight-reducing medications and continuous systemic administration of corticosteroids or immunosuppressants was also prohibited.

2.4 | Study endpoints

The primary efficacy endpoint was the change in HbA1c from baseline to end of treatment (EOT). Secondary efficacy endpoints included changes in FPG, body weight, fasting serum insulin (FSI), and waist

circumference from baseline to EOT, and the percentage of patients achieving the HbA1c targets (<6.5% and <7.0%) at EOT. Exploratory endpoints were changes in homeostatic model assessment of insulin resistance (HOMA-IR) and β -cell function (HOMA- β) from baseline to EOT. Key safety endpoints included the incidence of treatment-emergent adverse events (TEAEs) and TEAEs leading to discontinuation and changes in vital signs and clinical laboratory variables from baseline to EOT. TEAEs were defined as adverse events (AEs) that were observed after the first administration of the study medication for the treatment period.

2.5 | Statistical analyses

The sample size was calculated based on results from three previous studies: (1) dapagliflozin add-on to sitagliptin and metformin¹⁹; (2) dapagliflozin add-on to metformin²⁰; and (3) ipragliflozin add-on to metformin.¹⁵ Assuming the difference for changes in HbA1c from baseline to EOT between the ipragliflozin and placebo groups would be -0.45% with an SD of 0.80, approximately 67 patients per treatment group

would be required to detect superiority of ipragliflozin to placebo with 90% power and a significance level of 5% for a two-sided test. Assuming 5% of patients do not meet the criteria for the full analysis set (FAS), ~140 randomized patients would be required for this study.

The FAS consisted of randomized patients who received at least one dose of the study medication, and had at least one post-baseline measurement. The per-protocol set (PPS) was a subgroup of the FAS and consisted of eligible patients who received the study medication for the entire treatment period, received metformin and sitagliptin for ≥ 56 days, had a compliance rate with the study medication of $\geq 80\%$, did not use prohibited concomitant medications, and did not have any clinically significant protocol deviations. The safety analysis set (SAF) consisted of all patients who received at least one dose of the study medication during the treatment period.

Efficacy analyses were performed on the FAS population. Sensitivity analyses for HbA1c and FPG were repeated on the PPS population. Safety analyses were performed on the SAF. The mean differences in efficacy endpoints between the ipragliflozin and

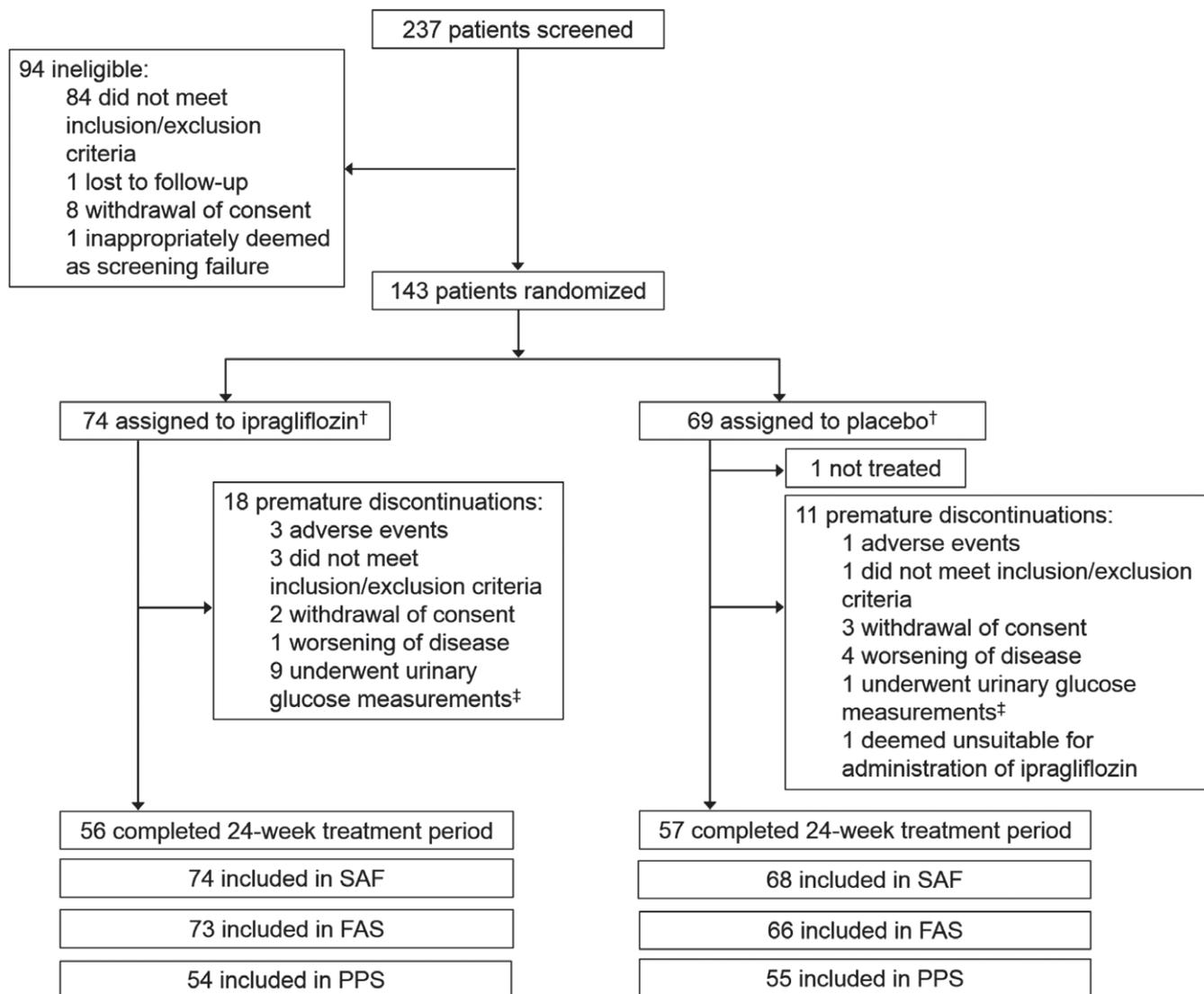


FIGURE 1 Patient disposition during the study period. †In combination with metformin ≥ 1500 mg/day (or ≥ 1000 mg/day at physician's discretion) and sitagliptin 100 mg/day. FAS, full analysis set; PPS, per protocol set; SAF, safety analysis set. ‡No urinary glucose measurements were permitted during the study

placebo groups were calculated using analysis of covariance (ANCOVA), with the respective baseline value as a covariate and treatment group as a fixed effect. Demographics, baseline characteristics and safety endpoints were summarized according to treatment group using descriptive statistics. Missing values at EOT were imputed using the last observation carried forward method. Efficacy data obtained after initiation of rescue therapy were excluded from the analysis. HOMA-IR and HOMA- β were calculated using the following formulas: HOMA-IR = [FSI (μ U/mL) \times FPG (mg/dL)]/405; HOMA- β = [360 \times FSI (μ U/mL)]/[FPG (mg/dL) - 63]. SAS Version 9.3 (SAS Institute Inc., Cary, North Carolina) was used for all statistical analyses and a *P* value <.05 was taken to indicate statistical significance.

3 | RESULTS

3.1 | Patient demographics and baseline characteristics

A total of 237 patients entered the study. Of these, 143 patients were randomized to receive ipragliflozin (*n* = 74) or placebo (*n* = 69). After randomization, 30 patients discontinued from the study and 113 patients (ipragliflozin: 56; placebo: 57) completed the 24-week treatment. The flow of patients through the study and reasons for discontinuation are summarized in Figure 1. The most commonly

TABLE 1 Patient demographics and baseline characteristics (full analysis set)

	Ipragliflozin (<i>n</i> = 73)	Placebo (<i>n</i> = 66)
Gender		
Men	37 (50.7)	32 (48.5)
Women	36 (49.3)	34 (51.5)
Age, years	57.62 (8.26)	57.44 (7.88)
BMI, kg/m ²	25.50 (3.07)	26.05 (3.79)
BMI \geq 25 kg/m ²	38 (52.1)	37 (56.1)
Body weight, kg	67.50 (12.50)	67.90 (10.98)
Waist circumference, cm	88.74 (8.10)	89.83 (9.08)
Duration of T2DM, months	139.41 (70.73)	135.98 (79.55)
Treatment with antidiabetic agents other than metformin and sitagliptin \leq 12 weeks prior to placebo run-in	17 (23.3)	12 (18.2)
HbA1c, %	7.90 (0.69)	7.92 (0.79)
FPG, mmol/L	8.77 (1.64)	8.85 (1.84)
FSI, μ U/mL	7.82 (4.96)	8.49 (5.50)
eGFR at start of treatment, mL/min/1.73 m ²	89.38 (13.61)	90.66 (17.47)
eGFR at start of treatment <90 mL/min/1.73 m ²	32 (45.1)	34 (51.5)

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; FSI, fasting serum insulin; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; T2DM, type 2 diabetes mellitus. Data are presented as *n* (%) or mean (SD). Percentages were calculated based on the number of patients with available data.

reported reason for discontinuation in the ipragliflozin group was urinary glucose measurements (*n* = 9), whereas worsening of disease (*n* = 4) and consent withdrawal (*n* = 3) were the most common reasons in the placebo group. There were 142 patients (ipragliflozin: 74; placebo: 68) in the SAF, 139 patients (ipragliflozin: 73; placebo: 66) in the FAS, and 109 patients (ipragliflozin: 54; placebo: 55) in the PPS.

Patient demographics and baseline characteristics were consistent across treatment groups (Table 1). The mean (SD) duration of exposure to the study medication was 146.58 (47.27) and 153.12 (42.21) days in the ipragliflozin and placebo groups, respectively. The mean (SD) compliance rates with the study medications were 96.89 (3.72)% and 96.84 (8.62)% in the ipragliflozin and placebo groups, respectively. One patient (1.4%) and 17 patients (25.8%) in the ipragliflozin and placebo groups, respectively, received rescue therapy with glimepiride during the treatment period.

3.2 | Efficacy

3.2.1 | Primary efficacy outcome

Figure 2A shows the change in mean HbA1c levels during treatment in both groups. HbA1c decreased significantly from baseline to the EOT in the ipragliflozin group compared with the placebo group. The mean (SD) HbA1c levels at baseline were 7.90 (0.69)% in the ipragliflozin group and 7.92 (0.79)% in the placebo group. The corresponding mean (SD) changes in HbA1c levels from baseline to EOT were -0.79% (0.59) and 0.03% (0.84), respectively, with an adjusted mean difference of -0.83% (95% CI -1.07, -0.59; *P* < .0001). In the subgroup analyses by gender, age, baseline HbA1c, and eGFR, HbA1c reductions from baseline to EOT remained significantly greater with ipragliflozin than placebo (Table S1). Significantly more patients in the ipragliflozin group had HbA1c <7.0% at EOT compared with placebo (44.4%; 32/72 vs 12.1%; 8/66; *P* < .0001). Similarly, a significantly higher proportion of patients in the ipragliflozin group had HbA1c <6.5% at EOT than the placebo group (12.5%; 9/72 vs 1.5%; 1/66; *P* = .0183). The results for HbA1c in the PPS population were similar to those in the FAS population (data not presented).

3.2.2 | Secondary efficacy outcomes

Figure 2B shows the change in mean FPG levels during treatment in both groups. FPG decreased significantly from baseline to EOT in the ipragliflozin group compared with placebo. The corresponding mean (SD) changes were -1.20 (1.76) mmol/L and 0.42 (1.78) mmol/L, respectively, with an adjusted mean difference of -1.64 mmol/L (95% CI -2.18, -1.10; *P* < .0001). The results for FPG in the PPS population were similar to those in the FAS population (data not presented).

Body weight decreased significantly from baseline to EOT in the ipragliflozin group compared with placebo. The corresponding mean (SD) changes were -1.96 (1.94) kg and -0.23 (1.69) kg, respectively, with an adjusted mean difference of -1.72 kg (95% CI -2.34, -1.10; *P* < .0001). More patients in the ipragliflozin group had a body weight reduction of \geq 5% at EOT than in the placebo group (19.7%; 14/71 vs 4.6%; 3/66). Similarly, waist circumference decreased significantly from baseline to EOT in the ipragliflozin group compared with placebo. The corresponding mean (SD) changes were -1.93 (3.26) cm

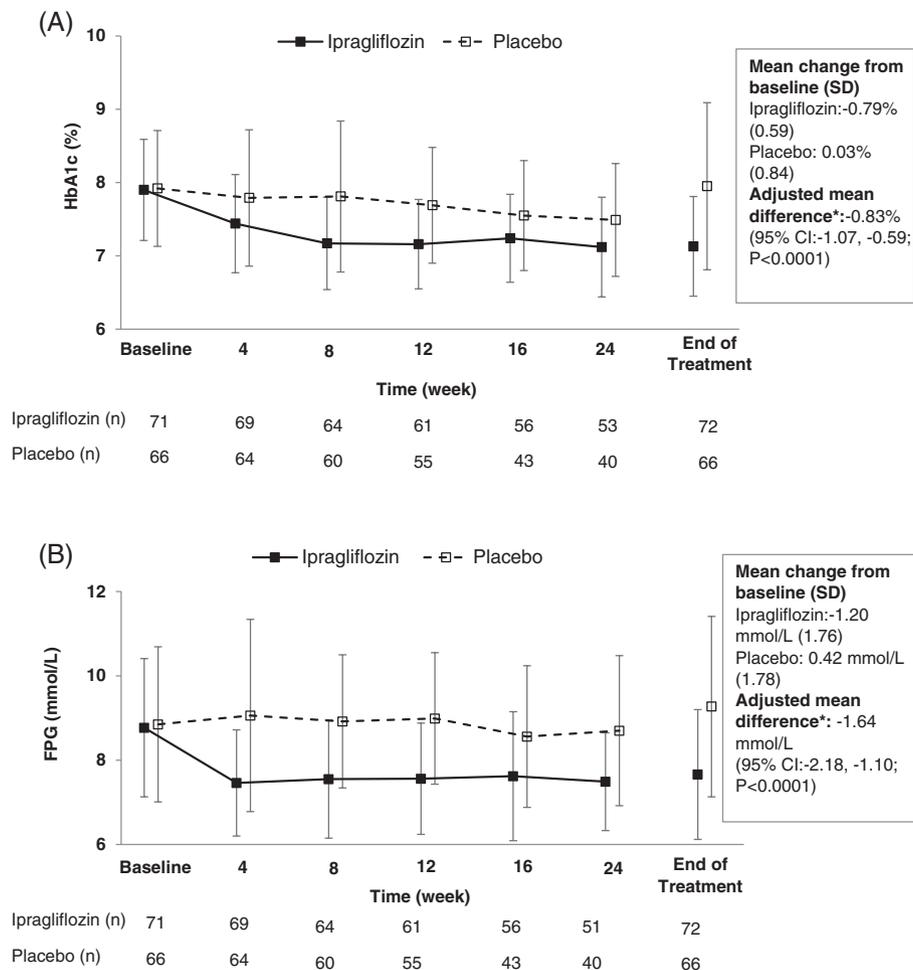


FIGURE 2 Time courses of A, glycated haemoglobin (HbA1c), and B, fasting plasma glucose (FPG) measurements. [†]Analysis of covariance (ANCOVA) including baseline value as a covariate, and treatment group as fixed effect

and -0.64 (3.80) cm, respectively, with an adjusted mean difference of -1.44 cm (95% CI $-2.78, -0.10$; $P = .0354$).

In the ipragliflozin group FSI decreased significantly from baseline to EOT compared with the placebo group. The corresponding mean (SD) changes were -1.14 (4.62) $\mu\text{U/mL}$ and 0.08 (4.18) $\mu\text{U/mL}$, respectively, with an adjusted mean difference of -1.50 $\mu\text{U/mL}$ (95% CI $-2.93, -0.07$; $P = .0404$). HOMA-IR decreased significantly from baseline to EOT in the ipragliflozin group compared with placebo. The corresponding mean (SD) changes were -0.63 (2.28) and 0.30 (1.95), respectively, with an adjusted mean difference of -0.99 (95% CI $-1.73, -0.25$; $P = .0092$). HOMA- β tended to increase from baseline to EOT in the ipragliflozin group (mean [SD] change 0.46 [31.48]) compared with placebo (mean [SD] change -2.54 [20.54]); however, the adjusted mean difference between groups was not statistically significant (1.47 [95% CI $-6.03, 8.98$]; $P = .6981$).

3.3 | Safety

A summary of TEAEs is provided in Table 2. The incidence of TEAEs and drug-related TEAEs was similar across groups. The majority of the TEAEs were mild or moderate in severity. No deaths were reported in this study. The incidence of TEAEs leading to permanent discontinuation was low in both groups (6.8% in the ipragliflozin group and 2.9%

in the placebo group). The most common TEAEs were nasopharyngitis and urticaria (4.1% each) in the ipragliflozin group and nasopharyngitis (7.4%) in the placebo group. There were no reports of hypoglycaemia, genital infection, volume depletion, and ketoacidosis in the ipragliflozin group. Incidences of urinary tract infection and polyuria/pollakiuria were low in both groups (ipragliflozin: 2.7% and 1.4%, respectively vs placebo: 1.5% for both). Table 3 shows the changes in clinical and laboratory variables from baseline to EOT in both groups. No clinically significant changes in renal function, haematology, and fluid and electrolyte balance variables were observed in either group. There was a trend towards slight improvements in blood pressure (BP) [systolic BP (SBP) -2.35 (10.47) mm Hg; diastolic BP (DBP) -1.49 (6.28) mm Hg], triglyceride (TG) levels [-33.21 (134.85) mg/dL], and HDL cholesterol levels [3.53 (8.04) mg/dL] at the EOT in the ipragliflozin group compared with the placebo group [SBP -1.14 (9.76) mm Hg; DBP -0.17 (5.53) mm Hg; TG levels 8.94 (85.65) mg/dL; HDL cholesterol 0.36 (5.90) mg/dL].

4 | DISCUSSION

In this study of Korean patients with T2DM inadequately controlled by metformin and sitagliptin, the addition of ipragliflozin significantly

TABLE 2 Overall summary of treatment-emergent adverse events (TEAEs) and selected TEAEs of interest (safety analysis set)

	Ipragliflozin (n = 74) n (%)	Placebo (n = 68) n (%)
TEAEs	38 (51.4)	34 (50.0)
TEAEs by severity		
Mild	27 (36.5)	23 (33.8)
Moderate	10 (13.5)	8 (11.8)
Severe	1 (1.4)	3 (4.4)
Serious TEAEs	7 (9.5)	4 (5.9)
Drug-related TEAEs	9 (12.2)	9 (13.2)
TEAEs leading to permanent discontinuation	5 (6.8)	2 (2.9)
Drug-related TEAEs leading to permanent discontinuation	4 (5.4)	1 (1.5)
TEAEs in ≥3.0% of patients in either treatment group		
Nasopharyngitis	3 (4.1)	5 (7.4)
Urticaria	3 (4.1)	2 (2.9)
Gastritis	1 (1.4)	3 (4.4)
ALT increased ^a	0 (0.0)	3 (4.4)
AST increased ^a	0 (0.0)	3 (4.4)
TEAEs of special interest		
Hypoglycaemia	0 (0.0)	1 (1.5)
Genital infection	0 (0.0)	0 (0.0)
Volume depletion-related event	0 (0.0)	0 (0.0)
Effects of ketoacidosis/increased ketone bodies	0 (0.0)	0 (0.0)
Polyuria/pollakiuria	1 (1.4)	1 (1.5)
Urinary tract infections	2 (2.7)	1 (1.5)

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; SAF, safety analysis set

^a Based on the investigator's judgment.

improved glycaemic variables after 24 weeks of treatment, compared with placebo. Improvements in body weight and insulin resistance and potential benefits on β -cell function and BP, TG levels, and HDL levels were also observed with ipragliflozin add-on therapy. Ipragliflozin add-on to dual therapy demonstrated a good safety and tolerability profile, with no previously unreported safety concerns observed.

We demonstrate that triple therapy with ipragliflozin add-on to metformin and sitagliptin significantly reduced HbA1c, FPG and body weight from baseline in patients with inadequately controlled T2DM (mean baseline HbA1c 7.90%). Significantly more patients reached HbA1c target at EOT with the addition of ipragliflozin compared with added placebo. Our results are in line with the results of recent randomized studies that examined the effects of SGLT2 inhibitors as add-on to metformin and a DPP-4 inhibitor. These studies demonstrated favourable decreases in glycaemic variables and body weight following the addition of an SGLT2 inhibitor.^{10,11} In a randomized phase III study of patients with T2DM whose condition was inadequately controlled by metformin plus saxagliptin, addition of 10 mg/day dapagliflozin significantly reduced HbA1c levels, FPG levels, and body weight compared with placebo. Dapagliflozin add-on also led to significantly more patients achieving HbA1c target than placebo.¹⁰ Similarly, in another randomized phase III study of patients

TABLE 3 Vital signs, clinical and laboratory parameters (safety analysis set)

	Ipragliflozin (n = 74)	Placebo (n = 68)
Systolic blood pressure, mm Hg	-2.35 (10.47)	-1.14 (9.76)
Diastolic blood pressure, mm Hg	-1.49 (6.28)	-0.17 (5.53)
Pulse rate, min	1.33 (8.55)	0.82 (6.92)
Total cholesterol, mg/dL	4.06 (23.15)	5.47 (20.20)
HDL cholesterol, mg/dL	3.53 (8.04)	0.36 (5.90)
LDL cholesterol, mg/dL	4.63 (20.09)	5.09 (17.77)
TG, mg/dL	-33.21 (134.85)	8.94 (85.65)
Haematology		
RBC $\times 10^6/\mu\text{L}$	0.27 (0.30)	0.05 (0.24)
Haemoglobin, g/dL	0.69 (0.81)	0.11 (0.62)
Haematocrit, %	2.39 (2.59)	0.40 (2.32)
Renal function		
BUN, mg/dL	1.86 (4.44)	0.18 (3.60)
Serum creatinine, mg/dL	0.00 (0.08)	-0.00 (0.08)
BUN/creatinine ratio	2.39 (5.85)	0.53 (4.93)
eGFR, mL/min/1.73 m ²	-0.17 (10.54)	0.98 (10.76)
Liver function		
AST, U/L	-1.83 (10.42)	1.80 (11.38)
ALT, U/L	-3.37 (12.30)	0.50 (14.92)
LDH, U/L	6.40 (56.80)	-3.62 (56.56)
ALP, U/L	0.37 (12.59)	-2.56 (9.16)
γ -GTP, U/L	-10.69 (24.82)	2.00 (22.99)
Total bilirubin, mg/dL	0.02 (0.24)	-0.03 (0.16)
Direct bilirubin, mg/dL	-0.00 (0.11)	-0.03 (0.11)
Fluid and electrolyte balance		
Na, mmol/L	-0.29 (2.81)	-0.62 (2.93)
K, mmol/L	0.04 (0.41)	-0.04 (0.44)
Cl, mmol/L	0.36 (2.97)	-0.15 (2.32)
Ca, mg/dL	0.04 (0.48)	-0.12 (0.39)
Mg, mg/dL	0.15 (0.21)	0.02 (0.12)
P, mg/dL	0.19 (0.52)	0.03 (0.55)
Urine pH	-0.24 (1.06)	-0.02 (0.94)
Urine osmotic pressure, mOsm/kgH ₂ O	101.30 (194.77)	4.64 (186.16)
Urine Na/creatinine ratio, mEq/g creatinine	-423.46 (6241.41)	922.60 (6180.34)
Urine K/creatinine ratio, mEq/g creatinine	391.22 (3290.36)	36.23 (2014.26)
Urine cl/creatinine ratio, mEq/g creatinine	-866.53 (7163.10)	1116.68 (6683.04)
Urine ca/creatinine ratio, mg/g creatinine	1620.40 (6737.78)	926.30 (6567.32)
Urine mg/creatinine ratio, mg/g creatinine	1776.00 (2187.29)	573.20 (2608.45)
Urine P/creatinine ratio, mg/g creatinine	14 339.22 (22 106.34)	608.92 (17 746.19)

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; Cre, creatinine; eGFR, estimated glomerular filtration rate; γ -GTP, γ -glutamyl transpeptidase; HDL, high density lipoprotein; LDH, lactate dehydrogenase; LDL, low density lipoprotein; RBC, red blood cells; TG, triglycerides. Mean (SD) changes from baseline to end of treatment.

inadequately controlled by metformin and linagliptin, addition of 10 mg/day empagliflozin significantly reduced HbA1c, FPG and body weight compared with placebo at the end of the 24-week treatment.¹¹ These findings provide evidence for the benefits of using SGLT2 inhibitors as an add-on in triple oral therapy to improve glycaemic control in patients inadequately controlled by metformin and DPP-4 inhibitors, with the added advantage of body weight reduction.

In the present study, we observed significant reduction in insulin resistance (HOMA-IR) and a trend towards improved β -cell function (HOMA- β) with ipragliflozin add-on therapy compared with placebo after 24 weeks of treatment. Previous studies of ipragliflozin monotherapy and ipragliflozin add-on to metformin have shown improvements in insulin resistance and β -cell function at the EOT.^{14,21} In a study in which patients were treated with ipragliflozin monotherapy, significant reductions in HOMA-IR levels and significant increases in HOMA- β levels from baseline were observed at the end of the 12-week treatment.²¹ In another study in patients whose T2DM was inadequately controlled by metformin, addition of ipragliflozin resulted in significant decrease in HOMA-IR levels compared with placebo after 24 weeks of treatment.¹⁴ Other studies of SGLT2 inhibitors also reported a significant decrease in insulin resistance and a significant increase in β -cell function at the EOT.^{22,23} Taken together, these findings suggest that the glucose-lowering effects of ipragliflozin, as for other SGLT2 inhibitors, can indirectly improve insulin sensitivity and β -cell function. Considering that insulin sensitivity and β -cell function tend to deteriorate as diabetes progresses, SGLT2 inhibitors may provide a valuable treatment option, especially in patients with longstanding T2DM.

Previous randomized studies of SGLT2 inhibitors as add-on to metformin and DPP-4 inhibitors have demonstrated improvements in BP after treatment.^{10,11} Recent studies of ipragliflozin add-on to metformin have demonstrated favourable changes in BP, TG levels, and HDL levels at EOT.^{15,16} Consistent with the findings of these studies, the present study showed slight improvements in BP, and TG and HDL levels with the addition of ipragliflozin. These findings demonstrate the potential of ipragliflozin to improve BP and lipid variables in addition to glycaemic variables in patients with T2DM.

The addition of SGLT2 inhibitors to dual oral therapy has been reported to be well tolerated in patients with inadequate glycaemic control after treatment with metformin and DPP-4 inhibitors.^{10,11} The overall incidence of AEs and the incidence of discontinuations because of AEs were similar between the SGLT2 inhibitor add-on group and the placebo group. Hypoglycaemia was infrequent in both groups.^{10,11} In line with the results of these randomized studies, the present study showed that the addition of ipragliflozin to metformin and sitagliptin was well tolerated, with no previously unreported safety concerns identified and no increased risk of hypoglycaemia compared with placebo. Recent evidence suggested the potential risk of developing diabetic ketoacidosis with SGLT2 inhibitors;^{24,25} however, no incidence of ketoacidosis was observed in our study.

A limitation of the present study was the relatively short study duration, which precluded assessment of the longer-term efficacy and safety of ipragliflozin add-on therapy in this population. The sample size used in our study was also relatively small. Although triple therapy with an SGLT2 inhibitor added on to metformin plus a DPP-4 inhibitor has been reported in previous studies, this is nevertheless the first

study to investigate the effects of ipragliflozin added to metformin and a DPP-4 inhibitor, and it provides important insights into the additional beneficial effects of ipragliflozin as an add-on to metformin and sitagliptin in Korean patients. Future research may focus on defining the long-term outcomes and safety profile of ipragliflozin add-on therapy in a broader patient population, alongside other SGLT2 inhibitors.

In conclusion, the addition of ipragliflozin to metformin and sitagliptin therapy in Korean patients with inadequately controlled T2DM resulted in significant improvements in glycaemic control compared with placebo. The improvement was associated with significant decreases in body weight and insulin resistance, with no observed or tolerability concerns compared with placebo. Ipragliflozin add-on therapy represents a valuable treatment option for patients failing on dual therapy with metformin and sitagliptin, particularly those who have concerns about weight gain or hypoglycaemia.

ACKNOWLEDGMENTS

T.S is an employee of Astellas Pharma Inc. and S.P is an employee of Astellas Pharma Korea, Inc. All other authors received funding support from Astellas Pharma Inc. to conduct this study. This study was funded by Astellas Pharma Korea, Inc. Medical writing and editorial support was funded by Astellas and provided by Wei Yi Kwok and Hui Hwa Choo from Tech Observer Asia Pacific Pte. Ltd.

ORCID

Soo Lim  <http://orcid.org/0000-0002-4137-1671>

Chang Hee Jung  <http://orcid.org/0000-0003-4043-2396>

Bong-Soo Cha  <http://orcid.org/0000-0003-0542-2854>

Moon-Kyu Lee  <http://orcid.org/0000-0002-8728-7184>

REFERENCES

1. International Diabetes Federation. *IDF Diabetes Atlas 7th edition*. 2015.
2. Korean Diabetes Association. *Diabetes Fact Sheet in Korea*. 2016.
3. Korean Diabetes Association. *Diabetes Fact Sheet*. 2015.
4. International Diabetes Federation. Recommendations for managing type 2 diabetes in primary care. 2017. www.idf.org/managing-type2-diabetes. Accessed October 2, 2017.
5. Ko SH, Hur KY, Rhee SY, et al. Antihyperglycemic agent therapy for adult patients with type 2 diabetes mellitus 2017: a position statement of the Korean Diabetes Association. *Diabetes Metab J*. 2017;41:337-348.
6. Freeman JS. Review of insulin-dependent and insulin-independent agents for treating patients with type 2 diabetes mellitus and potential role for sodium-glucose co-transporter 2 inhibitors. *Postgrad Med*. 2013;125:214-226.
7. Chao EC, Henry RR. SGLT2 inhibition—a novel strategy for diabetes treatment. *Nat Rev Drug Discov*. 2010;9:551-559.
8. Dey J. SGLT2 inhibitor/DPP-4 inhibitor combination therapy - complementary mechanisms of action for management of type 2 diabetes mellitus. *Postgrad Med*. 2017;129:409-420.
9. Scheen AJ. DPP-4 inhibitor plus SGLT-2 inhibitor as combination therapy for type 2 diabetes: from rationale to clinical aspects. *Expert Opin Drug Metab Toxicol*. 2016;12:1407-1417.
10. Mathieu C, Ranetti AE, Li D, et al. Randomized, double-blind, phase 3 trial of triple therapy with dapagliflozin add-on to saxagliptin plus metformin in type 2 diabetes. *Diabetes Care*. 2015;38:2009-2017.
11. Softeland E, Meier JJ, Vangen B, Toorawa R, Maldonado-Lutmirsky M, Broedl UC. Empagliflozin as add-on therapy in patients with type 2 diabetes inadequately controlled with linagliptin and

- metformin: a 24-week randomized, double-blind, parallel-group trial. *Diabetes Care*. 2017;40:201-209.
12. Kutoh E, Wada A, Murayama T, Hirate M. Ipragliflozin as an initial therapy in drug naive subjects with type 2 diabetes. *Drug Res (Stuttg)*. 2016;66:345-350.
 13. Schwartz SL, Akinlade B, Klasen S, Kowalski D, Zhang W, Wilpshaar W. Safety, pharmacokinetic, and pharmacodynamic profiles of ipragliflozin (ASP1941), a novel and selective inhibitor of sodium-dependent glucose co-transporter 2, in patients with type 2 diabetes mellitus. *Diabetes Technol Ther*. 2011;13:1219-1227.
 14. Kashiwagi A, Kazuta K, Goto K, Yoshida S, Ueyama E, Utsuno A. Ipragliflozin in combination with metformin for the treatment of Japanese patients with type 2 diabetes: ILLUMINATE, a randomized, double-blind, placebo-controlled study. *Diabetes Obes Metab*. 2015;17:304-308.
 15. Lu CH, Min KW, Chuang LM, Kokubo S, Yoshida S, Cha BS. Efficacy, safety, and tolerability of ipragliflozin in Asian patients with type 2 diabetes mellitus and inadequate glycemic control with metformin: results of a phase 3 randomized, placebo-controlled, double-blind, multicenter trial. *J Diabetes Investig*. 2016;7:366-373.
 16. Min KW, Ku BJ, Lee JH, et al. Addition of ipragliflozin to metformin treatment in Korean patients with type 2 diabetes mellitus: subgroup analysis of a phase 3 trial. *Diabetes Metab J*. 2017;41:135-145.
 17. Wilding JP, Ferrannini E, Fonseca VA, Wilpshaar W, Dhanjal P, Houzer A. Efficacy and safety of ipragliflozin in patients with type 2 diabetes inadequately controlled on metformin: a dose-finding study. *Diabetes Obes Metab*. 2013;15:403-409.
 18. Kashiwagi A, Isaka H, Kawano H, Kazuta K, Utsuno A, Yoshida S. Long-term safety, tolerability and efficacy of ipragliflozin in combination with a dipeptidyl peptidase-4 inhibitor in Japanese patients with type 2 diabetes mellitus inadequately controlled with a dipeptidyl peptidase-4 inhibitor alone - DAYLIGHT study. *Jpn Pharmacol Ther*. 2014;42:941-957.
 19. Jabbour SA, Hardy E, Sugg J, Parikh S, Study G. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled study. *Diabetes Care*. 2014;37:740-750.
 20. Bailey CJ, Gross JL, Pieters A, Bastien A, List JF. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2010;375:2223-2233.
 21. Kutoh E, Murayama T, Wada A, Hirate M. Distinct glucose-lowering mechanisms of ipragliflozin depending on body weight changes. *Drugs R D*. 2016;16:369-376.
 22. Ji L, Ma J, Li H, et al. Dapagliflozin as monotherapy in drug-naive Asian patients with type 2 diabetes mellitus: a randomized, blinded, prospective phase III study. *Clin Ther*. 2014;36:84-100.e109.
 23. Yang W, Han P, Min KW, et al. Efficacy and safety of dapagliflozin in Asian patients with type 2 diabetes after metformin failure: a randomized controlled trial. *J Diabetes*. 2016;8:796-808.
 24. Fralick M, Schneeweiss S, Paterno E. Risk of diabetic ketoacidosis after initiation of an SGLT2 inhibitor. *N Engl J Med*. 2017;376:2300-2302.
 25. Peters AL, Buschur EO, Buse JB, Cohan P, Diner JC, Hirsch IB. Euglycemic diabetic ketoacidosis: a potential complication of treatment with sodium-glucose cotransporter 2 inhibition. *Diabetes Care*. 2015;38:1687-1693.

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: Han K-A, Chon S, Chung CH, et al. Efficacy and safety of ipragliflozin as an add-on therapy to sitagliptin and metformin in Korean patients with inadequately controlled type 2 diabetes mellitus: A randomized controlled trial. *Diabetes Obes Metab*. 2018;20:2408–2415. <https://doi.org/10.1111/dom.13394>