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Efficacy and safety of pioglitazone versus dapagliflozin as an add-on to metformin and alogliptin combination therapy: the EPIDOTE study

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We investigated the efficacy and safety of pioglitazone compared to dapagliflozin when added to metformin plus alogliptin for patients with type 2 diabetes. The patients (n = 133) were randomized to receive pioglitazone (n = 65) or dapagliflozin (n = 68) in addition to metformin and alogliptin therapy for 26 weeks. The primary endpoint was a change in HbA1c. The non-inferiority margin for HbA1c reduction was 0.4%. The adjusted mean change of HbA1c at week 26 was − 0.75% with pioglitazone and − 0.88% with dapagliflozin (mean difference: 0.12% [95% CI − 0.09 to 0.34]). The adjusted mean change of HOMA-IR at week 26 was − 1.55 with pioglitazone and − 1.96 with dapagliflozin (mean difference: 0.41 [95% CI − 0.01 to 0.83]). Lipid profiles were similar between the groups. The proportion of patients achieving HbA1c < 6.5% was similar between groups. Pioglitazone added to metformin and alogliptin significantly improved glycemic control in patients with type 2 diabetes, and was non-inferior to dapagliflozin. This study suggests that pioglitazone could be an effective and safe option for patients with inadequate glycemic control on metformin and DPP4i.

Keywords Dipeptidyl-peptidase IV inhibitors, Drug therapy, Combination, Sodium-glucose transporter 2 inhibitors, Thiazolidinediones

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Type 2 diabetes is a chronic and progressive metabolic disorder which affects more than 530 million people worldwide[1]. Type 2 diabetes is associated with risks of multiple vascular complications, including cardiovascular disease, nephropathy, and retinopathy[2]. Achieving glycemic target can reduce the risk of these complications[3]. Clinical practice guidelines recommend glycemic target with HbA1c levels at < 7% or < 6.5%[4,5]. However, only one third to one half of subjects with type 2 diabetes achieve their glycemic targets[6].

To achievement and maintain glycemic target, combination therapy including metformin can be considered in subjects with type 2 diabetes[7]. If the glycemic target is not reached with two-drug combination therapy, a third-line agent can be added. Considering that the most common second-line combination therapy with metformin is dipeptidyl peptidase-4 inhibitor (DPP4i)[8], it is of interest to determine which third-line antidiabetic agent would be most suitable for subjects already treated with metformin and a DPP4i.

Sodium-glucose cotransporter-2 inhibitor (SGLT2i) lowers glucose levels by promoting urinary glucose excretion. In addition, these drugs have cardioprotective and renoprotective effects, as well as weight loss effects[9]. Therefore, current guidelines recommend SGLT2i as the preferred therapeutic option for subjects with type 2 diabetes who have established or are at high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease[5,10].

Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor-γ (PPARγ) agonists, improve insulin sensitivity in adipose tissue, muscle, and liver, thereby demonstrating strong glucose-lowering efficacy[11]. Due to cardiovascular safety concerns with rosiglitazone, the use of TZDs has decreased[12]. In addition, concerns about the side effects of TZDs' such as fluid retention, heart failure, weight gain, and fractures have reduced the use of these agents[13,14]. However, the TOSCA.IT study demonstrated that pioglitazone treatment did not increase the risk of composite outcomes (first occurrence of all-cause death, non-fatal myocardial infarction, non-fatal stroke, or urgent coronary revascularization)[15]. Previously, the Insulin Resistance Intervention after Stroke (IRIS) trial demonstrated that pioglitazone treatment reduced the risk of stroke or myocardial infarction[16]. Therefore, the therapeutic value of TZDs appears to be underrated.

The aim of this clinical trial was to assess the efficacy and safety of pioglitazone in comparison with dapagliflozin as an add-on in subjects with type 2 diabetes who did not have adequate blood glucose control with metformin and alogliptin dual therapy.

Methods

Population

Patients with type 2 diabetes (HbA1c 7.0–11.0%) after 12 weeks of DPP4i and metformin (≥ 1000 mg/day) were screened. The inclusion criteria were: aged 19–75 years with metabolic syndrome as defined previously[17]. The exclusion criteria were: a history of bladder cancer, taking systemic steroids, drugs for weight loss, insulin, or other diabetes medications except DPP4i and metformin within 3 months, a history of genetic diseases (such as galactose intolerance) and alcohol abuse.

Design

This was a multicenter, randomized, phase 4 study at 15 sites from 14 February 2020–16 January 2024. After the screening, eligible patients underwent a run-in period for 4 weeks (patients took stable-dose 25 mg alogliptin and metformin [≥ 1000 mg/day]). If the compliance was 80–120%, they were randomly assigned in 1:1 to pioglitazone or dapagliflozin group. The pioglitazone group received a fixed dose combination tablet (alogliptin/pioglitazone [25 mg/15 mg]) once daily, along with metformin twice daily. If HbA1c was ≥ 7.5% at week 12, a dose of pioglitazone can be up-titrated to 30 mg. The dapagliflozin group received a dapagliflozin tablet (10 mg) once daily, an alogliptin tablet (25 mg) once daily, and metformin tablets (≥ 500 mg) twice daily for 26 weeks. Metformin dose down-titration to 500 mg/day can be considered if patients developed hypoglycemia or gastrointestinal symptoms. At 12 and 26 weeks, efficacy and safety were assessed. At 28 weeks, the final safety was assessed via a phone call.

The study followed the principles of the Declaration of Helsinki and standards of good clinical practice[18]. The institutional review board (IRB) of each study site (Supplementary Table S1) approved the study. Informed consent was taken from all participants. We registered this study on ClinicalTrials.gov (identifier: NCT03499704) as the EPIDOTE Study.

Endpoints

HbA1c change from baseline to week 26 was set as the primary endpoint. The secondary endpoints were: (1) change in HOMA-IR from baseline to week 26, (2) change in lipid profiles from baseline to week 26, and (3) HbA1c < 6.5% achievement rate at week 26. The exploratory endpoints were changes in fasting plasma glucose (FPG) and HOMA-β from baseline to week 26, HbA1c < 6.5% achievement rate without hypoglycemia or treatment discontinuation at week 26, and proportion (%) of participants without receiving rescue therapy or treatment discontinuation at week 26. Rescue therapy was considered when FPG ≥ 240 mg/dL or HbA1c ≥ 8.0% at week 12. Sulphonylurea or insulin was used as a rescue medication according to the investigator's discretion. Incidences of treatment-emergent adverse events (TEAEs) were analyzed for safety assessment. Bladder cancer, pancreatitis, hypersensitivity reactions, and increased liver enzymes were collected as adverse events (AEs) of special interest. Routine laboratory tests, physical examinations, 12-lead electrocardiograms, and the incidence of hypoglycemia were also included as part of the safety assessment.

Statistical analysis

For the non-inferiority test on the primary endpoint, we calculated a sample size with 80% of power (two-sided 5.0%), a non-inferiority margin of 0.4%, true mean difference of 0.19%, and standard deviation of 1.2%. We

planned a minimum 156 patients (78 per group), accounting for 15% dropout rate. The non-inferiority margin was set in accordance with a regulatory guidelin[19]. The true mean difference was determined based on the adjusted mean changes in HbA1c from baseline observed with dapagliflozin versus placebo (−0.81%)[20] and pioglitazone versus placebo (−1.0%)[21].

For the analysis of HbA1c change, we used mixed models for repeated measurements (MMRM) which included groups, visits, baseline values, and interaction between the group and visit as fixed effects. If the upper limit of the 95% CI for the least square mean difference (pioglitazone-dapagliflozin) was less than 0.4%, non-inferiority of pioglitazone to dapagliflozin was confirmed. If the upper limit of the 95% CI for least square mean difference (pioglitazone-dapagliflozin) was less than 0%, superiority of pioglitazone to dapagliflozin was confirmed. In addition to a full analysis set (FAS) for the main efficacy analyses, the per-protocol set (PPS) were repeated as well. Because the efficacy analyses using the FAS and PPS showed similar results, we only present data from the FAS in this paper. To test the robustness of the major efficacy results (changes in HbA1c), sensitivity analyses were conducted on the FAS using the worst observation carried forward analysis method. We compared HbA1c change between the groups using analysis of covariance (ANCOVA). We perforemd subgroup analyses according to baseline HbA1c, sex, and age. To adjust for multiple outcome assessment, Bonferroni correction was used for subgroup analyses. We compared the changes in HOMA-IR and lipid profiles between the groups using MMRM. Because triglyceride values in lipid profiles often deviate from a normal distribution, a logarithmic transformation was applied only to the triglyceride endpoint before conducting the analysis using MMRM. We compared the changes in FPG and HOMA-β between the groups using a two sample t-test or Wilcoxon's signed rank test. Supplementary Table S2 showed the definitions of the analysets. Statistical significance was defined as a two-sided *P* value of 0.05, except for the non-inferiority and superiority analyses of the primary endpoint, which followed predefined thresholds. We used SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) for all analyses.

Results

Participant disposition and characteristics

Among the 164 participants screened for the study, 133 were randomized (pioglitazone group = 65, dapagliflozin group = 68) and 121 completed the study (pioglitazone group = 58, dapagliflozin group = 63). The numbers and reasons for screening failures and withdrawals from the study are presented in Supplementary Fig. S1. The mean age (59.2 ± 9.0 years vs. 57.8 ± 9.5 years), BMI (26.0 ± 3.9 kg/m^2 vs. 25.5 ± 2.7 kg/m^2), and HbA1c level (7.9% ± 0.9% vs. 7.7% ± 0.7%) were similar between the two groups (Table 1). The LDL-C level was significantly lower in the pioglitazone group than in the dapagliflozin group ($p = 0.047$).

Primary and secondary endpoints

HbA1c significantly decreased in both groups at week 12 and the level was maintained till week 26 (Fig. 1A). The level of HbA1c reduction at week 26 was similar between the groups (−0.75% in pioglitazone vs. −0.88% in dapagliflozin) and the 95% CI of the between-group difference (−0.09 to 0.34%) did not cross the prespecified non-inferiority margin (0.4%), demonstrating the non-inferiority of pioglitazone to dapagliflozin. Sensitivity analyses also showed no significant between-group difference in HbA1c changes at week 26 in full-analysis set (Supplementary Table S3). No significant between-group difference was found in the HbA1c change for the preplanned subgroups. Among patients aged ≥ 65 years, pioglitazone showed a trend toward greater, although not statistically significant, HbA1c reduction compared with dapagliflozin at week 26 (−1.04% vs. −0.72%, $p = 0.0477$) (Supplementary Table S4).

HOMA-IR (Mean ± SE) significantly decreased from baseline to week 26 in both groups (−1.55 ± 0.15 for pioglitazone, −1.96 ± 0.15 for dapagliflozin) without a significant between-group difference ($p = 0.0569$) (Fig. 1B). No significant changes were observed for the total cholesterol and LDL cholesterol levels within groups. The levels of HDL-C increased significantly in both groups, but the between-group difference was not significant ($p = 0.8528$). The levels of triglyceride decreased significantly in both groups, but the between-group difference was not significant ($p = 0.8328$). The proportion of participants achieving HbA1c < 6.5% at week 26 was 24.6% (15/61) in the pioglitazone group and 21.5% (14/65) in the dapagliflozin group, showing a statistically not significant difference between the groups ($p = 0.6842$) (Fig. 2). The detailed results of primary and secondary endpoints are summarized in Table 2.

Exploratory endpoints

FPG significantly decreased at week 26 in both groups ($p < 0.0001$). There was a numerical between-group difference, but it was not statistically significant ($p = 0.7051$). There was no significant change in HOMA-β in both groups. Two patients in the pioglitazone group required rescue therapy. The proportion of participants achieving HbA1c < 6.5% without hypoglycemia or treatment discontinuation due to adverse events at week 26 was not significantly different between the two groups (24.6% vs. 21.5%, $p = 0.6842$). In addition, the proportion of participants without receiving rescue therapy or treatment discontinuation due to adverse events at week 26 was not significantly different between the two groups (27.7% vs. 25.0%, $p = 0.7736$). The detailed results of the exploratory endpoints are summarized in Table 2.

Safety

The overall summary of TEAEs is presented in Table 3. In total, 26.6% of the pioglitazone group experienced 17 TEAEs (mild 15, moderate 2, severe 1) and 29.9% of the dapagliflozin group experienced 20 TEAEs (mild 15, moderate 6, severe 3). Among those TEAEs, 6 and 3 cases were identified as adverse drug reactions (ADRs) in the pioglitazone and dapagliflozin groups, respectively. There were no AEs of special interest in both groups. Two and three cases of AEs led to drug discontinuation in the groups, respectively. Three patients up-titrated

Characteristic	Pioglitazone (n = 64)	Dapagliflozin (n = 67)	*p* value
Age, yr	59.2 ± 9.0	57.8 ± 9.5	0.446
Male, n (%)	36 (56.3)	29 (43.3)	0.138
Body weight, kg	69.8 ± 12.4	67.0 ± 10.6	0.190
BMI, kg/m^2	26.0 ± 3.9	25.5 ± 2.7	0.858
HbA1c, %	7.9 ± 0.9	7.7 ± 0.7	0.528
FPG, mg/dL	156.6 ± 33.9	151.3 ± 34.3	0.201
HOMA-IR	4.2 ± 3.7	3.7 ± 3.3	0.315
HOMA-β	42.6 ± 29.4	41.4 ± 27.8	0.718
Total cholesterol, mg/dL	145.9 ± 25.9	150.9 ± 27.9	0.290
LDL-C, mg/dL	77.5 ± 23.2	86.2 ± 26.2	0.047
HDL-C, mg/dL	48.6 ± 13.8	46.9 ± 10.3	0.881
Triglyceride, mg/dL	166.0 ± 122.8	144.3 ± 59.6	0.767
eGFR, mL/min/1.73m^2	103.5 ± 25.1	101.9 ± 21.8	0.723

Table 1. Demographics and baseline characteristics. Data are expressed as mean ± standard deviation, or number (%). *BMI* body mass index; *eGFR* estimated glomerular filtration rate; *FPG* fasting plasma glucose; *HbA1c* glycated hemoglobin; *HDL-C* high-density lipoprotein cholesterol; *HOMA-IR* homeostasis model assessment of insulin resistance; *HOMA-β* homeostasis model assessment of β-cell function; *LDL-C* low-density lipoprotein cholesterol.

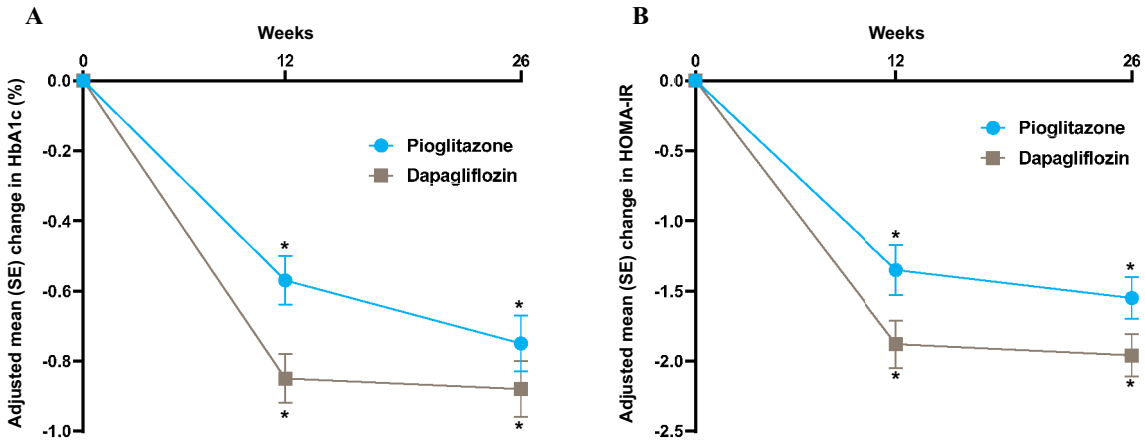

Fig. 1. Changes in efficacy parameters over time. **A** Adjusted mean changes from baseline in HbA1c. **B** Adjusted mean changes from baseline in HOMA-IR. HOMA-IR, homeostasis model assessment of insulin resistance; SE, standard error. *$p < 0.05$, statistically significant change within a group.

pioglitazone. There were no patients who down-titrated metformin in either group. No medically significant changes were found in the laboratory results, physical examinations, and electrocardiograms. There was no incidence of hypoglycemia in both groups.

Discussion

In this 26-week, open-label, randomized trial, pioglitazone demonstrated non-inferiority to dapagliflozin in terms of efficacy and safety in patients with type 2 diabetes inadequately controlled with metformin and alogliptin dual therapy, based on a non-inferiority margin of 0.4%. No significant differences were found between the pioglitazone group and dapagliflozin group in terms of HOMA-IR, lipid profiles, and the proportion of participants achieving HbA1c < 6.5%. Pioglitazone led to similar changes in FPG, HOMA-β. In addition, a similar proportion of participants achieved HbA1c < 6.5% without hypoglycemia or treatment discontinuation due to adverse events or proportion of participants without receiving rescue therapy or treatment discontinuation due to adverse events compared with dapagliflozin. No significant difference in treatment-related AEs was observed between the groups.

In the present study, pioglitazone was shown to be non-inferior to dapagliflozin in terms of mean reductions in HbA1c at week 26, with mean reductions of − 0.75% and − 0.88% for the pioglitazone and dapagliflozin groups, respectively. The robustness of the HbA1c reduction effect of pioglitazone was verified by a sensitivity analysis. The mean reduction in HbA1c in the pioglitazone group was similar to that reported in a previous trial

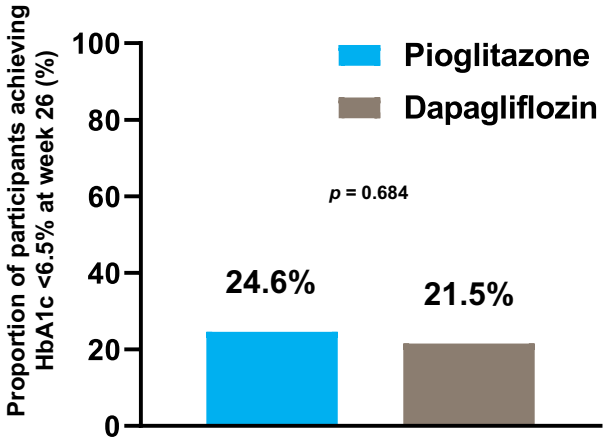

Fig. 2. Percentage of patients reaching target HbA1c.

of pioglitazone. In a randomized, open-label, active-controlled trial study involving Korean patients, the mean reduction in HbA1c at week 26 in patients treated with pioglitazone as an add-on to metformin and alogliptin was − 0.81%[22].

Pioglitazone was non-inferior to dapagliflozin in terms of mean reductions in HbA1c regardless of baseline HbA1c and sex. Interestingly, among patients aged ≥ 65 years, we observed a trend toward greater HbA1c reduction in the pioglitazone group compared with the dapagliflozin group. This may be attributed to the beneficial effects of pioglitazone on sarcopenia[23]. A previous study supported this possibility by demonstrating synergistic effects of pioglitazone and resistance training on muscle power in older women[24]. Considering these findings and the fact that the use of SGLT2i in frail older patients may require caution[25], pioglitazone could be a suitable alternative for this population.

Pioglitazone, a well-known insulin sensitizer, improves insulin resistance in skeletal muscle, liver, and adipose tissue by activating PPARγ[26]. Dapagliflozin improves insulin resistance in skeletal muscle[27,28]. These effects of each drug may contribute a similar degree of decrease in HOMA-IR between the pioglitazone and dapagliflozin groups.

Because insulin resistance is closely associated with pathogenesis of dyslipidemia[29], we expected that pioglitazone improved dyslipidemia by increasing insulin sensitivity. We found increased levels of total cholesterol, LDL-C, and HDL-C along with a decreased level of triglyceride in the pioglitazone group, which is consistent with a previous study[30]. There were no significant differences of changes of total cholesterol, LDL-C, HDL-C, and triglyceride levels between pioglitazone and dapagliflozin in this study. This can be explained by improved insulin sensitivity in both groups.

Aside from the reduction in HbA1c, the proportion of patients achieving HbA1c < 6.5% at week 26 was similar in both groups (24.6% in the pioglitazone group and 21.5% in the dapagliflozin group). In addition, the mean change from baseline in FPG at week 26 was − 24.74 mg/dL in the pioglitazone group and − 28.00 mg/dL in the dapagliflozin group, with no significant between-group difference. Considering these findings, the efficacy of pioglitazone in terms of glycemic control seems to be at least similar to that of dapagliflozin.

A previous study demonstrated that pioglitazone improved β-cell function[31]. However, the present study failed to detect significant increases in HOMA-β after the addition of pioglitazone. This result was similar to that reported in previous trials of this agent. In a randomized, open-label parallel-controlled study involving Korean patients, pioglitazone did not increase HOMA-β[22]. Also, similar studies involving Korean patients demonstrated no significant change in HOMA-β in the pioglitazone-treated group[32,33]. Considering that insulin secretory function decreases as the duration of diabetes increases[34], differences in the duration of diabetes of study population may contribute to different results in HOMA-β. Otherwise, reduced β-cell function in east Asian type 2 diabetes patients, relative to Caucasian type 2 diabetes patients, may contribute to different results in HOMA-β[35].

Several randomized clinical trials including the PROactive[36] and ADOPT[37] trials demonstrated that pioglitazone or rosiglitazone treatment was associated with increased risk of heart failure. However, in the IRIS trial[38] and a population-based cohort study[39], pioglitazone did not increase the risk of heart failure among patients with low risk of heart failure. In addition, a meta-analysis confirmed that pioglitazone increased the risk of heart failure only in patients with established cardiovascular disease[40]. In this study, we found no cases of heart failure in the pioglitazone group. Weight gain and edema are known side effects of pioglitazone, and these effects may be mediated by increased renal sodium and water reabsorption in the renal collecting duct[41]. However, we found only one case of generalized edema, one case of peripheral edema, and one case of weight gain in the pioglitazone group in this study. There was no case of AEs of special interest such as bladder cancer, pancreatitis, hypersensitivity reactions, and increased liver enzymes.

To the best of our knowledge, this is the first study to examine the efficacy and safety of pioglitazone in comparison with dapagliflozin as an add-on therapy to metformin and alogliptin combination therapy. In addition, the retention rate was high and various secondary outcomes were assessed. However, the study has several limitations. First, the open-label design may introduce potential bias. Second, the study included only

Variable	Pioglitazone (n = 64)	Dapagliflozin (n = 67)
Primary endpoint		
HbA1c, %		
Baseline	7.90 ± 0.85	7.74 ± 0.69
Week 12	7.31 ± 0.88	6.93 ± 0.45
p value for the change from baseline to week 12	< 0.0001	< 0.0001
LS mean change ± SE	− 0.57 ± 0.07	− 0.85 ± 0.07
LS mean difference (95% CI), *p* value†	0.29 (0.09 to 0.49), *p* value = 0.0054	
Week 26	7.10 ± 0.80	6.92 ± 0.51
p value for the change from baseline to week 26	< 0.0001	< 0.0001
LS mean change ± SE	− 0.75 ± 0.08	− 0.88 ± 0.08
LS mean difference (95% CI), *p* value†	0.12 (− 0.09 to 0.34), *p* value = 0.2629	
Secondary endpoints		
HOMA-IR		
Baseline	4.23 ± 3.72	3.67 ± 3.27
Week 26	2.41 ± 1.42	1.93 ± 1.11
p value for the change from baseline to week 26	< 0.0001	< 0.0001
LS mean change ± SE	− 1.55 ± 0.15	− 1.96 ± 0.15
LS mean difference (95% CI), *p* value†	0.41 (− 0.01 to 0.83), *p* value = 0.0569	
Total cholesterol, mg/dL		
Baseline	145.91 ± 25.87	150.91 ± 27.92
Week 26	155.28 ± 31.84	152.89 ± 32.52
p value for the change from baseline to week 26	0.0685	0.3621
LS mean change ± SE	7.54 ± 3.02	2.98 ± 2.93
LS mean difference (95% CI), *p* value†	4.56 (− 3.78 to 12.90), *p* value = 0.2810	
LDL-C, mg/dL		
Baseline	77.52 ± 23.20	86.19 ± 26.22
Week 26	84.57 ± 27.76	85.62 ± 29.04
p value for the change from baseline to week 26	0.1230	0.9406
LS mean change ± SE	5.11 ± 2.68	0.98 ± 2.59
LS mean difference (95% CI), *p* value†	4.14 (− 3.26 to 11.53), *p* value = 0.2705	
HDL-C, mg/dL		
Baseline	48.56 ± 13.82	46.87 ± 10.27
Week 26	52.64 ± 14.08	51.46 ± 11.01
p value for the change from baseline to week 26	0.0001	< 0.0001
LS mean change ± SE	4.00 ± 0.85	4.22 ± 0.82
LS mean difference (95% CI), *p* value†	− 0.22 (− 2.56 to 2.12), *p* value = 0.8528	
Triglyceride, mg/dL		
Baseline	166.02 ± 122.80	144.28 ± 59.61
Week 26	139.64 ± 72.12	127.42 ± 58.76
p value for the change from baseline to week 26	0.0319	0.0318
Log-transformed LS mean change ± SE‡	− 0.12 ± 0.05	− 0.14 ± 0.05
Log-transformed LS mean difference (95% CI), *p* value†‡	0.02 (− 0.11 to 0.16), *p* value = 0.7334	
Participants achieving HbA1c < 6.5% at week 26		
n (%)	15 (24.59)	14 (21.54)
p value for the difference between two groups	*p* value = 0.6842	
Exploratory endpoints		
FPG, mg/dL		
Baseline	156.55 ± 33.85	151.31 ± 34.29
Week 26	131.36 ± 27.23	123.51 ± 20.76
Change from baseline to week 26	− 24.74 ± 31.16	− 28.00 ± 34.44
p value	< 0.0001	< 0.0001
p value* for the difference between two groups	*p* value = 0.7051	
HOMA-β		
Baseline	42.62 ± 29.44	41.44 ± 27.82
Week 26	41.89 ± 26.74	40.13 ± 23.95
Change from baseline to week 26	− 0.47 ± 17.84	− 1.01 ± 23.25
Continued		

Variable	Pioglitazone (n = 64)	Dapagliflozin (n = 67)
p value	0.8390	0.9923
p value* for the difference between two groups	*p* value = 0.9685	
Participants achieving HbA1c < 6.5% without hypoglycemia or treatment discontinuation due to adverse events at week 26		
n (%)	15 (24.59)	14 (21.54)
p value	*p* value = 0.6842	
Participants without receiving rescue therapy or treatment discontinuation due to adverse events at week 26		
n (%)	13 (27.66)	11 (25.00)
p value	*p* value = 0.7736	

Table 2. Primary, secondary, and exploratory endpoints. Data are expressed as mean ± standard deviation, or number (%) unless otherwise specified with SE. *p* values were calculated using paired t-test or Wilcoxon's signed rank test for changes from baseline to week 26 within a group. *CI* confidence interval; *FPG* fasting plasma glucose; *HbA1c* glycated hemoglobin; *HDL-C* high-density lipoprotein cholesterol; *HOMA-IR* homeostasis model assessment of insulin resistance; *HOMA-β* homeostasis model assessment of β-cell function; *LDL-C* low-density lipoprotein cholesterol; *LS* least-squares; *SE* standard error. *p values were calculated using two sample t-test or Wilcoxon's signed rank test for changes between the groups. †p values were calculated using mixed model for repeated measure. ‡ A logarithmic transformation was applied to the TG values prior to analysis using MMRM, as TG values often deviate from a normal distribution.

	Pioglitazone (n = 64)	Dapagliflozin (n = 67)	*p* value
TEAEs	17 (26.6) [27]	20 (29.9) [31]	0.6760†
Mild	15 (23.4) [24]	15 (22.4) [19]	
Moderate	2 (3.1) [2]	6 (9.0) [8]	
Severe	1 (1.6) [1]	3 (4.5) [4]	
SAEs	1 (1.6) [1]	4 (6.0) [6]	0.3659‡
Diverticulum	0	1 (1.5) [2]	
Hemorrhoids	1 (1.6) [1]	0	
Pneumonia	0	2 (3.0) [2]	
Trigger finger	0	1 (1.5) [1]	
Esophageal carcinoma	0	1 (1.5) [1]	
AEs of special interest*	0	0	NA
ADRs	5 (7.8) [6]	3 (4.5) [3]	0.4859‡
Cystitis	0	1 (1.5) [1]	
Genital infection	0	1 (1.5) [1]	
Vaginal infection	0	1 (1.5) [1]	
Generalized edema	1 (1.6) [1]	0	
Peripheral edema	1 (1.6) [1]	0	
Weight gain	1 (1.6) [1]	0	
Worsening of diabetes	1 (1.6) [1]	0	
Headache	1 (1.6) [1]	0	
Pruritus	1 (1.6) [1]	0	

Table 3. Summary of adverse events. Data are expressed as number of patients (%) [number of events]. *ADR* adverse drug reaction; *AE* adverse event; *NA* not available; *TEAE* treatment-emergent adverse event. *AEs of special interest included bladder cancer, pancreatitis, hypersensitivity reactions, and increased liver enzymes. †Pearson's chi-square test, ‡Fisher's exact test.

a short treatment period; however, long-term studies of pioglitazone have shown that its beneficial effects on glycemic control can persist for more than two years[42,43]. Third, although the prespecified primary endpoint was achieved, under-enrollment (small sample size) may have contributed to the lack of significant differences in secondary, exploratory, or safety endpoints.

In conclusion, pioglitazone add-on therapy for 26 weeks decreased HbA1c levels in type 2 diabetes patients with insufficient glycemic control on metformin and alogliptin combination therapy. The effects of pioglitazone were non-inferior to those of dapagliflozin. In the safety parameters, there was no statistically significant difference in the incidence of adverse reactions between the pioglitazone group and dapagliflozin group. Taken

together, our study findings suggest that pioglitazone could be an effective and safe option for patients with inadequate glycemic control on metformin and DPP4i.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Author contributions

K.K., S.H.K., J.S.Y., and Y.B.A. conceptualized and designed the study. K.K., S.H.K., J.S.Y., K.W.L., E.S.K., I.K.J., J.H.K., S.Y.K., K.C.W., M.K., B.S.C., S.K., S.H.C., E.J.R., S.G.K., B.H.K., K.S.P., Y.C.J., T.W.H., and Y.B.A. collected the data. K.K. contributed to data interpretation, the statistical analysis, and drafted the manuscript. Y.B.A. is the guarantor of this work. All authors significantly contributed to the manuscript and approved the final version for publication.

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Declarations

Conflict of interest

Y.C.J. and T.W.H are employees of Celltrion Pharm, Inc. They were involved in data collection only. Otherwise, there was no conflict of interest.

Additional information

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