ORIGINAL ARTICLE

Randomized, Double-blind, Phase III Trial of Lobeglitazone Add-on to Metformin in Type 2 Diabetes (SENSITIZE INDIA)

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Abstract

Background: The efficacy and safety of lobeglitazone sulfate has been reported only in the Korean population, and no study has been conducted in India.

Materials and methods: In this 16-week randomized, double-blind, and multicenter study, the efficacy and safety of lobeglitazone sulfate 0.5 mg were evaluated with pioglitazone 15 mg. Type 2 diabetes mellitus (T2DM) patients with ≥7.5% glycated hemoglobin (HbA1c) ≤10.5% and on stable metformin dose were assigned to both treatment arms. The primary outcome was a mean change in HbA1c. Safety assessments included adverse events (AE), home-based glucose monitoring, vital parameters, electrocardiogram (ECG), and laboratory assessments.

Results: A total of 328 subjects were randomized equally in two groups. A statistically significant reduction in HbA1c at week 16 in the lobeglitazone group with the least square (LS) mean change: 1.01 [standard error (SE): 0.09] ($p < 0.0001$) was seen. The LS mean difference between the two groups was 0.05 (SE: 0.12) [95% confidence interval (CI): −0.18, 0.27], which was statistically significant ($p = 0.0013$). Statistically significant reductions were also observed in fasting and postprandial glucose. Treatment-emergent Aes (TEAE) were comparable between both groups.

Conclusion: Lobeglitazone 0.5 mg once daily was found to be efficacious and safe in the treatment of T2DM in the Indian population. Lobeglitazone significantly improved glycemic parameters and was noninferior to pioglitazone; hence, it could be a promising insulin sensitizer in T2DM management in India.

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Introduction

Glycemic control is the central goal in the treatment of type 2 diabetes mellitus (T2DM). Several orally administered glucose-lowering agents have been developed for the treatment of diabetes. Metformin remains the first-line low-cost treatment option for the majority of patients, with good glucose-lowering efficacy and an acceptable safety profile. However, a large number of patients with type 2 diabetes have inadequately controlled diabetes despite treatment with metformin and need an additional glucose-lowering agent.

Most patients with impaired glucose tolerance or noninsulin-dependent DM and around 25% of nonobese people with normal oral glucose tolerance have resistance to insulin-stimulated glucose absorption.[1] When insulin secretion is insufficient to overcome insulin resistance, hyperglycemia arises due to decreased insulin action. Due to compensatory hyperinsulinemia, β-cell lipotoxicity, and increased islet inflammation, insulin resistance reduces pancreatic β-cell function.[2,3] These factors result in increased β-cell apoptosis and progressive decreases in insulin secretory capacity. A rise in a number of cardiovascular risk factors is linked to insulin resistance.[4–8] Dyslipidemia, which is caused by insulin resistance, lowers adiponectin, small dense low-density lipoprotein particles, and high-density lipoprotein cholesterol and increases triglycerides and plasma-free fatty acids.[4,8–10] Steatohepatitis and hepatic steatosis are mostly caused by insulin resistance (nonalcoholic steatohepatitis).[10] Thiazolidinediones (TZDs) primarily affect adipose tissue and reduce insulin resistance by lowering hepatic triglycerides, lowering visceral fat mass and activity, and raising subcutaneous fat mass through the activation of peroxisome proliferator-activated receptor (PPAR) γ.[4,7,11,12] The main mechanism by which TZDs mitigate the negative consequences of insulin resistance is through the reduction of insulin resistance. TZDs reduce insulin resistance and increase the effectiveness of endogenous insulin, which lowers both fasting and postprandial hyperglycemia.

With an IC50 of 20 and 18 nM, respectively, lobeglitazone sulfate is a TZD that works by activating PPAR-α/γ dual agonist. It was created in Korea by Chong Kun Dang Pharmaceutical to treat diabetes, and it differs significantly from the other two PPAR agonists, pioglitazone and rosiglitazone, in that it has PPAR-α activity. In South Korea and India, the medication is authorized for the management of T2DM. In a 24-week randomized, double-blind, multicenter clinical trial, lobeglitazone sulfate 0.5 mg once daily was found to be safe and effective when compared to a placebo in treating naïve Korean people with T2D.[13]

Prior to the initiation of this study, no study on lobeglitazone in India was conducted. Hence, a study was conducted with the primary objective of evaluating the efficacy of lobeglitazone sulfate 0.5 mg once daily in comparison with pioglitazone 15 mg once daily in subjects with T2DM with inadequate glycemic control on metformin (≥1500 mg/day). The secondary objective was to evaluate the safety of lobeglitazone sulfate 0.5 mg once daily in comparison with pioglitazone 15 mg once daily in subjects with T2DM.

Materials and Methods

Trial Design

This was a 16-week, multicenter, randomized, double-blind, double-dummy, active-controlled, parallel-group trial to compare the safety and effectiveness of pioglitazone (15 mg) once daily vs lobeglitazone sulfate (0.5 mg) once a day. The study was conducted from December 2021 to September 2022 across 20 sites in India. The study was designed and monitored following the Sponsor procedures complying with the ethical principles of good clinical practice by following the declaration of Helsinki, as required by the regulatory authority of India. The study was reviewed by an Institutional Ethics Committee (EC) in India at each

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investigator site. Proper approval from EC was obtained by each investigator before the initiation of the study. The trial was registered with the number CTRI/2021/12/038391. The study protocol is available from http://ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=63033&EncHid=&userName=lobeglitazone

Participants

The trial comprised male and female T2DM patients who were at least 18 years old and no older than 65 years old, had a glycated hemoglobin (HbA1c) of at least 7.5% and ≤10.5% at screening, and were on a stable dose of metformin (≥ 1500 mg/day) as monotherapy for at least 10 weeks previous to screening. Patients excluded were with a history of T1DM, metabolic acidosis or diabetic ketoacidosis, a history of more than one episode of hypoglycemia, body mass index of >45 kg/m^2, elevated thyroid stimulating hormone levels, abnormal liver function parameters, a significant history of cardiovascular events, ejection fraction of <50% on two-dimensional echocardiography and on antidiabetic medications other than metformin.

Randomization and Masking

The following therapies were randomly assigned to eligible individuals: arm 1—lobeglitazone sulfate 0.5 mg administered as one tablet once daily and a matching placebo of pioglitazone tablet for 16 weeks. Arm 2—pioglitazone 15 mg, one tablet once daily, and a matching placebo of lobeglitazone sulfate tablet for 16 weeks. Each randomized subject received two tablets in the morning. Treatments were administered for 16 weeks. Throughout the course of the trial, subjects received metformin at stable dosages of ≥1500 mg daily under open-label conditions. Metformin was dispensed in the form of 500 and 1000 mg sustained-release tablets and was taken along with the study medication. Based on the investigator's discretion, different numbers of tablets were taken in the morning and evening.

An interactive web response system was used to assign each eligible participant a unique randomization number [interactive web response system (IWRS)] progressively. A distinct material pack code that was connected to the computer-generated randomization method was used to identify each study medication. The pack of study materials was assigned at each visit through. Study drugs and their dummy placebo were identical and presented in the same packaging to ensure blinding of the medication. The randomization code of a withdrawn subject was not reused. The IWRS provided the investigator(s) or pharmacists with the randomization codes allocated to the subjects, concealing the treatment allocation.

Procedures

Treatment started at visit 1, and subsequent visits two, three, four, and five were conducted after 4, 8, 12, and 16 weeks of treatment. At the time of the run-in visit, subjects received a glucometer and a diary to record information regarding the delivery of study drugs, adverse events (AEs), and self-monitored blood glucose levels. Assessment of efficacy parameters like HbA1c, fasting blood glucose (FBG), postprandial plasma glucose (PPG), and safety parameters like lipid profile, urine analysis, liver function tests, and hematology were performed in the centralized laboratory following standard procedures. Vital parameters and electrocardiogram were taken at the time of each visit as per standard protocols. Weighing scales of the same make were centrally provided to the sites. Subjects could discontinue the investigational product or comparator at the discretion of the investigator for valid reasons, as well as voluntarily discontinue study participation before the completion of the study.

Subjects meeting prespecified rescue criteria [fasting plasma glucose (FPG) >240 mg/dL at week 4; week 8; HbA1c >8.5% or FPG >200 mg/dL at week 12] were eligible for open-label rescue medication. Antidiabetic medications, except other TZDs or their combinations, were permitted as rescue medication. Change in dose of metformin was not permitted. Records of treatment compliance for each subject were kept during site visits till the completion of the study.

Efficacy and Safety Assessment

The mean difference in HbA1c levels between the pioglitazone and lobeglitazone sulfate groups from baseline to week 16 was the primary efficacy endpoint. Changes in fasting insulin, PPG, insulin resistance, fasting glucose, homeostasis model assessment-insulin resistance (HOMA-IR), and HOMA-β, as well as the percentage of subjects who achieved a therapeutic glycemic response and the percentage of subjects in need of rescue medication, were the secondary endpoints.

Treatment-emergent AEs (TEAE), laboratory testing (hematology, biochemistry, and urine analysis), vital signs, electrocardiogram (ECG), and physical examination were used to evaluate safety. Every AE that occurred throughout the study was documented, starting from the point of enrolment. Self-monitored blood glucose readings and hypoglycemic events were collected in the subject diary and reviewed by the investigator at each visit.

Data Quality Assurance

The study monitor conducted on-site and remote monitoring visits, reviewing electronic case report forms (eCRFs) for accuracy and completeness. The investigator answered data questions as needed. Data generated during the completion of study-specific procedures were recorded in the subject's source documents or medical records. The eCRF was created by transcribing the data. The investigator was in charge of making sure all the data put in the eCRFs was adequate and accurate.

Statistical Analysis

With 164 participants in each treatment group (pioglitazone and lobeglitazone sulfate), a power of 90% was estimated at a one-sided significance level of 5%, an assumed standard deviation of 1.1% of HbA1c, and a 20% dropout rate to show that lobeglitazone sulfate was not inferior to pioglitazone in terms of HbA1c change from baseline at week 16, with a noninferiority (NI) margin of 0.40. The international guidelines for the development of antidiabetic agents (United States Food and Drug Administration guidance document 2008, Diabetes Mellitus: Developing drugs and biologics) are compliant with the NI margin of 0.40, which was chosen based on the effect size of the active comparator (pioglitazone 15 mg) in placebo-controlled studies. The continuous baseline variables (characteristics) of patients in two groups were summarized in terms of mean and standard deviation, while the categorical variable gender was expressed as frequency and percentage. Using the mixed model repeated measure (MMRM) technique, the difference in HbA1c between lobeglitazone sulfate 0.5 mg and pioglitazone 15 mg was compared from baseline to weeks 4, 8, 12, and 16 (end of treatment). Data of subjects while receiving rescue medication was considered missing. Imputation of missing data was performed only when analysis of covariance (ANCOVA) was used. For this investigation, the last observation carried forward (LOCF) was used. The MMRM approach was used to evaluate several secondary endpoints, such as mean change in FPG, PPG, HOMA-β, HOMA-IR, and fasting insulin, using the same variables. The primary analysis set was the per protocol analysis set, which comprised all randomized subjects who received at least one dosage of study medication, finished the study, and did not have any significant protocol deviations. Using Statistical Analysis System® software 9.4, all scheduled analyses were executed

following database lock, with a *p*-value of <0.05 deemed statistically significant.

Results

A total of 438 patients were screened across 20 centers in India. Out of these, 110 did not meet one or more inclusion criteria, and 328 subjects were randomized in a 1:1 ratio to lobeglitazone sulfate 0.5 mg group (164) and pioglitazone 15 mg group (164). Eight patients from the lobeglitazone sulfate group and 12 subjects from the pioglitazone group were discontinued during the study due to reasons: loss to follow-up, noncompliance to procedures, or self-withdrawal (Fig. 1). The final per-protocol population was 156 and 152 in lobeglitazone sulfate and pioglitazone group, respectively. The study duration was December 2021 to September 2022.

The demographic and baseline characteristics were similar between the two therapy groups (Table 1). The participants in the pioglitazone 15 mg group had a mean age of 49.7 (9.35) years, whereas the lobeglitazone sulfate 0.5 mg group had a mean age of 51.1 (9.13) years. The difference in age between the two groups was not statistically significant. The gender distribution in the two groups was nearly identical, with 41.8% of the lobeglitazone group and 43.4% of the pioglitazone group being female. There was no significant difference observed in the subjects' body weight, height, eGFR, HbA1c, FBG, PPG, HOMA-β, and Insulin between the two groups. Drug compliance was defined as utilizing at least 80% of the prescribed study medicines by the subjects. For the lobeglitazone sulfate 0.5 mg group, the mean [standard deviation (SD)] total drug compliance was 99.7% (1.17%), while for the pioglitazone 15 mg group, it was 99.6% (1.26%).

Primary Efficacy Endpoint

For the PP group, the MMRM approach was used to analyze the primary effectiveness objective, which is the change in HbA1c (%) values from baseline to week 16 (Table 2). Both therapy groups and all visits showed a decrease in the mean HbA1c values. The lobeglitazone sulfate 0.5 mg group's HbA1c levels decreased in the per-protocol population from baseline to week 16 in a statistically significant and clinically meaningful way, with a least squares (LS) mean change of—1.01 (SE 0.09) ($p < 0.0001$). Between the two groups, the LS mean difference was 0.05 (SE 0.12) [95% confidence interval (CI) −0.18, 0.27]. The 95% confidence interval's upper limit was less than the NI margin (0.40), indicating that lobeglitazone sulfate 0.5 mg was not inferior to pioglitazone 15 mg ($p = 0.0013$). Furthermore, in terms of lowering the mean change in HbA1c% levels from baseline to weeks 4, 8, and 12, the lobeglitazone sulfate 0.5 mg group was significantly noninferior to the pioglitazone 15 mg group ($p < 0.05$). The results were validated using LOCF-ANCOVA with the modified intent-to-treat (mITT) population.

Secondary Efficacy Endpoint

Using the MMRM approach, mean changes in plasma glucose levels during fasting and postprandial periods from baseline to week 16 were examined in the mITT population. In the lobeglitazone sulfate 0.5 mg group, there was a statistically significant decrease in FPG levels from baseline to week 16. At week 16, the lobeglitazone sulfate 0.5 mg group experienced an LS mean [standard error (SE)] change of −41.31 (3.25) mg/dL ($p < 0.0001$), while the pioglitazone 15 mg group experienced a decrease of −35.54 (3.09) mg/dL. Comparable improvement in FPG levels was suggested by the statistically not significant [−5.76 (95% CI −14.27, 2.74) mg/dL; $p = 0.183$] LS mean difference between the two groups in change from baseline to week 16. Within the treatment groups, the change in FPG levels from baseline at weeks 4, 8, and 12 was statistically significant ($p < 0.0001$), whereas the LS mean difference

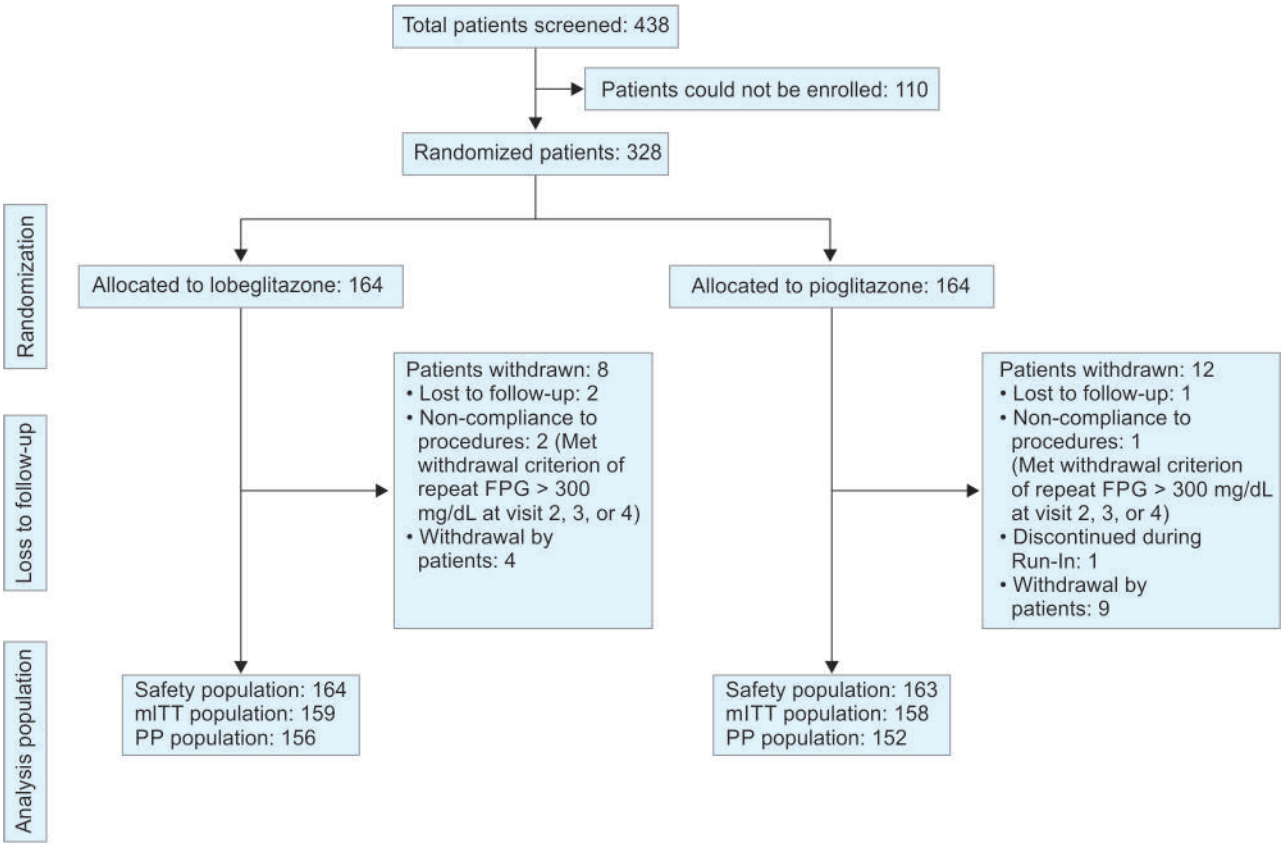

Fig. 1: Consolidated standards of reporting trials diagram

Table 1: Baseline characteristics of patients in two treatment groups (mITT population)

Parameter	*Statistical parameter*	*Group*	
		Pioglitazone N = 159	*Lobeglitazone N = 158*
Age (years)	*n*	159	158
	Mean (SD)	49.7 (9.35)	51.1 (9.13)
	Median	49.9	51.3
	Minimum, maximum	26.2, 65.1	26.8, 65.0
Gender, *n* (%)	Male	90 (56.6)	92 (58.2)
	Female	69 (43.4)	66 (41.8)
Body weight (kg)	Mean (SD)	70.7 (11.80)	71.1 (11.11)
	Median	68.5	70.6
	Minimum, maximum	49.4, 102.8	45.3, 98.0
Height (cm)	Mean (SD)	162.2 (8.31)	161.7 (8.87)
	Median	162.0	162.0
	Minimum, maximum	130.0, 181.0	142.0, 187.3
eGFR (mL/minute/1.73m^2)	Mean (SD)	100.9 (28.25)	95.6 (24.65)
	Median	97.0	90.0
	Minimum, maximum	47.0, 226.0	47.0, 193.0
FBG (mg/dL)	Mean (SD)	169.6 (54.94)	179.2 (61.95)
	Median	160.0	168.5
	Minimum, maximum	(81.0, 523.0)	(85.0, 435.0)
Postprandial blood glucose (mg/dL)	Mean (SD)	251.3 (70.37)	246.3 (67.52)
	Median	252.0	242.0
	Minimum, maximum	(75.0, 485.0)	(84.0, 472.0)
HOMA-β	Mean (SD)	67.7 (86.26)	79.8 (133.97)
	Median	42.4	47.3
	Minimum, maximum	(4.8, 813.9)	(1.8, 1435.7)
HOMA-IR	Mean (SD)	6.3 (6.0)	7.9 (7.08)
	Median	4.5	5.7
	Minimum, maximum	(0.6, 43.2)	(0.4, 33.0)
Insulin (mU/L)	Mean (SD)	15.3 (13.59)	18.3 (16.46)
	Median	11.3	12.5
	Minimum, maximum	(2.4, 100.6)	(0.8, 99.7)

eGFR: estimated glomerular filtration rate, HbA1c: glycosylated hemoglobin; HOMA: homeostasis model assessment

between the two groups was not significant ($p > 0.05$). The lobeglitazone sulfate 0.5 mg group showed a statistically significant decrease in PPG from baseline to week 16. At week 16, the lobeglitazone sulfate 0.5 mg group experienced an LS mean (SE) decrease of –41.24 (5.81) mg/dL ($p < 0.0001$), while the pioglitazone 15 mg group experienced a change of –32.87 (5.57) mg/dL ($p < 0.0001$). The two groups' LS mean difference in PPG levels from baseline to week 16 was statistically not significant [–8.37 (95% CI –23.59, 6.84) mg/dL; $p = 0.279$], indicating that the two groups' PPG levels had improved similarly. Additionally, the PPG levels in both treatment groups changed from baseline at weeks 4, 8, and 12 ($p < 0.05$), and the LS mean difference between the two groups was not significant ($p > 0.05$) (Table 3).

Similarly, the MMRM technique was applied to the mITT population to examine changes in fasting insulin, HOMA-IR, and HOMA-β values from baseline week 16 (Table 4). In the lobeglitazone group, there was a statistically significant decrease in insulin resistance. The lobeglitazone sulfate 0.5 mg group experienced an LS mean (SE) change in HOMA-β levels of 13.47 (16.54) from baseline to week 16, while the pioglitazone 15 mg group experienced a change of –11.04 (16.13). The lobeglitazone sulfate 0.5 mg group experienced an LS mean (SE) change in HOMA-IR levels at week 16 of –2.41 (0.65) ($p = 0.0003$), while the pioglitazone 15 mg group experienced - 2.57 (0.64). At week 16, the lobeglitazone sulfate 0.5 mg group experienced an LS mean (SE) change in fasting insulin levels of –2.77 (1.65) mU/L, while the pioglitazone 15 mg group experienced a change of –4.75 (1.60) mU/L. The statistical analysis revealed that there was no significant difference ($p > 0.05$) between the two groups, indicating that the changes in HOMA-β, HOMA-IR, and fasting insulin levels were similar. At week 12, there was no statistically significant difference between the two groups' baseline values for any of these parameters, with the exception of HOMA-β in the lobeglitazone sulfate 0.5 mg group ($p = 0.027$). At week 12, there were no statistically significant differences between the two groups ($p > 0.05$).

Table S1 shows the percentage of cumulative participants that achieved response for FBG and HbA1c at various time points for the mITT population. For both measures, the proportions that differed between the two groups at different visits were not statistically significant. Additionally, there was a statistically insignificant difference in weight between the two therapy groups from baseline to week 12/16 (Table S2).

Table 2: Between and within-group comparison of glycosylated hemoglobin (HbA1c percentage) at different time points (PP, population): MMRM

Visit	*Statistics*	*Pioglitazone (N = 156)*	*Lobeglitazone (N = 152)*	*p-value*[‡]
Baseline	Mean (SD)	8.56 (0.94)	8.50 (0.89)	0.566
	Median	8.50	8.35	
	Minimum, maximum	(6.0, 11.6)	(6.9, 12.6)	
Baseline—week 4 (day 29)	LSM (SE); (95% CI)	−0.10 (0.09); (−0.27, 0.08)	−0.19 (0.09); (−0.36, −0.01)	
	p-value[†]	0.277	0.037	
	Difference: LSM (SE); (95% CI)	−0.09 (0.12); (−0.33, 0.15)		<0.0001
Baseline—week 8 (day 57)	LSM (SE); (95% CI)	−0.41 (0.09); (−0.60, −0.23)	−0.53 (0.09); (−0.71, −0.35)	
	p-value[†]	<0.0001	<0.0001	
	Difference: LSM (SE); (95% CI)	−0.12 (0.13); (−0.37, 0.13)		<0.0001
Baseline—week 12 (day 85)	LSM (SE); (95% CI)	−0.74 (0.09); (−0.92, −0.55)	−0.84 (0.09); (−1.02, −0.65)	
	p-value[†]	<0.0001	<0.0001	
	Difference: LSM (SE); (95% CI)	−0.10 (0.13); (−0.35, 0.15)		<0.0001
Baseline—week 16 (day 113)	LSM (SE); (95% CI)	−1.06 (0.08); (−1.22, −0.89)	−1.01 (0.09); (−1.19, −0.84)	
	p-value[†]	<0.0001	<0.0001	
	Difference: LSM (SE); (95% CI)	0.05 (0.12); (−0.18, 0.27)		0.0013

LSM, least square mean; SE, standard error; difference obtained as lobeglitazone–pioglitazone, [†]obtained for within-group change from baseline; [‡]obtained for one-sided NI test with margin 0·4; MMRM, mixed model repeated measure

Safety Evaluation

In the safety population, 39 participants out of 327 (11.93%) suffered TEAEs. Table 5 provides an overview of all TEAEs by preferred word (PT) and organ class (SOC) in the Medical Dictionary for Regulatory Activities (MedDRA) system. The two groups' overall incidence of TEAEs was similar, with 19 (11.7%) in the group receiving lobeglitazone sulfate 0.5 mg and 20 (12.2%) in the group receiving pioglitazone 15 mg. No serious AE or death was reported during the study, and all the AEs were mild to moderate. In the lobeglitazone 0.5 mg group, 16 subjects (9.8%) had mild, and three subjects (1.8%) had moderate-intensity events. One patient (0.6%) who had a mild event was considered to be related to lobeglitazone sulfate, while 15 subjects (9.2%) with mild events and three subjects (1.8%) with moderate events were unrelated to the drug. In the pioglitazone 15 mg group, 17 subjects (10.4%) had mild, and three subjects (1.8%) had moderate-intensity events, and none were related to the drug.

Furthermore, at baseline, the hematological (Table S3) and biochemistry (Table S4) parameters were similar, and at the study's conclusion, there were no statistically significant variations in the mean values amongst treatment groups. Furthermore, no changes in the laboratory, ECG parameters, vital signs, or any other finding specific to the individual participant that would be clinically significant were observed (data not shown).

Discussion

This is the first clinical trial assessing the safety and effectiveness of lobeglitazone sulfate 0.5 mg in individuals with T2DM from India who are not controlling their blood sugar levels adequately even after taking metformin. Lobeglitazone sulfate 0.5 mg once daily demonstrated a statistically significant and clinically relevant reduction in HbA1c levels at week 16 in this randomized, double-blind, and active comparator investigation. The decrease was comparable to 15 mg of pioglitazone. Over a 16-week period, lobeglitazone caused an HbA1c (%) level drop of −1.01. A similar effect size was reported with pioglitazone (HbA1c reduction of −0.8 to −1.3) in phase III studies.[14] Interestingly, at weeks 4, 8, and 12, HbA1c (%) reductions were numerically larger in magnitude with lobeglitazone compared to pioglitazone with a treatment difference of −0.09, −0.12, and −0.10, respectively, suggesting its potential to cause an early reduction in glycemic parameters. NI of lobeglitazone with pioglitazone, as observed in this study, was also demonstrated in an earlier 24-week, randomized, double-blind clinical trial, providing replicate evidence of glucose-lowering efficacy of lobeglitazone.[15] The HbA1c drop from baseline in the 24-week research was −0.74% in both groups and when added to metformin, lobeglitazone sulfate was determined to be noninferior in efficacy when compared to pioglitazone. The FPG, PPG, and insulin parameters significantly decreased, according to the results of the secondary endpoint analysis. In our investigation, the decreases in FPG and PPG were similar for the two groups.

A major contributor to the pathophysiology of T2DM, insulin resistance is a powerful predictor of heart disease, myocardial infarction, and stroke.[16–18] Insulin resistance was linked to a 64% increase in the risk of stroke (hazard ratio 1/64, 95% CI 1.29, 2.08) and a 28% increase in the risk of coronary heart disease (hazard ratio 1.28, 95% CI 1.10, 1.50) in a 22-year follow-up analysis.[19] In this trial, the lobeglitazone group had a reduction in IR (HOMA-IR) of more than two units (−2.41 units). It has been demonstrated that the risk of cardiovascular events is significantly affected by a one-unit variation in HOMA-IR.[18]

In every pioglitazone registration clinical study, there was a dose-dependent increase in weight. In the United States placebo-controlled monotherapy trials, patients receiving pioglitazone experienced an average weight change of 0.5–2.8 kg, whereas those receiving placebo experienced an average weight change of–1.3 to–1.9 kg.[14] However, in this study, the weight did not change significantly in the pioglitazone and lobeglitazone groups. This might be attributed to the diet and exercise counseling of patients during the study. There was a small, nonsignificant mean increase of 0.68% (SD: 5.149%) in hematocrit and a mean change of 0.3 mEq/L (SD: 4.52 mEq/L) in the sodium levels in the lobeglitazone group. This is inconsistent with the known fluid retention effect of the TZD class of drugs. Although the exact mechanism of fluid retention and

Table 3: Between and within-group comparison of FPG and PPG at different time points (mITT population): MMRM

Visit	*Parameter*	*Statistics*	*Pioglitazone (N = 159)*	*Lobeglitazone (N = 158)*	*p-value*[‡]
Baseline: week 4 (day 29)	FBG (mg/dL)	LSM (SE); (95% CI)	−20.09 (3.19); (−26.37, −13.81)	−19.59 (3.18); (−25.84, −13.34)	
		p-value[†]	<0.0001	<0.0001	
		Difference: LSM (SE); (95% CI)	0.50 (4.38); (−8.13, 9.13)		0.909
	Postprandial blood glucose (mg/dL)	LSM (SE); (95% CI)	−18.01 (6.11); (−30.03, −5.99)	−23.23 (6.06); (−35.16, −11.30)	
		p-value[†]	0.0034	0.0002	
		Difference: LSM (SE); (95% CI)	−5.21 (8.38); (−21.70, 11.27)		0.534
Baseline: week 8 (day 57)	FBG (mg/dL)	LSM (SE); (95% CI)	−21.66 (3.09); (−27.74, −15.59)	−29.41 (3.10); (−35.52, −23.30)	
		p-value[†]	<0.0001	<0.0001	
		Difference: LSM (SE); (95% CI)	−7.75 (4.25); (−16.12, 0.62)		0.069
	Postprandial blood glucose (mg/dL)	LSM (SE); (95% CI)	−18.85 (5.84); [−30.34, −7.35]	−25.64 (5.87); [−37.20, −14.09]	
		p-value[†]	0.0014	<0.0001	
		Difference: LSM (SE); (95% CI)	−6.80 (8.02); (−22.58, 8.99)		0.397
Baseline: week 12 (day 85)	FBG (mg/dL)	LSM (SE); (95% CI)	−36.60 (3.07); (−42.65, −30.56)	−33.69 (3.09); (−39.79, −27.60)	
		p-value[†]	<0.0001	<0.0001	
		Difference: LSM (SE); (95% CI)	2.91 (4.22); (−5.40, 11.21)		0.491
	Postprandial blood glucose (mg/dL)	LSM (SE); (95% CI)	−31.92 (5.54); (−42.82, −21.01)	−39.70 (5.58); (−50.67, −28.73)	
		p-value[†]	<0.0001	<0.0001	
		Difference: LSM (SE); (95% CI)	−7.78 (7.57); (−22.69, 7.12)		0.305
Baseline: week 16 (day 113)	FBG (mg/dL)	LSM (SE); (95% CI)	−35.54 (3.09); (−41.62, −29.46)	−41.31 (3.25); [-47.71,-34.90]	
		p-value[†]	<0.0001	<0.0001	
		Difference: LSM (SE); (95% CI)	−5.76 (4.32); (−14.27, 2.74)		0.183
	Postprandial blood glucose (mg/dL)	LSM (SE); (95% CI)	−32.87 (5.57); (−43.84, −21.90)	−41.24 (5.81); (−52.67, −29.81)	
		p-value[†]	<0.0001	<0.0001	
		Difference: LSM (SE); (95% CI)	-8.37 (7.72); (−23.59, 6.84)		0.279

LSM, least square mean; SE, standard error; difference obtained as lobeglitazone–pioglitazone; [†]obtained for within-group change from baseline; [‡]obtained for between-group change from baseline; MMRM, mixed model repeated measure

weight gain with TZDs is not known, the role of sodium uptake from renal tubules, potentially with the involvement of cotransporters, has been hypothesized.[20,21] The higher affinity of lobeglitazone to PPAR-γ compared to other TZDs, resulting in a 30 times smaller dose of lobeglitazone (0.5 mg) compared to pioglitazone (15 mg), has the potential to retain antidiabetic effects with reduced side effects.[22]

In this study, no serious AEs or deaths occurred in the study population. No subject reported severe hypoglycemia or an event of cardiac failure. AEs of hypoglycemia are known with the administration of glucose-lowering agents; however, TZD have a relatively lower risk of hypoglycemia. In this study, three subjects (1.8%) reported mild (level 1) hypoglycemia in the lobeglitazone group. This incidence is similar to a 2% incidence of hypoglycemia reported with pioglitazone.[14] An important AE associated with the use of TZDs is cardiac failure; however, no such event was reported during the study. In similar studies, TZD usage has been linked to mild-to-moderate edema AEs. In a pioglitazone clinical trial, edema was reported by 4.8% of pioglitazone-treated patients vs 1.2% of placebo-treated patients.[14] Edema incidence of 1–2.5% has been reported in the placebo arm in different studies.[23] In this study, two subjects (1.2%) in the lobeglitazone group reported mild peripheral edema, which resolved during the study. One of the

Table 4: Between and within-group comparison of mean change in HOMA-B, HOMA-IR, and fasting insulin from baseline (mITT population)—MMRM

Visit	*Parameter*	*Statistics*	*Pioglitazone (N = 159)*	*Lobeglitazone (N = 158)*	*p-value‡*
Baseline—week 12 (day 85)	HOMA-β	LSM (SE); (95% CI)	21.81 (32.09); (−41.39, 85.01)	71.51 (32.19); (8.12, 134.91]	
		p-value†	0.497	0.027	
		Difference: LSM (SE); (95% CI)	49.70 (44.55); (−38.06, 137.47)		0.266
	HOMA-IR	LSM (SE); (95% CI)	−1.63 (0.89); (−3.38, 0.12)	−0.97 (0.89); (−2.71, 0.78)	
		p-value†	0.068	0.278	
		Difference: LSM (SE); (95% CI)	0.66 (1.21); (−1.72, 3.05)		0.586
	Insulin (mU/L)	LSM (SE); (95% CI)	−1.60 (2.14); (−5.81, 2.62)	0.66 (2.15); (−3.57, 4.89)	
		p-value†	0.456	0.758	
		Difference: LSM (SE); (95% CI)	2.26 (2.92); (−3.48, 8.00)		0.439
Baseline—week 16 (day 113)	HOMA-β	LSM (SE); (95% CI)	−11.04 (16.13); (−42.82, 20.74)	13.47 (16.54); (−19.12, 46.06)	
		p-value†	0.494	0.416	
		Difference: LSM (SE); (95% CI)	24.51 (20.19); (−15.32, 64.35)		0.226
	HOMA-IR	LSM (SE); (95% CI)	−2.57 (0.64); (−3.82, −1.32)	−2.41 (0.65); (−3.70, −1.13)	
		p-value†	<0.0001	0.0003	
		Difference: LSM (SE); (95% CI)	0.15 (0.82); (−1.46, 1.77)		0.852
	Insulin (mU/L)	LSM (SE); (95% CI)	−4.75 (1.60); (−7.90, −1.60]	−2.77 (1.65); (−6.02, 0.48)	
		p-value†	0.003	0.095	
		Difference: LSM (SE); [95% CI]	1.98 (2.08); (−2.11, 6.07)		0.341

LSM, least square mean; SE, standard error; difference obtained as lobeglitazone–pioglitazone; †obtained for within-group change from baseline; ‡obtained for between-group change from baseline; HOMA-β, homeostatic model assessment–percentage β-cell; HOMA-IR, homeostatic model assessment–insulin resistance; MMRM, mixed model repeated measure

limitations of the study is the duration of follow-up, which could have been longer to establish long-term safety.

Conclusion

To sum up, the primary pathophysiological flaw in type 2 diabetes is insulin resistance, and the only class of antidiabetic medications that address insulin resistance exclusively is TZD. Lobeglitazone (0.5 mg) is a new dual PPAR agonist that was recently approved in India. This trial, the first on lobeglitazone in Indian patients, showed that lobeglitazone was just as effective as pioglitazone (15 mg) in treating metformin-uncontrolled type 2 diabetes in Indian patients without posing a significant risk to safety. In the study, lobeglitazone significantly improved glycemic parameters and was well tolerated. Lobeglitazone was found to be noninferior to pioglitazone in terms of change in fasting insulin, HOMA-IR, and HOMA-β; hence, it may be a promising insulin sensitizer for the management of type 2 diabetes in India.

Evidence before Study

We did a PubMed search in September 2022 for publications in English, using the term "lobeglitazone," and got 42 hits with pharmacokinetic studies, randomized trials, and review articles. Lobeglitazone has been approved in Korea since 2013, and all the Korean studies showed clinically meaningful improvements in HbA1c, other glycemic parameters, insulin resistance, and lipid parameters with lobeglitazone either as a monotherapy or in combination with one or more anti-hyperglycemic medications. Pharmacokinetic studies of lobeglitazone with other classes of antidiabetic medications like sitagliptin, dapagliflozin, warfarin, amlodipine, and ketoconazole have not shown any major drug–drug interactions or tolerability issues. We found only one article evaluating the efficacy and safety of lobeglitazone added to metformin in patients with T2DM in the Korean population.

Added Value of This Study

This is the first study of lobeglitazone conducted in the non-Korean population (Indian study). In this randomized, double-blind, active control, and add-on to the metformin study, there was a statistically significant reduction in glycemic parameters. The mean change from baseline in HbA1c percentage in the lobeglitazone 0.5 mg group was noninferior to that in the pioglitazone 15 mg group. There were no major safety concerns reported in the study. Lobeglitazone was safe and well tolerated. This study confirmed the efficacy and safety of lobeglitazone 0.5 mg in the non-Korean (Indian) population.

Implications of All the Available Evidence

Thiazolidinediones (TZD) act on insulin resistance, the core defect of diabetes, and have been used for treating diabetes for more than three decades. Lobeglitazone, a novel dual PPAR agonist, is a favorable alternative to the existing glitazones for treating type 2 diabetes with good efficacy and tolerability.

Contributors

The collection, interpretation, and analysis of the data, as well as the manuscript's revision, were all done by the authors. All authors agreed to be held accountable for all aspects of the work, including making sure that any concerns about the accuracy or integrity of any part of the work are duly investigated and resolved. They also had complete access to all of the study's data and final say over whether

Table 5: Summary of subjects with TEAE (safety population)

System organ class preferred term	*Pioglitazone (N = 164)*	*Lobeglitazone (N = 163)*
	n (%)	
Any event	20 (12.2)	19 (11.7)
Blood and lymphatic system disorder	3 (1.8)	0
Lymphopenia	1 (0.6)	0
Thrombocytopenia	2 (1.2)	1 (0.6)
Gastrointestinal disorders	2 (1.2)	3 (1.8)
Diarrhea	2 (1.2)	2 (1.2)
Dyspepsia	0	1 (0.6)
General disorders and administration site conditions	2 (1.2)	3 (1.8)
Asthenia	1 (0.6)	0
Edema peripheral (mild)	0	2 (1.2)
Pyrexia	1 (0.6)	1 (0.6)
Infections and infestations	1 (0.6)	1 (0.6)
Urinary tract infection	1 (0.6)	1 (0.6)
Injury, poisoning, and procedural complications	0	1 (0.6)
Clavicle fracture	0	1 (0.6)
Investigations	0	1 (0.6)
Liver function tests increased	0	1 (0.6)
Metabolism and nutrition disorders	8 (4.9)	7 (4.3)
Dyslipidemia	4 (2.4)	3 (1.8)
Hyperglycemia	1 (0.6)	0
Hypertriglyceridemia	0	1 (0.6)
Hypoglycemia	3 (1.8)	3 (1.8)
Nervous system disorders	3 (1.8)	3 (1.8)
Diabetic neuropathy	1 (0.6)	0
Dizziness	0	1 (0.6)
Headache	2 (1.2)	2 (1.2)
Psychiatric disorders	1 (0.6)	1 (0.6)
Insomnia	1 (0.6)	1 (0.6)
Respiratory, thoracic, and mediastinal disorders	2 (1.2)	0
Cough	1 (0.6)	0
Oropharyngeal pain	1 (0.6)	0

Percentages were based on the number of subjects in the safety population in the respective treatment group; system organ class and preferred terms were coded using the MedDRA version 24.0 or the latest available dictionary; if a subject experienced more than one episode of an AE, the subject was counted once for that event

to submit the work for publication. Verifying study data and designing the study were tasks completed by MT, RK, and WW.

Declaration of Interests

SJ received consulting fees from Glenmark. The rest of the authors do not have any competing interests.

Data Sharing

Any questions or concerns related to clinical trial data mentioned in this manuscript can be addressed to Glenmark's clinicaltrialsdisclosuredesk@glenmarkpharma.com mail.

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References

1. Reaven GM. Role of insulin resistance in human disease (syndrome X): an expanded definition. Annu Rev Med 1993;44:121–131.
2. Pernicova I, Korbonits M. Metformin–mode of action and clinical implications for diabetes and cancer. Nat Rev Endocrinol 2014;10(3):143–156.
3. Prentki M, Nolan CJ. Islet beta cell failure in type 2 diabetes. J Clin Invest 2006;116(7):1802–1812.
4. Savage DB, Petersen KF, Shulman GI. Disordered lipid metabolism and the pathogenesis of insulin resistance. Physiol Rev 2007;87(2):507–520.
5. Lebovitz HE, Banerji MA. Treatment of insulin resistance in diabetes mellitus. Eur J Pharmacol 2004;490(1-3):135–146.
6. Czech MP. Insulin action and resistance in obesity and type 2 diabetes. Nat Med 2017;23(7):804–814.
7. . Lebovitz HE. Oxford Textbook of Endocrinology and Diabetes, 2nd Edition. Oxford: OXFORD University Press; 2011.
8. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988;37(12):1595–1607.
9. Lebovitz HE, Banerji MA. Insulin resistance and its treatment by thiazolidinediones. Recent Prog Horm Res 2001;56:265–294.

10. Shulman GI. Ectopic fat in insulin resistance, dyslipidemia, and cardiometabolic disease. N Engl J Med 2014;371(12):1131–1141.
11. Tontonoz P, Spiegelman BM. Fat and beyond: the diverse biology of PPARgamma. Annu Rev Biochem 2008;77:289–312.
12. Olefsky JM, Saltiel AR. PPAR gamma and the treatment of insulin resistance. Trends Endocrinol Metab 2000;11(9):362–368.
13. Kim SG, Kim DM, Woo JT, et al. Efficacy and safety of lobeglitazone monotherapy in patients with type 2 diabetes mellitus over 24-weeks: a multicenter, randomized, double-blind, parallel-group, placebo controlled trial. PLoS One 2014;9(4):e92843.
14. ACTOS (pioglitazone hydrochloride) tablets for oral use: US Prescribing Information. Link: label (fda.gov); Revised: 07/2011
15. Jin SM, Park CY, Cho YM, et al. Lobeglitazone and pioglitazone as add-ons to metformin for patients with type 2 diabetes: a 24-week, multicentre, randomized, double-blind, parallel-group, active-controlled, phase III clinical trial with a 28-week extension. Diabetes Obes Metab 2015;17(6):599–602.
16. Schernthaner G, Currie CJ, Schernthaner GH. Do we still need pioglitazone for the treatment of type 2 diabetes? A risk-benefit critique in 2013. Diabetes Care 2013;36(Suppl 2):S155–S161.
17. Kahn CR, Chen L, Cohen SE. Unraveling the mechanism of action of thiazolidinediones. J Clin Invest 2000;106(11):1305–1307.
18. Bonora E, Formentini G, Calcaterra F, et al. HOMA-estimated insulin resistance is an independent predictor of cardiovascular disease in type 2 diabetic subjects: prospective data from the Verona Diabetes Complications Study. Diabetes Care 2002;25(7):1135–1141.
19. Pyörälä M, Miettinen H, Halonen P, et al. Insulin resistance syndrome predicts the risk of coronary heart disease and stroke in healthy middle-aged men: the 22-year follow-up results of the Helsinki Policemen Study. Arterioscler Thromb Vasc Biol 2000;20(2):538–544.
20. Bełtowski J, Rachańczyk J, Włodarczyk M. Thiazolidinedione-induced fluid retention: recent insights into the molecular mechanisms. PPAR Res 2013;2013:628628.
21. Horita S, Nakamura M, Satoh N, et al. Thiazolidinediones and edema: recent advances in the pathogenesis of thiazolidinediones-induced renal sodium retention. PPAR Res 2015;2015:646423.
22. Lee MA, Tan L, Yang H, et al. Structures of PPARγ complexed with lobeglitazone and pioglitazone reveal key determinants for the recognition of antidiabetic drugs. Sci Rep 2017;7(1):16837.
23. Mudaliar S, Chang AR, Henry RR. Thiazolidinediones, peripheral edema, and type 2 diabetes: incidence, pathophysiology, and clinical implications. Endocr Pract 2003;9(5):406–416.

Table S1: Proportion of cumulated subjects achieving response for glycemic parameters (mITT population)

Parameter	*Visit*	*Statistical parameter*	*Group*	
			Pioglitazone N = 159	*Lobeglitazone N = 158*
HbA1c (mg/dL)	Week 4	*n* (%)	55 (34.6)	46 (29.1)
		Difference (%)	−5.4	
		95% CI	(−15.7, 5.0)	
		p-value	0.312	
	Week 8	*n* (%)	91 (57.2)	84 (53.2)
		Difference (%)	−4.1	
		95% CI	(−15.0, 6.9)	
		p-value	0.466	
	Week 12	*n* (%)	117 (73.6)	103 (65.2)
		Difference (%)	−8.4	
		95% CI	(−18.5, 1.7)	
		p-value	0.105	
	Week 16	*n* (%)	124 (78.0)	111 (70.3)
		Difference (%)	−7.7	
		95% CI	(−17.3, 1.9)	
		p-value	0.116	
FBG (mg/dL)	Week 4	*n* (%)	73 (45.9)	83 (52.5)
		Difference (%)	6.6	
		95% CI	(−4.4, 17.6)	
		p-value	0.239	
	Week 8	*n* (%)	106 (66.7)	117 (74.1)
		Difference (%)	7.4	
		95% CI	(−2.6, 17.4)	
		p-value	0.150	
	Week 12	*n* (%)	127 (79.9)	127 (80.4)
		Difference (%)	0.5	
		95% CI	(−8.3, 9.3)	
		p-value	0.910	
	Week 16	*n* (%)	138 (86.8)	137 (86.7)
		Difference (%)	−0.1	
		95% CI	(−7.5, 7.4)	
		p-value	0.982	

p-value obtained using Pearson's Chi-squared test; 95% confidence interval of the difference%; HbA1c responders, ≥0.7% reduction from baseline in HbA1c or a target HbA1c of <7%; FPG responders, ≥30 mg/dL reduction from baseline in FPG or a target FPG of <126 mg/dL

Table S2: Between and within-group comparison of mean change in weight from baseline (mITT population): MMRM

Visit	*Parameter*	*Statistics*	*Pioglitazone (N = 159)*	*Lobeglitazone (N = 158)*	*p-value‡*
Baseline—week 12 (day 85)	Weight (kg)	LSM (SE); (95% CI)	−0.06 (0.09); (−0.25, 0.14)	−0.02 (0.09); (−0.22, 0.17)	
		p-value†	0.551	0.817	
		Difference: LSM (SE); (95% CI)	0.04 (0.14); (−0.23, 0.30)		0.790
Baseline—week 16 (day 113)	Weight (kg)	LSM (SE); (95% CI)	−0.15 (0.12); (−0.39, 0.08]	−0.17 (0.12); [−0.41, 0.07]	
		p-value†	0.189	0.155	
		Difference: LSM (SE); (95% CI)	−0.02 (0.17); (−0.34, 0.31)		0.923

LSM, least square mean; SE, standard error; difference obtained as lobeglitazone–pioglitazone; †obtained for within-group change from baseline; ‡obtained for between-group change from baseline; MMRM, mixed model repeated measure

Table S3: Clinical laboratory assessment: hematology–safety population

Parameter	*Visit*	*Statistical parameter*	*Group*	
			Pioglitazone N = 164	*Lobeglitazone N = 163*
		n	156	149
Absolute basophils ($\times10^3$/uL)	Baseline—week 16	Mean (SD)	−0.02 (0.07)	−0.002 (0.07)
		Minimum, maximum	−0.22, 0.15	−0.16, 0.19
Absolute eosinophils ($\times10^3$/uL)	Baseline—week 16	Mean (SD)	0.01 (0.29)	0.01 (0.14)
		Minimum, maximum	−0.51, 3.15	−0.61, 0.63
Absolute lymphocytes ($\times10^3$/uL)	Baseline—week 16	Mean (SD)	−0.03 (0.70)	−0.09 (0.69)
		Minimum, maximum	−2.61, 2.94	−1.90, 2.31
Absolute monocytes ($\times10^3$/uL)	Baseline—week 16	Mean (SD)	0.002 (0.25)	0.01 (0.21)
		Minimum, maximum	−1.45, 0.84	−0.52, 0.75
Absolute neutrophils ($\times10^3$/uL)	Baseline—week 16	Mean (SD)	−0.25 (1.47)	−0.16 (1.59)
		Minimum, maximum	−4.59, 4.29	−5.57, 6.18
Basophils (%)	Baseline—week 16	Mean (SD)	−0.25 (1.01)	−0.02 (0.92)
		Minimum, maximum	−2.5, 2.5	−2.5, 2.4
Eosinophils (%)	Baseline—week 16	Mean (SD)	0.02 (3.54)	0.24 (1.86)
		Minimum, maximum	−19.5, 26.0	−8.2, 5.8
Ery. mean corpuscular hemoglobin (pg)	Baseline—week 16	Mean (SD)	−0.34 (3.47)	−0.35 (2.61)
		Minimum, maximum	−12.1, 9.9	−11.0, 8.9
Ery. mean corpuscular volume (fl)	Baseline—week 16	Mean (SD)	4.92 (10.44)	4.22 (8.51)
		Minimum, maximum	−28.1, 35.5	−20.4, 36.8
Erythrocytes ($\times10^6$/uL)	Baseline—week 16	Mean (SD)	−0.09 (0.69)	−0.13 (0.54)
		Minimum, maximum	−2.63, 2.18	−1.84, 1.27
Hematocrit (%)	Baseline—week 16	Mean (SD)	1.20 (7.58)	0.68 (5.15)
		Minimum, maximum	−35.0, 21.5	−20.9, 14.9
Hemoglobin (gm/dL)	Baseline—week 16	Mean (SD)	−0.45 (2.38)	−0.55 (1.57)
		Minimum, maximum	−12.3, 7.6	−6.3, 3.8
Leukocytes ($\times10^3$/uL)	Baseline—week 16	Mean (SD)	−0.29 (1.89)	−0.24 (2.09)
		Minimum, maximum	−5.94, 5.73	−7.87, 7.40
Lymphocytes (%)	Baseline—week 16	Mean (SD)	0.66 (8.51)	−0.44 (7.65)
		Minimum, maximum	−19.3, 53.8	−26.4, 19.9
Monocytes (%)	Baseline—week 16	Mean (SD)	0.41 (3.13)	0.42 (2.74)
		Minimum, maximum	−14.4, 10.5	−6.7, 10.0
Neutrophils (%)	Baseline—week 16	Mean (SD)	−0.82 (10.07)	−0.19 (8.64)
		Minimum, maximum	−40.4, 29.7	−21.5, 24.8
Platelets ($\times10^3$/uL)	Baseline—week 16	Mean (SD)	−6.3 (75.32)	−8.8 (67.08)
		Minimum, maximum	−264, 245	−274, 215

Ery., erythrocytes

Table S4: Clinical laboratory assessment: kidney function test–safety population

Parameter	*Visit*	*Statistical parameter*	*Group*	
			Pioglitazone N =164	*Lobeglitazone N =163*
Creatinine (mg/dL)	Baseline—week 16	*n*	154	151
		Mean (SD)	0.02 (0.20)	0.01 (0.19)
		Minimum, maximum	−0.50, 0.90	−0.60, 1.10
Potassium (mEq/L)	Baseline—week 16	Mean (SD)	0.06 (0.66)	−0.03 (0.59)
		Minimum, maximum	−2.5, 3.0	−2.4, 1.3
Sodium (mEq/L)	Baseline—week 16	Mean (SD)	0.2 (4.45)	0.3 (4.52)
		Minimum, maximum	−13, 11	−27, 11