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Lobeglitazone improves glycaemic control as add-on therapy to empagliflozin plus metformin in patients with type 2 diabetes mellitus: A double-blind, randomised, placebo-controlled trial

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Abstract

Aims: This study aimed to evaluate the efficacy and safety of triple therapy with lobeglitazone 0.5 mg as an add-on treatment compared with placebo in patients with type 2 diabetes mellitus (T2DM) inadequately controlled with metformin and empagliflozin.

Materials and Methods: In this Phase 3, multicentre, double-blind, randomised trial, patients with T2DM who had an insufficient response to metformin (≥1000 mg/day) and empagliflozin 10 mg/day (Study 1) or 25 mg/day (Study 2) were randomised to receive either lobeglitazone 0.5 mg/day, or placebo once daily for 24 weeks. Participants then entered an open-label extension phase for an additional 28 weeks, bringing the total treatment duration to 52 weeks. The primary endpoint was the change from baseline in glycated haemoglobin (HbA1c) at 24 weeks.

Results: At 24 weeks, the mean change in HbA1c was significantly greater with lobeglitazone than with placebo, regardless of the background empagliflozin dose (−0.71%; 95% confidence interval, −0.88 to −0.55; $p < 0.001$ in Study 1 and −0.62%; −0.79 to −0.45; $p < 0.001$ in Study 2). A higher proportion of patients

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achieved HbA1c levels <7% with lobeglitazone compared to placebo (48.7% vs. 13.4% in Study 1, and 44.4% vs. 13.0% in Study 2; $p < 0.001$). Although the incidence of adverse events was numerically different between groups, no statistically significant differences were observed, indicating a generally comparable profile for the triple combination therapy with metformin, empagliflozin, and lobeglitazone.

Conclusions: Lobeglitazone as an add-on to empagliflozin and metformin significantly improved glycaemic control in patients with T2DM inadequately controlled on metformin and empagliflozin dual therapy. The treatment was well tolerated, with a low incidence of adverse events.

KEYWORDS
clinical trial, metformin, SGLT2 inhibitor, thiazolidinediones, type 2 diabetes

1 | INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder characterised by insulin resistance and impaired insulin secretion by pancreatic β-cells, leading to elevated blood glucose levels and the development of diabetes-related complications. As a progressive disease marked by declining β-cell function, T2DM often cannot be effectively managed with monotherapy alone, and additional treatments are typically required to maintain adequate glycaemic control over time. Achieving and sustaining optimal glycaemic control, often through the use of combination therapy, is critical for preventing the long-term microvascular and macrovascular complications associated with T2DM.[1]

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a relatively new class of glucose-lowering agents that act via an insulin-independent mechanism. These agents have demonstrated not only effective glycaemic control but also significant cardiovascular and renal benefits in patients with T2DM.[2,3] Clinical guidelines, including the consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), highlight these benefits and recommend SGLT2 inhibitors as a key component in managing patients with T2DM who have cardiovascular or renal comorbidities.[4–6] Empagliflozin, an SGLT2 inhibitor, is frequently used in combination with metformin to improve glycaemic control, reduce body weight, and lower blood pressure in patients with T2DM, with a favourable safety and tolerability profile.[7,8]

Thiazolidinediones (TZDs), such as pioglitazone and lobeglitazone, are a class of oral antidiabetic drugs (OADs) that enhance insulin sensitivity and have been used to improve glycaemic control in patients with T2DM.[9] Beyond lowering glucose, TZDs in combination therapies provide insulin-sparing effects, improved lipid profiles, greater durability of glycaemic control, and complementary mechanisms of action with other OADs.[9] Although generally well tolerated, TZDs are associated with fluid retention, weight gain, increased risk of congestive heart failure and fracture, and a possible link to bladder cancer.[10–12] In clinical trials involving triple therapy with pioglitazone, metformin, and SGLT2 inhibitors, significant reductions in HbA1c and fasting plasma glucose (FPG) were observed without an increased risk of hypoglycaemia.[13–15]

In 2023, combination therapy using a thiazolidinedione and an SGLT2 inhibitor in addition to metformin was included in the national health insurance coverage for type 2 diabetes management in South Korea, following updated clinical guidelines and insurance policy revisions. However, there remains a lack of clinical trial data specifically evaluating the efficacy of lobeglitazone, a TZD, as a third add-on OAD in patients who have not achieved adequate glycaemic control with metformin and an SGLT2 inhibitor. Therefore, this study aims to assess the efficacy and safety of adding lobeglitazone to a treatment regimen of empagliflozin and metformin in patients with inadequately controlled T2DM. By exploring the potential benefits and risks of this triple therapy, we seek to provide valuable insights into the management of T2DM, particularly for patients requiring more intensive therapies to achieve optimal glycaemic control.

2 | MATERIALS AND METHODS

2.1 | Study design and study participants

These multicentre, randomised, double-blind, placebo-controlled Phase 3 studies were conducted in Korea (Study 1: 22 sites; Study 2: 19 sites) from September 2017 to December 2021 (ClinicalTrials.gov identifier: NCT03739125, NCT03627182). Patients with T2DM, aged ≥19 to ≤75 years, with a body mass index (BMI) ≥24 and ≤45 kg/m^2 and C-peptide >1.0 ng/mL were eligible for enrolment if they had an HbA1c level between ≥7% and ≤10%, despite receiving combination therapy with stable doses of metformin (≥1000 mg/day) and empagliflozin (10 mg/day or 25 mg/day) for at least 10 weeks prior to screening. Additionally, patients using monotherapies, metformin (<1000 mg/day) and empagliflozin (10 mg/day or 25 mg/day) or combinations of other hypoglycaemic agents excluding the protocol-specified regimen underwent a 10-week open-label stabilisation phase in which all other oral hyperglycaemic agents were discontinued and replaced with metformin (≥1000 mg/day) and empagliflozin

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(10 mg/day or 25 mg/day), with no dose adjustments allowed during this period. Ultimately, patients with T2DM and HbA1c levels between 7.0% and 10.0% at screening, following the 2-week run-in period, were included in the study. Key exclusion criteria included: use of insulin therapy for more than 7 consecutive days within the prior 3 months; use of TZDs within the past 3 months; history of hypersensitivity to TZDs, biguanides, or SGLT2 inhibitors; other types of diabetes; severe diabetic complications (e.g., uncontrolled proliferative diabetic retinopathy or severe diabetic neuropathy); and a history of severe heart failure or clinically significant liver or kidney dysfunction. Full inclusion and exclusion criteria are detailed in the study protocol (Supplementary S1 and S2).

Eligible participants were randomised in a 1:1 ratio to receive either lobeglitazone or placebo. Throughout the study, participants continued stable doses of metformin (≥1000 mg/day) and empagliflozin (10 mg/day or 25 mg/day), along with dietary and exercise regimens. Follow-up visits were conducted at 4- to 12-week intervals (Weeks 4, 12, 24, 28, 40, and 52). Rescue therapy with glimepiride (1–4 mg/day) was permitted for participants whose FPG exceeded 240 mg/dL on two consecutive measurements or if deemed necessary by the investigator. The study design included a 2-week single-blind run-in period before randomisation and a 24-week double-blind treatment phase; the 2-week single-blind run-in was included to stabilise background glycaemic control (HbA1c 7–10%) and to reinforce compliance by pre-exposing subjects to the same triple regimen (metformin + empagliflozin + placebo) as in the treatment phase. Then participants entered a 28-week open-label extension phase; except for those meeting criteria for withdrawal or those unwilling to continue, continued the clinical trial for up to 52 weeks. During the extension, concomitant antidiabetic therapies (metformin and empagliflozin) could not be modified; participants were required to maintain their pre-extension regimens, and all were given lobeglitazone in an open-label manner. Patients who consented could participate in a 28-week open-label extension, resulting in a total treatment duration of up to 52 weeks. The study protocol and associated documents were approved by the institutional review board of each participating centre. Written informed consent was obtained from all eligible participants before enrolment. The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and all applicable local regulations.

2.2 | Endpoints and assessments

The primary endpoint of the study was the mean change in HbA1c from baseline after 24 weeks of double-blind treatment with lobeglitazone 0.5 mg/day compared to placebo, both administered in addition to empagliflozin (10 mg/day or 25 mg/day) and metformin (≥1000 mg/day). Secondary endpoints included the mean change from baseline in other glycaemic parameters, such as HbA1c, FPG, homeostatic model assessment of β-cell function (HOMA-β), homeostatic model assessment of insulin resistance (HOMA-IR), and the quantitative insulin sensitivity check index (QUICKI), at both 24 and 52 weeks. The proportion of patients achieving a therapeutic glycaemic response, defined as HbA1c levels of <6.5% and <7.0% at 24 and 52 weeks, was also assessed. Additional endpoints included changes in lipid profiles at 24 and 52 weeks, encompassing total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL-C, small dense LDL-C, free fatty acids (FFA), and apolipoproteins (Apo AI, B, and CIII). All blood samples for efficacy assessments were analysed at a central laboratory. Safety endpoints included the evaluation of treatment-emergent adverse events (TEAEs) and results from complete blood counts, serum chemistry analyses, and 12-lead electrocardiograms. Self-monitored hypoglycaemia was defined as a blood glucose level < 70 mg/dL accompanied by typical adrenergic symptoms such as sweating, palpitations, trembling, or tingling, whereas severe hypoglycaemia was characterised by cognitive dysfunction requiring external assistance for recovery.

2.3 | Statistical analysis

A sample size was calculated to ensure at least 90% power to detect a difference in HbA1c reduction between treatment groups at a two-sided significance level of 0.05. The calculation assumed a true mean difference of −0.44, and a common standard deviation of 0.94. A dropout rate of 15% was applied for Study 1, yielding a required sample size of 226 subjects, while a 10% dropout rate was assumed for Study 2, resulting in a required sample size of 214 subjects.

The full analysis set (FAS) included all patients who received at least one dose of the study medication and had at least one post-randomisation HbA1c measurement within the protocol-defined visit window of the primary evaluation time point (Week 24). The per-protocol set (PPS) consisted of patients from the FAS who completed the 24-week treatment period, had both the baseline and the primary evaluation visit at Week 24 conducted within the protocol-defined visit windows and did not have any other major protocol deviations. An analysis of covariance (ANCOVA) with the stratification factor (baseline HbA1c ≤ 8.5% or >8.5%) included as a covariate was used to analyse the primary efficacy endpoint. For the FAS, missing data were handled using the last observation carried forward method considering the visit window. Baseline characteristics and efficacy results presented in this manuscript are based on the FAS. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA), with statistical significance defined as $p < 0.05$.

3 | RESULTS

Among the 227 patients who completed the initial 24-week study in Study 1, a total of 195 continued into the extension phase (placebo: $n = 92$; empagliflozin 10 mg: $n = 103$) (Figure 1A). In Study 2, 216 patients were treated during the initial 24-week phase, and 193 continued into the extension phase (placebo: $n = 95$; empagliflozin 25 mg: $n = 98$) (Figure 1B). Baseline characteristics were similar across treatment groups in the Full Analysis Set (FAS) (Table 1). For Study 1, the mean age was 56.61 ± 9.75 years, the mean duration of

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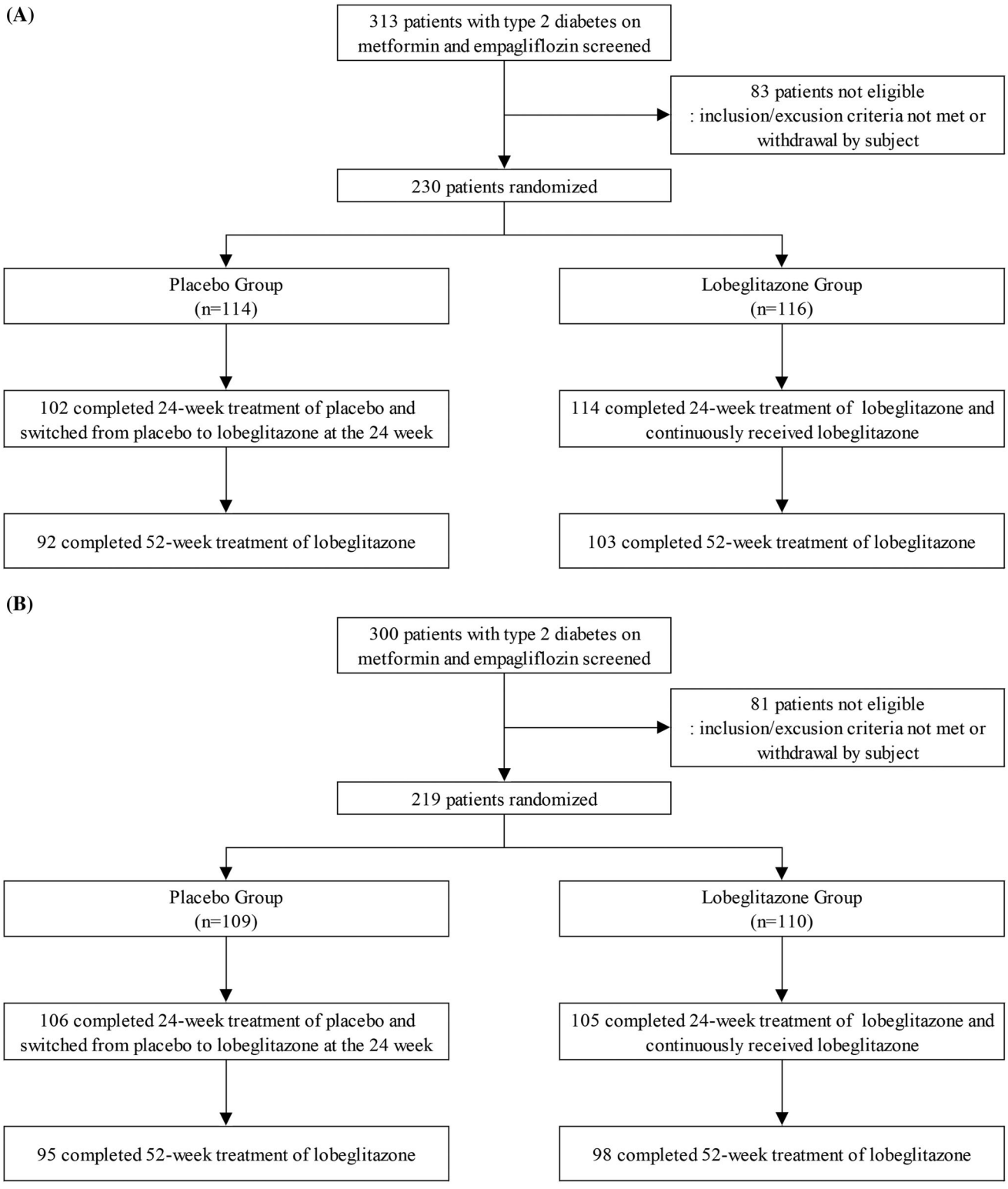

FIGURE 1 Study flowchart for Study 1 (empagliflozin 10 mg + metformin) (A) and Study 2 (empagliflozin 25 mg + metformin) (B).

diabetes was 8.77 ± 6.57 years, and the mean HbA1c was 7.98 ± 0.71%, which was comparable to the baseline characteristics in Study 2 (mean age: 56.83 ± 9.37 years; mean duration of diabetes: 9.88 ± 5.68 years; mean HbA1c: 7.97 ± 0.68%). The mean daily doses of metformin were also similar between studies: 1340.75 ± 424.14 mg in Study 1 and 1366.90 ± 428.63 mg in Study 2.

3.1 | Efficacy

The adjusted mean differences in HbA1c at Week 24 from baseline versus placebo were −0.71% (95% CI: −0.88 to −0.55, $p < 0.001$) for Study 1 and −0.62% (95% CI: −0.79 to −0.45, $p < 0.001$) for Study 2, with sustained efficacy observed through Week 52 during the

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TABLE 1 Baseline characteristics of the study participants.

	Study 1 (empagliflozin 10 mg + metformin)			Study 2 (empagliflozin 25 mg + metformin)		
	Total (*N* = 227)	Placebo (*N* = 112)	Lobeglitazone (*N* = 115)	Total (*N* = 216)	Placebo (*N* = 108)	Lobeglitazone (*N* = 108)
Sex (*n*, %)						
Male	126 (55.51)	60 (53.57)	66 (57.39)	100 (46.30)	45 (41.67)	55 (50.93)
Female	101 (44.49)	52 (46.43)	49 (42.61)	116 (53.70)	63 (58.33)	53 (49.07)
Age (years)	56.61 ± 9.75	55.70 ± 10.27	57.50 ± 9.17	56.83 ± 9.37	56.63 ± 9.23	57.04 ± 9.54
Duration of diabetes (years)	8.77 ± 6.57	8.81 ± 6.80	8.73 ± 6.36	9.88 ± 5.68	9.00 ± 4.96	10.77 ± 6.21
Body weight (kg)	70.27 ± 11.84	71.01 ± 11.73	69.54 ± 11.97	69.21 ± 11.54	67.76 ± 11.64	70.65 ± 11.31
BMI (kg/m^2)	26.27 ± 3.09	26.45 ± 3.13	26.10 ± 3.05	26.16 ± 3.10	25.79 ± 2.83	26.53 ± 3.32
Waist circumference (cm)	89.70 ± 8.95	89.86 ± 8.76	89.56 ± 9.16	89.70 ± 8.50	88.72 ± 8.95	90.68 ± 7.94
Systolic blood pressure (mmHg)	124.77 ± 11.91	123.11 ± 11.39	126.38 ± 12.23	122.06 ± 11.43	121.40 ± 11.74	122.73 ± 11.12
Diastolic blood pressure (mmHg)	77.91 ± 9.39	77.46 ± 8.77	78.35 ± 9.99	75.81 ± 9.09	76.26 ± 9.32	75.36 ± 8.88
HbA1c (%)	7.98 ± 0.71	7.96 ± 0.68	8.00 ± 0.73	7.97 ± 0.68	8.04 ± 0.74	7.90 ± 0.62
FPG (mg/dL)	141.38 ± 25.87	140.62 ± 25.25	142.12 ± 26.55	137.33 ± 27.60	134.47 ± 24.17	140.19 ± 30.49
Insulin (μU/mL)	9.03 ± 4.07	9.14 ± 3.61	8.93 ± 4.49	8.94 ± 3.68	8.98 ± 3.76	8.90 ± 3.62
HOMA-IR	3.19 ± 1.66	3.19 ± 1.39	3.19 ± 1.89	3.07 ± 1.55	3.05 ± 1.63	3.09 ± 1.49
HOMA-β	45.39 ± 24.48	47.06 ± 25.63	43.76 ± 23.31	48.22 ± 25.37	49.19 ± 24.19	47.26 ± 26.57
QUICKI	0.33 ± 0.02	0.33 ± 0.02	0.33 ± 0.02	0.33 ± 0.02	0.33 ± 0.02	0.33 ± 0.02
eGFR (mL/min/1.73 m^2)	95.11 ± 13.68	96.84 ± 13.61	93.43 ± 13.60	94.90 ± 13.73	94.30 ± 13.56	95.51 ± 13.92
Total cholesterol (mg/dL)	156.24 ± 34.26	154.84 ± 37.38	157.60 ± 31.04	158.60 ± 38.97	156.62 ± 40.89	160.58 ± 37.03
Triglyceride (mg/dL)	150.78 ± 104.69	141.24 ± 80.24	160.06 ± 123.62	144.83 ± 83.94	137.80 ± 86.02	151.86 ± 81.60
HDL-C (mg/dL)	52.35 ± 11.85	52.31 ± 12.14	52.38 ± 11.61	52.06 ± 11.99	51.49 ± 12.28	52.62 ± 11.72
LDL-C (mg/dL)	91.77 ± 31.48	91.64 ± 34.95	91.90 ± 27.85	94.01 ± 35.12	93.05 ± 37.05	94.97 ± 33.22
Antihypertensive drugs (*n*, %)	93 (40.97)	38 (33.93)	55 (47.83)	88 (40.74)	37 (34.26)	51 (47.22)
Lipid-lowering drugs (*n*, %)	36 (15.86)	12 (10.71)	24 (20.87)	172 (79.63)	89 (82.41)	83 (76.85)
Metformin dose (mg/day)	1340.75 ± 424.14	1367.19 ± 424.50	1315.00 ± 424.05	1366.90 ± 428.63	1339.25 ± 412.20	1394.81 ± 444.81

Note: Values are presented as mean ± standard deviation or number (%).
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; HDL-C, high density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-β, homeostatic model assessment of β-cell function; LDL-C, low density lipoprotein cholesterol; QUICKI, quantitative insulin sensitivity check index.

open-label extension phase (Tables 2 and S1). Reductions in FPG at Week 24 were also significantly greater with lobeglitazone than with placebo. The adjusted mean differences in change from baseline FPG versus placebo were −18.25 mg/dL (95% CI: −23.96 to −12.54, $p < 0.001$) in Study 1 and −13.83 mg/dL (95% CI: −19.16 to −8.50, $p < 0.001$) in Study 2 (Figures 2 and 3). A greater proportion of participants achieved target HbA1c levels below 7% with lobeglitazone (48.7% in Study 1 and 44.44% in Study 2) compared to placebo (13.39% in Study 1 and 12.96% in Study 2) (Figures 2 and 3). Subgroup analyses by age, sex, hypertension status, and diabetes duration showed consistent and statistically significant treatment effects across all categories (data not shown). Lobeglitazone therapy also improved markers of β-cell function and insulin resistance. HOMA-β increased significantly compared with placebo, with adjusted mean differences of 12.01 (95% CI: 6.19–17.83, $p < 0.001$) in Study 1 and 11.40 (95% CI: 5.95–16.85, $p < 0.001$) in Study 2. In contrast, HOMA-IR significantly decreased, reflecting enhanced insulin sensitivity, with adjusted mean differences of −0.72 (95% CI: −1.06 to −0.37, $p < 0.001$) in Study 1 and −0.47 (95% CI: −0.76 to −0.18, $p = 0.002$) in Study 2.

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TABLE 2 Changes in clinical parameters from baseline.

	Study 1 (empagliflozin 10 mg + metformin)		Study 2 (empagliflozin 25 mg + metformin)	
	Placebo	Lobeglitazone	Placebo	Lobeglitazone
HbA1c (%)[a]				
Baseline	7.89 ± 0.63	8.00 ± 0.73	8.01 ± 0.73	7.89 ± 0.61
Week 24	7.75 ± 0.81	7.12 ± 0.76	7.94 ± 0.91	7.19 ± 0.76
LS mean (SE) change from baseline	−0.27 (0.07)	−0.98 (0.06)	−0.16 (0.07)	−0.78 (0.07)
LS mean difference (95% CI)	−0.71 (−0.88, −0.55); <0.001		−0.62 (−0.79, −0.45); <0.001	
FPG (mg/dL)[a]				
Baseline	138.41 ± 23.66	141.23 ± 24.61	133.88 ± 24.99	138.84 ± 30.17
Week 24	138.72 ± 24.69	122.72 ± 26.18	135.06 ± 19.55	123.27 ± 25.46
LS mean (SE) change from baseline	4.90 (2.48)	−13.35 (2.32)	1.93 (2.12)	−11.90 (2.11)
LS mean difference (95% CI)	−18.25 (−23.96, −12.54); <0.001		−13.83 (−19.16, −8.50); <0.001	
HOMA-IR[a]				
Baseline	3.08 ± 1.30	2.99 ± 1.48	2.98 ± 1.64	3.07 ± 1.50
Week 24	3.10 ± 1.42	2.34 ± 1.49	2.86 ± 1.27	2.41 ± 0.95
LS mean (SE) change from baseline	0.14 (0.15)	−0.58 (0.14)	−0.15 (0.12)	−0.62 (0.11)
LS mean difference (95% CI)	−0.72 (−1.06, −0.37); <0.0001		−0.47 (−0.76, −0.18); 0.002	
HOMA-β[a]				
Baseline	47.52 ± 25.94	43.17 ± 21.92	49.01 ± 24.74	47.95 ± 26.65
Week 24	46.62 ± 23.49	55.08 ± 31.03	45.76 ± 20.79	56.38 ± 32.41
LS mean (SE) change from baseline	−2.57 (2.47)	9.44 (2.31)	−5.01 (2.18)	6.39 (2.15)
LS mean difference (95% CI)	12.01 (6.19, 17.83); <0.001		11.40 (5.95, 16.85); <0.001	
QUICKI[a]				
Baseline	0.33 ± 0.02	0.33 ± 0.02	0.33 ± 0.02	0.33 ± 0.02
Week 24	0.33 ± 0.02	0.34 ± 0.03	0.33 ± 0.02	0.34 ± 0.02
LS mean (SE) change from baseline	0.00 (0.00)	0.01 (0.00)	0.00 (0.00)	0.01 (0.00)
LS mean difference (95% CI)	0.01 (0.01, 0.02); <0.001		0.01 (0.00, 0.01); <0.001	
Systolic blood pressure (mmHg)[b]				
Baseline	122.18 ± 11.26	126.26 ± 12.38	120.87 ± 11.54	122.80 ± 11.22
Week 24	122.96 ± 12.99	126.72 ± 13.46	122.70 ± 11.36	124.17 ± 11.11
Mean (SD) change	0.78 ± 12.01	0.47 ± 11.73	1.83 ± 10.56	1.36 ± 11.63
Mean difference (95% CI)	−0.32 (−3.58, 2.95)		−0.47 (−3.56, 2.63)	
Diastolic blood pressure (mmHg)[b]				
Baseline	76.52 ± 8.09	78.23 ± 9.93	76.08 ± 9.29	75.68 ± 8.94
Week 24	75.82 ± 8.01	77.56 ± 10.70	76.90 ± 8.76	75.62 ± 8.77
Mean (SD) change	−0.69 ± 7.87	−0.67 ± 9.27	0.82 ± 8.33	−0.06 ± 8.29
Mean difference (95% CI)	0.02 (−2.36, 2.40)		−0.88 (−3.19, 1.44)	
Body weight (kg)[b]				
Baseline	70.86 ± 11.11	69.71 ± 12.04	67.80 ± 11.72	70.95 ± 11.39
Week 24	70.06 ± 10.86	70.94 ± 11.67	66.98 ± 11.83	72.79 ± 11.84
Mean (SD) change	−0.81 ± 2.16	1.29 ± 2.29	−0.82 ± 1.81	1.84 ± 2.21
Mean difference (95% CI)	2.09 (1.48, 2.71); <0.001		2.66 (2.10, 3.22); <0.001	
Waist circumference (cm)[b]				
Baseline	89.46 ± 8.05	89.67 ± 9.16	88.57 ± 9.18	90.74 ± 7.85
Week 24	89.31 ± 8.08	90.17 ± 9.09	87.55 ± 9.00	91.82 ± 8.53
Mean (SD) change	−0.15 ± 3.11	0.49 ± 3.31	−1.02 ± 3.83	1.08 ± 3.45
Mean difference (95% CI)	0.64 (−0.24, 1.53)		2.10 (1.08, 3.11); <0.001	

Note: Values are presented as mean ± standard error unless otherwise indicated.

Abbreviations: CI, confidence interval; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-β, homeostatic model assessment of β-cell function; QUICKI, quantitative insulin sensitivity check index; SD, standard deviation; SE, standard error.

[a]FAS; ANCOVA with baseline HbA1c stratification factor (≤8.5% or >8.5%), and baseline values (except HbA1c) as covariates.

[b]Safety analysis set. Between-group comparisons were performed using Student's *t*-test.

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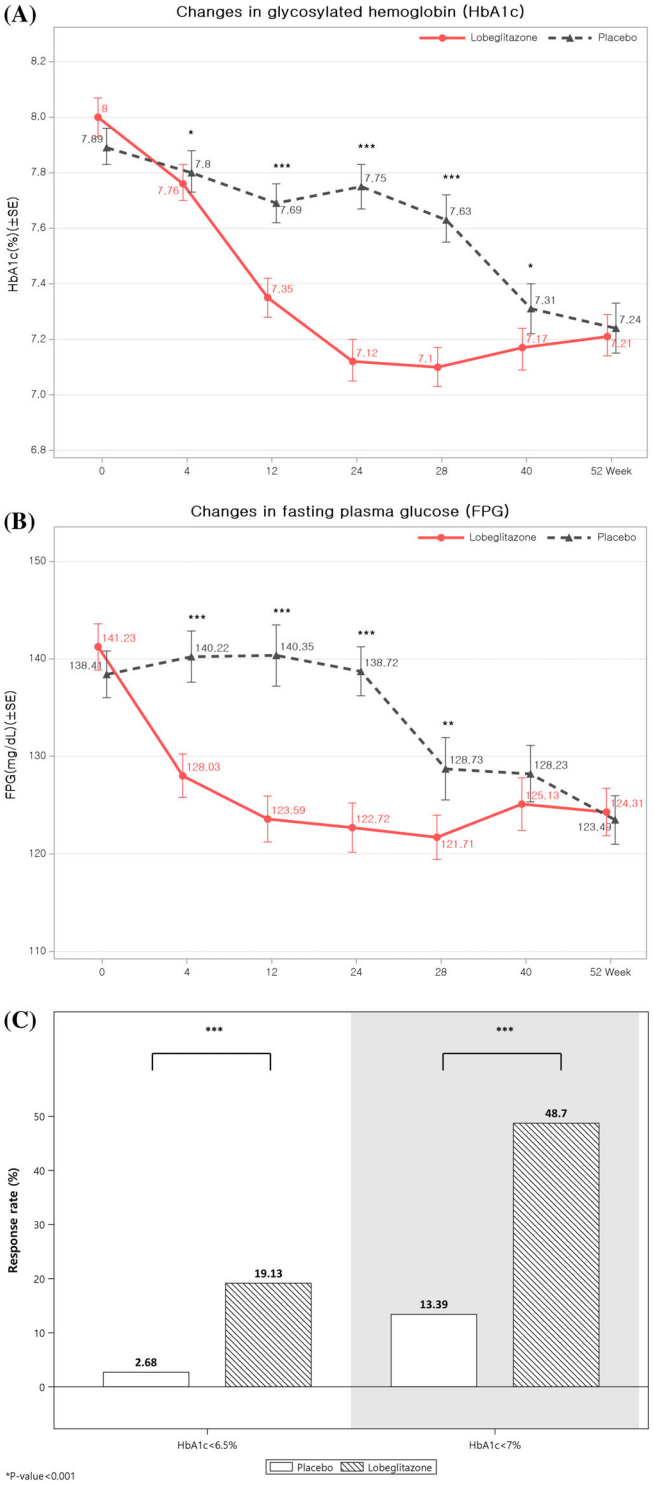

FIGURE 2 (A) Changes in glycosylated haemoglobin (HbA1c). (B) Changes in fasting plasma glucose (FPG). (C) Proportions of participants who achieved HbA1c targets of <7% and <6.5% at Week 24 from baseline for Study 1. *<0.05, **<0.01, ***<0.001, footnotes denote statistically significant differences between groups.

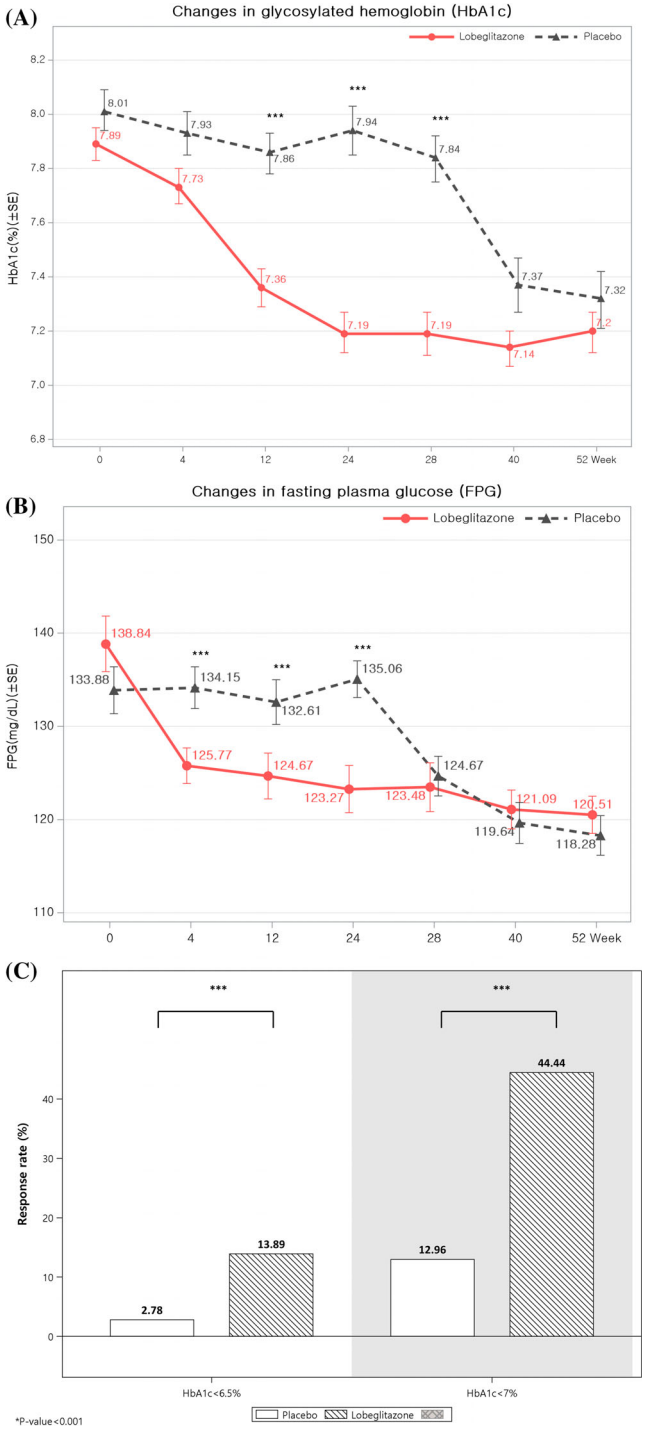

FIGURE 3 (A) Changes in glycosylated haemoglobin (HbA1c). (B) Changes in fasting plasma glucose (FPG). (C) Proportions of participants who achieved HbA1c targets of <7% and <6.5% at Week 24 from baseline for Study 2. *<0.05, **<0.01, ***<0.001, footnotes denote statistically significant differences between groups.

3.2 | Other metabolic parameters

Compared with placebo, lobeglitazone significantly increased HDL-C levels at Week 24 (Table 3). The adjusted mean differences in change from baseline HDL-C versus placebo were 4.68 mg/dL (95% CI: 2.51–6.84, $p < 0.001$) in Study 1 and 3.11 mg/dL (95% CI: 0.95–5.28, $p = 0.005$) in Study 2. Lobeglitazone therapy also resulted in a significant decrease in FFA and Apo-B compared with placebo at Week 24 (Table 3). However, no significant differences were observed in TC, TG or LDL-C levels. Lobeglitazone treatment was associated with

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TABLE 3 Changes in metabolic parameters from baseline.

	Study 1 (empagliflozin 10 mg + metformin)		Study 2 (empagliflozin 25 mg + metformin)	
	Placebo	Lobeglitazone	Placebo	Lobeglitazone
Total cholesterol (mg/dL)				
Baseline	154.34 ± 37.50	157.65 ± 31.36	153.90 ± 36.72	160.61 ± 37.21
Week 24	157.11 ± 33.00	157.70 ± 30.88	159.15 ± 35.79	164.43 ± 38.55
LS mean (SE) change from baseline	4.92 (2.95)	3.13 (2.72)	4.42 (2.71)	4.58 (2.69)
LS mean difference (95% CI)	−1.78 (−8.74, 5.17)		0.16 (−6.66, 6.99)	
Triglyceride (mg/dL)				
Baseline	144.41 ± 84.24	160.88 ± 126.71	134.56 ± 85.69	150.60 ± 81.87
Week 24	148.58 ± 74.32	135.19 ± 90.08	138.52 ± 72.74	131.20 ± 107.36
LS mean (SE) change from baseline	−7.34 (8.19)	−26.55 (7.59)	−2.19 (8.81)	−18.51 (8.64)
LS mean difference (95% CI)	−19.21 (−38.57, 0.15)		−16.32 (−38.40, 5.75)	
HDL-C (mg/dL)				
Baseline	52.76 ± 12.27	52.08 ± 11.59	51.45 ± 12.40	52.42 ± 11.44
Week 24	52.78 ± 13.16	57.02 ± 13.15	52.41 ± 12.46	56.34 ± 12.88
LS mean (SE) change from baseline	0.94 (0.92)	5.62 (0.85)	0.97 (0.86)	4.09 (0.85)
LS mean difference (95% CI)	4.68 (2.51, 6.84); <0.001		3.11 (0.95, 5.28); 0.005	
LDL-C (mg/dL)				
Baseline	90.39 ± 35.05	92.09 ± 27.69	90.27 ± 33.06	95.38 ± 33.12
Week 24	92.29 ± 29.98	89.88 ± 28.95	93.72 ± 34.29	95.95 ± 34.55
LS mean (SE) change from baseline	4.89 (2.61)	0.86 (2.41)	2.95 (2.51)	1.17 (2.49)
LS mean difference (95% CI)	−4.03 (−10.19, 2.14)		−1.78 (−8.10, 4.53)	
Non HDL-C (mg/dL)				
Baseline	101.58 ± 37.52	105.57 ± 30.99	102.44 ± 34.83	108.19 ± 34.65
Week 24	104.33 ± 31.07	100.68 ± 31.37	106.74 ± 35.90	108.09 ± 37.40
LS mean (SE) change from baseline	3.77 (2.89)	−2.45 (2.67)	3.41 (2.74)	0.26 (2.71)
LS mean difference (95% CI)	−6.21 (−13.05,0.62)		−3.15 (−10.04, 3.74)	
FFA (uEq/L)				
Baseline	819.99 ± 277.37	747.99 ± 311.25	737.13 ± 264.11	709.63 ± 300.44
Week 24	783.77 ± 301.04	668.39 ± 303.13	765.07 ± 308.28	615.66 ± 273.02
LS mean (SE) change from baseline	−26.22 (33.06)	110.06 (30.19)	34.44 (30.79)	105.97 (30.33)
LS mean difference (95% CI)	−83.84 (−161.78, −5.90); 0.03		−140.42 (−217.66, −63.17); <0.001	
Apo-AI (mg/dL)				
Baseline	153.58 ± 24.20	155.29 ± 24.52	152.99 ± 28.05	154.04 ± 23.86
Week 24	154.56 ± 28.41	154.08 ± 24.07	156.81 ± 25.77	155.53 ± 22.78
LS mean (SE) change from baseline	2.77 (2.33)	0.73 (2.15)	3.94 (1.91)	1.96 (1.88)
LS mean difference (95% CI)	−2.04 (−7.54, 3.46)		−1.98 (−6.75, 2.80)	
Apo-B (mg/dL)				
Baseline	85.52 ± 25.07	88.94 ± 23.11	87.09 ± 24.08	90.36 ± 23.43
Week 24	86.06 ± 21.77	80.24 ± 21.28	90.75 ± 27.18	86.36 ± 24.10
LS mean (SE) change from baseline	0.71 (1.84)	−7.36 (1.70)	2.91 (1.96)	−4.05 (1.93)
LS mean difference (95% CI)	−8.07 (−12.41, −3.72); <0.001		−6.96 (−11.88, −2.05); 0.006	
Apo-CIII (mg/dL)				
Baseline	12.00 ± 5.46	12.85 ± 6.32	11.43 ± 5.23	12.75 ± 6.01
Week 24	12.34 ± 5.62	12.31 ± 5.09	12.56 ± 5.90	12.70 ± 5.67
LS mean (SE) change from baseline	0.27 (0.48)	−0.28 (0.45)	0.93 (0.47)	0.13 (0.46)
LS mean difference (95% CI)	−0.54 (−1.68, 0.59)		−0.80 (−1.98, 0.38)	

Abbreviations: Apo, apoprotein; CI, confidence interval; FFA, free fatty acid; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; LS, least square; SE, standard error.

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a significant increase in body weight compared to placebo at Week 24. The adjusted mean differences in weight gain from baseline were 2.09 kg (95% CI: 1.48–2.71, $p < 0.001$) in Study 1 and 2.66 kg (95% CI: 2.10–3.22, $p < 0.001$) in Study 2. Waist circumference also increased modestly with lobeglitazone treatment, with adjusted mean differences versus placebo of 0.64 cm (95% CI: −0.24 to 1.53, $p = 0.153$) in Study 1 and 2.10 cm (95% CI: 1.08–3.11, $p < 0.001$) in Study 2 at Week 24. Both systolic and diastolic blood pressure showed no significant change with lobeglitazone treatment at Week 24, in Study 1 and Study 2.

3.3 | Adverse events

A summary of adverse events (AEs) is presented in Tables 4 and 5 at Week 24. In Study 1, treatment-emergent adverse events (TEAEs) occurred in 30.43% of patients receiving lobeglitazone and 24.11% of those receiving placebo ($p = 0.235$), and adverse drug reactions (ADRs) occurred in 16.52% vs. 10.71% ($p = 0.203$), respectively. One serious adverse event (SAE) (rotator cuff syndrome) was reported in the lobeglitazone group and four SAEs in the placebo group ($p = 0.209$), none of which were considered related to study treatment. In Study 2, two SAEs occurred in the lobeglitazone group and six in the placebo group ($p = 0.171$). All events, including anal haemorrhage, anal polyp, large intestine polyp, and pulmonary mass, were assessed as unlikely to be drug-related, and treatment was continued. Across both studies, no clinically significant changes were observed in laboratory safety parameters, including renal function and electrolyte levels. Importantly, no confirmed hypoglycaemic events occurred during the study period.

4 | DISCUSSION

In these randomised, placebo-controlled trials, we evaluated the efficacy and safety of lobeglitazone 0.5 mg as an adjunctive treatment in patients with T2DM who had inadequate glycaemic control despite treatment with metformin and empagliflozin at doses of 10 mg/day or 25 mg/day. The addition of lobeglitazone as a third therapeutic agent significantly improved glycaemic control over 24- and 52-week periods, without any reported episodes of hypoglycaemia. Notably, the addition of lobeglitazone to metformin and empagliflozin resulted in a significantly higher proportion of patients achieving the glycaemic target of HbA1c <7%, compared to placebo, regardless of the empagliflozin dose (48.7% vs. 13.4% in Study 1 and 44.4% vs. 13.0% in Study 2). Lobeglitazone reduced HbA1c levels by an average of 0.8% to 1.0% at 24 weeks, and this glycaemic improvement was sustained through 52 weeks, indicating sustained glycaemic control. In addition, lobeglitazone improved insulin resistance and β-cell function, and favourably modified lipid profiles by lowering TG, FFA, and Apo-B, while increasing HDL-C levels in patients with T2DM.

A meta-analysis of randomised clinical trials and observational studies reported that only about one-third of patients with T2DM achieve the target HbA1c level of <7%, although slight improvements have been noted in recent years.[16] In Korea, similarly, only about half of patients with diabetes reach good glycaemic control (HbA1c <7%) despite steady progress over time.[17] When glycaemic targets are not achieved with monotherapy, treatment guidelines recommend intensifying therapy by adding a second and then a third agent. Triple combination therapy is being increasingly adopted and has been shown to result in greater HbA1c reductions.[4–6] In a network meta-analysis comparing various triple therapy regimens, adding a third drug to existing dual therapy led to significant additional mean HbA1c reductions ranging from −0.56% to −0.94%. TZDs were ranked as the most effective class for HbA1c reduction, although they were associated with significant weight gain.[18]

Among various combination therapies, using TZDs with SGLT2 inhibitors offers a multifaceted approach to managing T2DM by addressing several underlying pathophysiological mechanisms. While TZDs improve insulin sensitivity and β-cell function, SGLT2 inhibitors promote glycosuria and natriuresis independently of insulin action.[19,20] This complementary mechanism of action may explain the observed benefits in glycaemic control, weight reduction, and blood pressure control.[13–15] Additionally, the natriuretic effects of SGLT2 inhibitors may counterbalance the fluid retention commonly associated with TZD use, potentially reducing the risk of TZD-related heart failure.[20] Emerging evidence further suggests that combining TZDs with SGLT2 inhibitors confers complementary vascular protection. Real-world data indicate that this combination lowers the risk of heart failure despite prior safety concerns with TZDs.[21] In a large national cohort from Taiwan, combination therapy was associated with reduced risk of 3-point MACE (aHR 0.76, 95% CI 0.66–0.88), heart failure (aHR 0.67, 95% CI 0.55–0.82), and stroke (aHR 0.72, 95% CI 0.58–0.91), compared to other OHA combinations.[22] Moreover, this combination therapy with pioglitazone and an SGLT2 inhibitor demonstrated a lower risk of both MACE and heart failure than either pioglitazone or an SGLT2 inhibitor alone, suggesting enhanced protective effects from the combination.[22]

Both lobeglitazone and pioglitazone demonstrated significant glycaemic efficacy when added to dual therapy with metformin and an SGLT2 inhibitor, though magnitudes varied between agents. In clinical trials, pioglitazone reduced HbA1c by −0.35% at 15 mg and up to −0.81% at 30 mg, whereas lobeglitazone 0.5 mg lowered HbA1c by −0.78% to −0.98% at 24 weeks. The proportion of participants achieving HbA1c <7% was comparably high, reaching ∼52% with pioglitazone and ∼ 44–49% with lobeglitazone.[13] Beyond glycaemic control, pioglitazone exerted pleiotropic effects including improvements in insulin resistance, lipid metabolism and vascular function. Pioglitazone has consistently been shown to lower plasma triglycerides and free fatty acids while increasing HDL cholesterol, with a modest rise in total and LDL cholesterol but a shift towards larger, less atherogenic LDL particles.[23] Similarly, lobeglitazone enhanced β-cell function (HOMA-β) and insulin sensitivity (HOMA-IR, QUICKI), and produced comparable lipid effects, including significant increases in HDL-C and reductions in FFA, and ApoB, supporting its potential metabolic and vascular benefits. Taken together, these findings suggest that

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TABLE 4 Adverse events for Study 1.

	Placebo ($N = 112$)	Lobeglitazone ($N = 115$)	p-value[a]
TEAE	27 (24.11)	35 (30.43)	0.285[C]
ADR	12 (10.71)	19 (16.52)	0.203[C]
Constipation	2 (1.79)	3 (2.61)	
Abdominal discomfort	–	1 (0.87)	
Abdominal pain	1 (0.89)	–	
Chronic gastritis	1 (0.89)	–	
Dyspepsia	1 (0.89)	–	
Tooth impacted	1 (0.89)	–	
Cystitis	1 (0.89)	1 (0.87)	
Dermatitis infected	–	1 (0.87)	
Otitis media	1 (0.89)	-	
Periodontitis	-	1 (0.87)	
Osteoporosis	-	2 (1.74)	
Arthralgia	-	1 (0.87)	
Intervertebral disc protrusion	1 (0.89)	–	
Musculoskeletal pain	1 (0.89)	–	
Chest discomfort	–	1 (0.87)	
Face oedema	–	1 (0.87)	
Oedema	–	1 (0.87)	
Oedema peripheral	–	1 (0.87)	
Hypoesthesia	–	2 (1.74)	
Cerebral infarction	1 (0.89)	–	
Headache	–	1 (0.87)	
Blood thyroid stimulating hormone decreased	–	1 (0.87)	
Helicobacter test positive	1 (0.89)	–	
Pruritus genital	1 (0.89)	1 (0.87)	
Dermatitis	1 (0.89)	–	
Dermatitis contact	–	1 (0.87)	
Eye inflammation	–	1 (0.87)	
Radius fracture	–	1 (0.87)	
Dysuria	–	1 (0.87)	
SAE	4 (3.57)	1 (0.87)	0.209[F]
Large intestine polyp	1 (0.89)	–	
Arthritis bacterial	1 (0.89)	–	
Rotator cuff syndrome	–	1 (0.87)	
Diffuse large b-cell lymphoma	1 (0.89)	–	
Cerebral infarction	1 (0.89)	–	
Discontinuation due to AE	2 (1.79)	–	0.242[F]

Note: Data are presented as numbers (%).
Abbreviations: ADR, adverse drug reaction; AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
[a]Between-group comparisons were performed using the Chi-square test (C) or Fisher's exact test (F), as appropriate.

lobeglitazone achieves glycaemic efficacy comparable to pioglitazone at a lower dose, with additional benefits on insulin sensitivity and lipid metabolism that may support long-term metabolic health.

The addition of lobeglitazone to a regimen of empagliflozin and metformin was well tolerated. At Week 24, the incidence of adverse events was comparable across all groups, with infrequent adverse drug reactions and no hypoglycaemia; only a single case of peripheral oedema was noted in the lobeglitazone arm. No cases of heart failure, bladder cancer, or bone fracture occurred, although the study was neither of sufficient size nor duration to exclude these risks. Notably, emerging evidence suggests that lobeglitazone may exert a more neutral effect on bone mineral density compared with pioglitazone.[24] Although lobeglitazone treatment was associated with significant weight gain compared to placebo, the magnitude was less than that previously reported with TZDs, which averaged 3–4 kg within 6 months and up to 5 kg over several years.[25,26] Modest increases in waist circumference were also observed, consistent with recent meta-analyses,[27,28] reflecting redistribution of fat from visceral to subcutaneous depots rather than true central adiposity expansion. The glucosuric and weight-reducing effects of SGLT2 inhibitors may help offset the fluid retention and weight gain typically associated with TZD therapy. While not observed in this trial, TZDs have been linked to worsening of diabetic macular oedema, a risk that may be attenuated by the diuretic effects of SGLT2 inhibitors.[29,30] Overall, our findings highlight the safety and tolerability of this combination therapy, suggesting that the complementary mechanisms of action may mitigate class-specific adverse effects and enhance its clinical utility.

Our study has some limitations. First, the study was conducted exclusively in Korean patients, who often exhibit insulin secretory dysfunction as a predominant pathogenic feature of T2DM.[31,32] This may limit the generalizability of our findings to populations with different underlying pathophysiological mechanisms. Therefore, additional studies in diverse ethnic groups are necessary to better understand the efficacy and safety profile of this therapy across various patient populations. Second, the follow-up period was relatively short, which limited our ability to fully assess the long-term efficacy and safety of the triple therapy comprising lobeglitazone, empagliflozin, and metformin. However, the additional 6-month extension phase provided some insight into the effects of lobeglitazone over at least 1 year. Further research with longer follow-up is warranted to evaluate the sustained outcomes of this combination. Third, the true incidence of hypoglycaemia may have been underestimated because asymptomatic episodes cannot be reliably detected without continuous glucose monitoring, and our evaluation was limited to symptomatic and self-monitored events. Moreover, because enrolment was limited to participants with fasting C-peptide levels >1.0 ng/mL, our findings are most applicable to individuals with preserved β-cell function and may not extend to those with advanced insulin secretory failure. Finally, this study focused solely on empagliflozin as the SGLT2 inhibitor. Future research should investigate the long-term efficacy and tolerability of combining lobeglitazone with other SGLT2 inhibitors in clinical settings. Such studies would provide broader insights

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TABLE 5 Adverse events for Study 2.

	Placebo ($N = 109$)	Lobeglitazone ($N = 110$)	p-value[a]
TEAE	37 (33.94)	31 (28.18)	0.357[C]
ADR	19 (17.43)	13 (11.82)	0.240[C]
Arthralgia	2 (1.83)	1 (0.91)	
Bone pain	1 (0.92)	–	
Intervertebral disc disorder	1 (0.92)	–	
Pain in extremity	1 (0.92)	–	
Spinal column stenosis	–	1 (0.91)	
Dyspepsia	2 (1.83)	–	
Chronic gastritis	1 (0.92)	–	
Duodenal ulcer	1 (0.92)	–	
Nausea	–	1 (0.91)	
Nasopharyngitis	–	2 (1.82)	
Cystitis	–	1 (0.91)	
Onychomycosis	–	1 (0.91)	
Pharyngitis	1 (0.92)	–	
Diabetic foot	1 (0.92)	–	
Dermatitis	–	1 (0.91)	
Pruritus	1 (0.92)	-	
Urticaria	–	1 (0.91)	
Diabetic retinopathy	1 (0.92)	–	
Dry eye	1 (0.92)	–	
Eye pruritus	1 (0.92)	–	
Uveitis	1 (0.92)	–	
Gout	1 (0.92)	–	
Hyperglycaemia	1 (0.92)	–	
Hypoesthesia	1 (0.92)	–	
Paraesthesia	1 (0.92)	–	
Benign prostatic hyperplasia	–	1 (0.91)	
Vulvovaginal pruritus	1 (0.92)	–	
Cough	2 (1.83)	–	
Hypoacusis	–	1 (0.91)	
Face oedema	–	1 (0.91)	
Micturition urgency	–	1 (0.91)	
Arteriosclerosis	–	1 (0.91)	
SAE	6 (5.50)	4 (3.64)	0.171[F]
Anal haemorrhage	–	1 (0.91)	
Anal polyp	–	1 (0.91)	
Duodenal ulcer	1 (0.92)	–	
Large intestine polyp	–	1 (0.91)	
Diabetic foot	1 (0.92)	–	
Intervertebral disc protrusion	1 (0.92)	–	
Foot fracture	1 (0.92)	–	
Gastrointestinal tract adenoma	1 (0.92)	–	
Carpal tunnel syndrome	1 (0.92)	–	
Pulmonary mass	–	1 (0.91)	
Discontinuation due to AE	3 (2.75)	–	0.122[F]

Note: Data are presented as numbers (%).
Abbreviations: ADR, adverse drug reaction; AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
[a]Between-group comparisons were performed using the Chi-square test (C) or Fisher's exact test (F), as appropriate.

into the potential of SGLT2 inhibitors in combination therapy with lobeglitazone.

Despite the limitations of our study, it provides valuable insights into the efficacy and safety of combination therapy with lobeglitazone, empagliflozin, and metformin in Korean patients with T2DM who exhibit inadequate glycaemic control. This research is particularly significant as it addresses a gap in the literature, given the limited data available on this specific combination regimen in Korean populations. Our findings are consistent with previous randomised controlled trials (RCTs) involving SGLT2 inhibitors and pioglitazone, which have demonstrated favourable outcomes, including improved glycaemic control and mitigated weight gain. To our knowledge, this is the first RCT to evaluate lobeglitazone in combination with empagliflozin, demonstrating comparable glycaemic efficacy to pioglitazone at a much lower dose (0.5 mg vs. 15–30 mg). The study expands the evidence base for metformin–TZD–SGLT2 inhibitor combination therapy and supports lobeglitazone as a low-dose, well-tolerated alternative—particularly relevant for Asian populations.

5 | CONCLUSION

The addition of lobeglitazone to a regimen of metformin and empagliflozin (10 mg or 25 mg) was both effective and well tolerated in patients with T2DM who had not achieved their glycaemic targets. It was well tolerated without increasing the risk of hypoglycaemia. These findings support the use of lobeglitazone as a viable add-on therapy for patients inadequately controlled with metformin and empagliflozin, thereby expanding personalised treatment options for managing T2DM.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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SUPPORTING INFORMATION

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

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