Improvement of Glycemic Control, Triglycerides, and HDL Cholesterol Levels With Muraglitazar, a Dual (α/γ) Peroxisome Proliferator–Activated Receptor Activator, in Patients With Type 2 Diabetes Inadequately Controlled With Metformin Monotherapy

A double-blind, randomized, pioglitazone-comparative study

David M. Kendall, MD[1]
Cindy J. Rubin, MD[2]
Pharis Mohideen, MD[2]
Jean-Marie Ledeine, MSC[3]
Rene Belder, MD[2]
Jorge Gross, MD[4]
Paul Norwood, MD[5]
Michael O'Mahony, MD[6]
Kenneth Sall, MD[7]
Greg Sloan, MD[8]
Anthony Roberts, MBBS[9]
Fred T. Fiedorek, MD[2]
Ralph A. DeFronzo, MD[10]

OBJECTIVE — We sought to evaluate the effects of muraglitazar, a dual (α/γ) peroxisome proliferator–activated receptor (PPAR) activator within the new glitazar class, on hyperglycemia and lipid abnormalities.

RESEARCH DESIGN AND METHODS — A double-blind, randomized, controlled trial was performed in 1,159 patients with type 2 diabetes inadequately controlled with metformin. Patients received once-daily doses of either 5 mg muraglitazar or 30 mg pioglitazone for a total of 24 weeks in addition to open-label metformin. Patients were continued in a double-blind fashion for an additional 26 weeks.

RESULTS — Analyses were conducted at week 24 for HbA_{1c} (A1C) and at week 12 for lipid parameters. Mean A1C at baseline was 8.12 and 8.13% in muraglitazar and pioglitazone groups, respectively. At week 24, muraglitazar reduced mean A1C to 6.98% (−1.14% from baseline), and pioglitazone reduced mean A1C to 7.28% (−0.85% from baseline; $P < 0.0001$, muraglitazar vs. pioglitazone). At week 12, muraglitazar and pioglitazone reduced mean plasma triglyceride (−28 vs. −14%), apolipoprotein B (−12 vs. −6%), and non-HDL cholesterol (−6 vs. −1%) and increased HDL cholesterol (19 vs. 14%), respectively ($P < 0.0001$ vs. pioglitazone for all comparisons). At week 24, weight gain (1.4 and 0.6 kg, respectively) and edema (9.2 and 7.2%, respectively) were observed in the muraglitazar and pioglitazone groups; at week 50, weight gain and edema were 2.5 and 1.5 kg, respectively, and 11.8 and 8.9%, respectively. At week 50, heart failure was reported in seven patients (five with muraglitazar and two with pioglitazone), and seven deaths occurred: three from sudden death, two from cerebrovascular accident, and one from pancreatic cancer in the muraglitazar group and one from perforated duodenal ulcer in the pioglitazone group.

CONCLUSIONS — We found that 5 mg muraglitazar resulted in greater improvements in A1C and lipid parameters than a submaximal dose of 30 mg pioglitazone when added to metformin. Weight gain and edema were more common when muraglitazar was compared with a submaximal dose of pioglitazone.

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Glitazars are a new class of oral antidiabetic agents that activate nuclear receptors known as peroxisome proliferator–activated receptors (PPARs). Three PPAR subtypes have been characterized: PPARα, -γ, and -β/δ. Upon ligand binding, each receptor subtype mediates distinct physiological effects on glucose homeostasis and lipid metabolism. Activation of PPARγ reduces insulin resistance and improves glycemic control, whereas activation of PPARα reduces triglyceride levels and increases concentrations of HDL cholesterol (1,2). Muraglitazar, a dual (α/γ) PPAR activator in the glitazar class, activates PPARα and -γ, thereby improving hyperglycemia and lipid abnormalities (i.e., reducing triglycerides and increasing HDL cholesterol) simultaneously.

Type 2 diabetes is a complex disorder

From the [1]International Diabetes Center and the University of Minnesota, Minneapolis, Minnesota; [2]Bristol-Myers Squibb, Princeton, New Jersey; [3]Bristol-Myers Squibb, Braine-l'Alleud, Belgium; the [4]Centro De Pesquisa Em Diabetes, Rio Grande Do Sul, Brazil; [5]Valley Research, Fresno, California; [6]Corunna Medical Services, Ontario, Canada; the [7]Sall Research Medical Center, Bellflower, California; the [8]Emerald Coast Research Group, Chipley, Florida; [9]South Australian Endocrine Clinical Research, Keswick Adelaide, Australia; and the [10]University of Texas Health Sciences Center at San Antonio, San Antonio, Texas.

Address correspondence and reprint requests to Ralph A. DeFronzo, MD, Department of Medicine, Division of Diabetes, University of Texas Health Sciences Center at San Antonio, Building HSC-DTL, Room 3.380S, 7703 Floyd Curl Dr., San Antonio, TX 78229. E-mail: albarado@uthscsa.edu.

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Abbreviations: apo, apolipoprotein; CHF, congestive heart failure; CRP, C-reactive protein; CVD, cardiovascular disease; FFA, free fatty acid; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; LOCF, last observation carried forward; NYHA, New York Heart Association; PAI-1, plasminogen activator inhibitor type 1; PPAR, peroxisome proliferator–activated receptor.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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comprising multiple metabolic and vascular abnormalities, including insulin resistance, dyslipidemia, and vascular inflammation. Each of these abnormalities represents a major risk factor for the development of cardiovascular disease (CVD) (3–5). Reducing the markedly increased risk for CVD in patients with type 2 diabetes is believed to be dependent on effective management of multiple risk factors (3). The current randomized double-blind study was conducted to evaluate the effects of muraglitazar on glycemic and lipid parameters and to compare the efficacy and tolerability of muraglitazar with that of pioglitazone—a PPARγ activator—in patients with type 2 diabetes inadequately controlled with metformin monotherapy.

RESEARCH DESIGN AND METHODS

— The primary objective of this study was to compare the change in HbA_{1c} (A1C) levels achieved after 24 weeks of treatment when adding either 5 mg muraglitazar or 30 mg pioglitazone to metformin in patients with inadequately controlled (A1C ≥7.0 to ≤10.0%) type 2 diabetes on metformin monotherapy. Secondary end points assessed the percentage of change from baseline in fasting lipid levels (triglyceride, HDL cholesterol, apolipoprotein B [apoB], non-HDL cholesterol) after 12 weeks (presented as average values obtained from weeks 11 and 12) of treatment. Other efficacy variables assessed at week 24 included the proportion of patients achieving A1C <7.0, <6.5, and <6.0%; change from baseline in fasting plasma glucose (FPG) and fasting insulin; analysis of homeostasis model assessment of insulin resistance (HOMA-IR); percentage change from baseline in free fatty acid (FFA) and LDL cholesterol; and percentage change from baseline in high-sensitivity C-reactive protein (CRP) and plasminogen activator inhibitor type 1 (PAI-1). Safety and tolerability information reported during the 24-week study and from the 26-week extension (for a total of 50 weeks on treatment) also was evaluated.

Men and women aged 18–70 years with type 2 diabetes and inadequate glycemic control who were taking stable doses of metformin (1,500–2,550 mg/day) for at least 6 weeks were eligible for study participation. Patients were required to have a fasting C-peptide concentration ≥1.0 ng/ml (0.34 mmol/l), BMI ≤41 kg/m^2, and mean serum triglyceride concentration ≤600 mg/dl (6.78 mmol/l). Women of childbearing potential were required to use effective methods of contraception. Patients taking stable doses of statins for at least 6 weeks before randomization were eligible for enrollment and continued therapy at their baseline statin doses during weeks 1–12. After week 12, investigators were permitted to add lipid-regulating therapy (except for the combination of a statin plus a fibrate) or adjust the dose of current therapy if clinically necessary.

Exclusion criteria included symptomatic type 2 diabetes, defined as polyuria or polydipsia with >10% weight loss in the preceding 3 months; history of diabetic ketoacidosis or hyperosmolar nonketotic coma; designation of class III/IV heart failure according to New York Heart Association (NYHA) criteria; and treatment with niacin, ezetimibe, or bile-acid binding agents within 6 weeks, with fibrates within 8 weeks, or with probucol within 1 year of randomization. Patients could not use other oral glucose-lowering therapy, with the exception of metformin, during the 6 weeks before screening.

All patients gave written informed consent to participate in the study, and the institutional review board of each participating center approved its protocol. Qualified investigators conducted the study in accordance with good clinical practice and under the principles of the Declaration of Helsinki, its amendments, and applicable regulations and guidelines.

This was a multicenter randomized double-blind parallel-group active-controlled trial designed to show the noninferiority of 5 mg muraglitazar added to metformin versus 30 mg pioglitazone added to metformin by evaluating the change in A1C from baseline to week 24. Patients were drawn from 234 centers located in 13 countries. Patients who met screening and inclusion criteria participated in a 2-week placebo lead-in phase. Patients remained on metformin at doses (open-label, 500-mg tablets) equal to or less than the baseline dose according to the following schedule: baseline metformin doses of 1,500 to <2,000 mg/day were switched to 1,500 mg/day; baseline metformin doses of 2,000 to <2,500 mg/day were switched to 2,000 mg/day; and baseline metformin doses of 2,500–2,550 mg/day were switched to 2,500 mg/day. At the end of the lead-in phase, patients were randomly assigned to one of two treatment groups: once-daily 5 mg muraglitazar or 30 mg pioglitazone. This dose of pioglitazone was selected because at the time of protocol development and study initiation, 30 mg pioglitazone was the maximum dose approved for use in combination with metformin. Because the maximally effective dose of pioglitazone is 45 mg/day, the clinical significance of differences between muraglitazar- and pioglitazone-treated groups, both with respect to efficacy and safety parameters, should not be overinterpreted. Double-blind study medication was administered before the morning meal along with the open-label dose of metformin taken twice daily for 24 weeks. Dose titration of double-blind medications or open-label metformin was not permitted. Patients who completed the initial 24 week period were eligible to continue into a 26-week double-blind extension. The same double-blind treatment (plus open-label metformin) assigned during the initial 24-week period was continued without change during the subsequent 26-week extension. Patients were discontinued from the study for lack of glycemic control if FPG (measured twice within 3–5 days) was >240 mg/dl at week 6, >220 mg/dl at week 8, or >200 mg/dl at weeks 12, 16, or 20. Additionally, patients were discontinued from the study if A1C was >8% at weeks 30 or 37.

Safety was assessed via patient-reported adverse events, clinical observations, and regular monitoring of vital signs, physical examinations, and laboratory findings. There was no formal adjudication of coronary heart disease death, nonfatal myocardial infarction, stroke, or other clinical end points. In addition, subjects were not followed for occurrence of these clinical events if they had been discontinued because of lack of efficacy, side effects, or other cause.

Assays

Blood and urine samples were obtained at specified time points for laboratory evaluations. With the exception of urine pregnancy tests, which were performed at local investigative sites, all scheduled laboratory tests were performed and analyzed at central laboratories.

Plasma A1C levels were determined using high-performance liquid chromatography (Variant II hemoglobin testing system; BioRad, Hercules, CA), and plasma glucose, triglyceride, total cholesterol, HDL cholesterol, LDL cholesterol, and FFA levels were determined using enzymatic colorimetic assays (reagents obtained from Roche Diagnostics, India-

Table 1—*Patient demographics, baseline disease characteristics, and primary reason for discontinuation*

	Muraglitazar	Pioglitazone
n	587	572
Demographics		
Age (years)	55.3 ± 8.6	54.1 ± 9.1
Men (%)	45.8	49.0
Race		
White/black/other (%)	89.6/8.3/2.0	89.9/7.0/3.1
Ethnicity		
Hispanic/Latino (%)	15.0	18.7
Non-Hispanic/Latino (%)	85.0	81.3
BMI (kg/m^2)	32.0 ± 4.6	32.0 ± 4.6
Body weight (kg)	90.2 ± 17.4	91.0 ± 17.2
Diabetes duration (years)	6.0 ± 5.0	5.8 ± 5.1
Mean metformin dose (mg/day)	1,854	1,851
Disease characteristics		
A1C (%)	8.12	8.13
Fasting plasma glucose (mg/dl)	179	178
Fasting insulin (μU/ml)	15	15
FFAs (mEq/l)	0.66	0.66
Lipids		
Triglycerides (mg/dl)	206	203
HDL cholesterol (mg/dl)	46	46
ApoB (mg/dl)	101	101
Non-HDL cholesterol (mg/dl)	152	151
LDL cholesterol (mg/dl)	113	113
High-sensitivity CRP (mg/l)	3.16	3.19
PAI-1 (ng/ml)	43.8	41.9
Primary reason for discontinuation (week 24)		
Total discontinuations	65 (11.1)	90 (15.7)
Lack of glycemic efficacy	18 (3.1)	36 (6.3)
Consent withdrawn	16 (2.7)	30 (5.2)
Adverse event	15 (2.6)	8 (1.4)
Lost to follow-up	7 (1.2)	7 (1.2)
Poor compliance/noncompliance	4 (0.7)	4 (0.7)
No longer met inclusion criteria	2 (0.3)	4 (0.7)
Pregnancy*	1 (0.2)	1 (0.2)
Death	2 (0.3)	0 (0.0)†

Data are means ±SD or *n* (%), unless otherwise indicated. *Both pregnancies resulted in normal healthy births; †one subject in the pioglitazone group died (perforated duodenal ulcer) after discontinuing the study because of an adverse event (calculus urinary).

napolis, IN). Non-HDL cholesterol was computed as the difference between total cholesterol and HDL cholesterol.

ApoB and high-sensitivity CRP levels were determined using immunoturbidimetric assays. Plasma samples were combined with either anti-human apoB antiserum or anti-human high-sensitivity CRP antibody. The intensity of the turbidity (which is proportional to the concentration of antibody-antigen complexes) was measured at 340 nm for apoB and 700 nm for high-sensitivity CRP.

Plasma insulin concentrations were determined using an enzymatic immunosorbent assay (Immulite Diagnostic Products, Los Angeles, CA), and PAI-1 concentrations were determined using an enzyme-linked immunosorbent assay (TintElize; Trinity BioTech, Bray, Ireland).

Statistical analyses

All analyses for mean change or mean percentage of change from baseline were adjusted for baseline level using ANCOVA. Point estimates and 95% CIs were constructed for within-group adjusted mean (percentage) changes from baseline and for the difference in mean (percentage) change from baseline between the muraglitazar and pioglitazone treatment groups. Efficacy and safety analyses were performed on data collected from all randomly assigned patients who received at least one dose of double-blind study medication. To be included in the efficacy analyses on change from baseline, patients had to have valid baseline and post-baseline data. Patients were only included in the analyses of A1C and lipid variables if they received at least 6 weeks of double-blind treatment; analyses of FPG and fasting insulin included only those patients who received at least 8 days of double-blind therapy. HOMA-IR values were computed using the following equation: (1/22.5) × FPG × fasting plasma insulin. The methodology of last observation carried forward (LOCF) was used for efficacy parameters.

Muraglitazar was noninferior to pioglitazone if the upper limit of the two-sided 95% CI of the difference in A1C change from baseline to week 24 LOCF between the two treatment groups was ≤0.25%. If noninferiority was demonstrated and the upper limit of the two-sided 95% CI was <0, the superiority of muraglitazar was tested at a two-sided significance level of 0.05 using the same ANCOVA model.

RESULTS

Patient demographics and disposition

A total of 2,173 patients were screened, and 1,202 patients received placebo study medication during the lead-in phase. Of these, 1,159 patients were randomly assigned to double-blind treatment, 1,004 (87%) patients completed the initial 24-week period, and 762 (66%) patients completed the entire 50-week period. Treatment groups were well matched with respect to baseline demographic and disease characteristics (Table 1). Baseline A1C values were 8.12 and 8.13% in the muraglitazar and pioglitazone groups, respectively. Mean duration (means ± SD) of diagnosed diabetes was 5.9 ± 5.0 years. A similar percentage (~25%, 143 patients in the muraglitazar group and 143 patients in the pioglitazone group) of patients were on concomitant statin therapy at baseline and at week 24 (i.e., 149 patients in the muraglitazar group and 150 patients in the pioglitazone group), indicating that few patients added a lipid-lowering drug during the course of the study. Hypertriglyceridemia, defined as blood triglyceride values ≥150 mg/dl, was observed at baseline in 352 patients in the muraglitazar

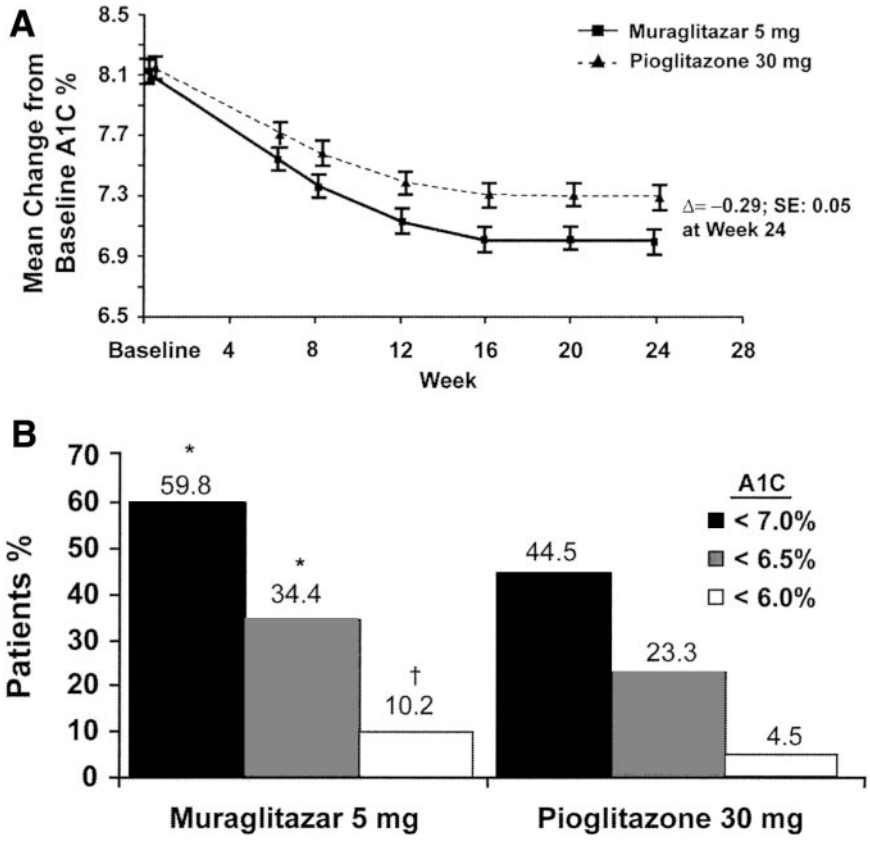

Figure 1—A: *Mean change from baseline in A1C (and 95% CI) over time.* B: *Distribution of patients reaching target A1C levels at week 24. Number of patients with available data: muraglitazar,* n = *569; pioglitazone,* n = *550.* *P < *0.0001 vs. pioglitazone;* †P = *0.0004 vs. pioglitazone.*

group and in 335 patients in the pioglitazone group.

Glycemic parameters

A1C. Muraglitazar and pioglitazone both lowered A1C levels from baseline. The reduction in A1C was significantly greater in the muraglitazar group than in the pioglitazone group (Fig. 1). At week 24, mean A1C levels were 6.98% (−1.14% from baseline) with muraglitazar and 7.28% (−0.85% from baseline) with pioglitazone (difference −0.29%, 95% CI −0.39 to −0.19, $P < 0.0001$). At week 24, a larger percentage of patients treated with muraglitazar achieved target A1C levels <7 or <6.5% (60 and 34%, respectively) compared with patients treated with pioglitazone (45 and 23%, respectively) (Fig. 1).

FPG and insulin concentrations. Reductions in FPG and in insulin levels were significantly greater in the muraglitazar group than in the pioglitazone group. After 24 weeks of therapy, FPG values were reduced 44 and 33 mg/dl in the muraglitazar and pioglitazone groups, respectively ($P < 0.0001$). Mean changes from baseline in fasting insulin levels were −5.0 μU/ml for muraglitazar-treated patients and −3.6 μU/ml for pioglitazone-treated patients ($P < 0.0001$).

HOMA-IR. Baseline HOMA-IR was 6.6 μU/ml · mmol/l in both groups. At week 24, HOMA-IR was reduced to 3.3 μU/ml · mmol/l (−48.6% from baseline) in the muraglitazar-treated group and 4.1 (−37.1) in the pioglitazone-treated group ($P < 0.0001$).

FFAs. Reductions in FFAs at week 12 were significantly greater in the muraglitazar group (−30% from baseline) than in the pioglitazone group (−21% from baseline) ($P < 0.0001$). FFA levels at week 12 were 0.47 and 0.53 mEq/l in the muraglitazar and pioglitazone groups, respectively.

Lipid parameters

At week 12, the mean percentage change from baseline in fasting triglyceride levels was greater with muraglitazar (−28%) than pioglitazone (−14%) ($P < 0.0001$) (Fig. 2). In the subset of patients with triglyceride levels ≥150 mg/dl at baseline (mean triglyceride was 265 mg/dl in both groups), muraglitazar therapy was associated with a significantly greater reduction in triglyceride than pioglitazone therapy (−35 vs. −19%, $P < 0.0001$). At week 12, increases in HDL cholesterol were greater in the muraglitazar group (19% from baseline) versus the pioglitazone group (14% from baseline; $P < 0.0001$) (Fig. 2). Mean percentage changes in LDL cholesterol levels from baseline to week 12 were similar in both groups. Muraglitazar and pioglitazone both reduced apoB (−12 and −6%, respectively) and non-HDL cholesterol (−6 and −1%) concentrations at week 12 (both $P < 0.0001$ for muraglitazar vs. pioglitazone) (Fig. 2). Initiation of or changes to the dosage of lipid-regulating medications was permitted after week 12; changes in lipid parameters (triglyceride, HDL cholesterol, apoB, non-HDL cholesterol, and LDL cholesterol) at week 24 were similar to those observed at week 12).

High-sensitivity CRP and PAI-1

After 24 weeks of therapy, high-sensitivity CRP was 2.4 mg/l (−30.2% from baseline) in the muraglitazar group and 2.7 mg/l (−23.6% from baseline) in the pioglitazone group ($P = 0.04$). PAI-1 was 30.7 ng/ml (−30.4% from baseline) at week 24 in the muraglitazar group and 34.4 ng/ml (−21.5% from baseline) in the pioglitazone group ($P = 0.0002$).

Safety

The overall incidence of adverse events during the study during week 50 was similar in the muraglitazar (72%) and pioglitazone (69%) groups. Serious adverse events were reported for 8.2% ($n = 48$) of patients in the muraglitazar group and 5.8% ($n = 33$) of patients in the pioglitazone group. Adverse events (excluding edema) observed in ≥5% of patients in the muraglitazar and pioglitazone groups were nasopharyngitis (8.3 vs. 8.0%), hypertension (8.0 and 7.3%), arthralgia (7.2 and 7.0%), headache (5.6 and 5.6%), upper respiratory tract infection (5.6 and 6.8%), back pain (5.5 and 4.4%), and pain in extremity (5.1 and 3.0%).

Body weight. Increases in body weight were observed in both groups at weeks 24 and 50. The change (mean ± SE) in body weight was greater in muraglitazar-treated patients (+1.4 ± 0.14 kg) compared with those receiving pioglitazone (+0.6 ± 0.15 kg, $P < 0.0001$). At week 50 the increases in body weight were

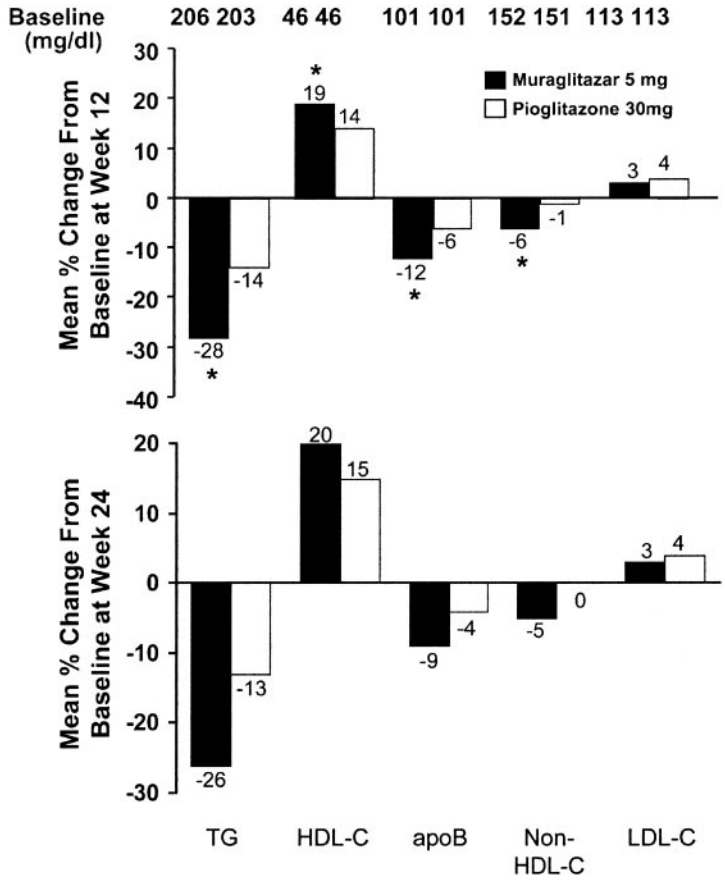

Figure 2—*Mean percentage change from baseline in lipid parameters at weeks 12 and 24. HDL-C, HDL cholesterol; LDL-C, HDL cholesterol; TG, triglyceride.* *P < *0.0001 vs. pioglitazone.*

+2.5 ± 1.8 and 1.5 ± 1.8 kg, respectively ($P < 0.0001$).

Edema. Edema-related adverse events at week 24 were observed in 9.2% of patients treated with muraglitazar and 7.2% of patients treated with pioglitazone ($P = 0.33$). At week 50, 11.8% of patients in the muraglitazar group and 8.9% of patients in the pioglitazone group reported at least one edema-related event ($P = 0.19$). All edema-related adverse events were graded as either mild or moderate, with the exception of one severe adverse event reported in each treatment group. Two patients in the muraglitazar group and one patient in the pioglitazone group discontinued from the study because of edema-related adverse events.

Heart failure. At week 24, there were three cases of mild to moderate heart failure reported in the muraglitazar group and one case reported in the pioglitazone group. Between weeks 24 and 50, there were two additional cases of heart failure reported in the muraglitazar group and one additional case reported in the pioglitazone group. Of these subjects, four in the muraglitazar group and one in the pioglitazone group had their heart failure event reported as a serious adverse event. The events were reported as mild ($n = 1$), moderate ($n = 3$), and very severe ($n = 1$) in the muraglitazar group and mild ($n = 1$) and severe ($n = 1$) in the pioglitazone group. Four of the five subjects in the muraglitazar group were treated with diuretics, with resolution of the events within 5–16 days. One subject in the muraglitazar group who experienced heart failure had a serious adverse event of myocardial infarction and died within a few hours. The heart failure event of one subject in the pioglitazone group resolved with treatment in 9 days, and the event in the other subject resolved with treatment in 96 days. One subject in the muraglitazar group continued in the study after the heart failure event, whereas the five others (three muraglitazar, two pioglitazone) discontinued according to protocol design. All seven patients had histories of cardiac disease, which included NYHA class II heart failure ($n = 2$), severe hypertension ($n = 1$), and coronary artery disease with elevated NT-proBNP (NH_2-terminal prohormone brain natriuretic peptide) levels ($n = 2$) in the muraglitazar group and NYHA class I heart failure ($n = 1$) and coronary artery disease ($n = 1$) in the pioglitazone group.

Cardiovascular events and deaths. A total of 22 patients (12 [2.0%] in the muraglitazar group and 10 [1.7%] in the pioglitazone group) had a coronary or cerebrovascular event reported as an adverse event during the 50-week period. Over the 50-week period, six deaths were reported in the muraglitazar group, and one death was reported in the pioglitazone group. Five of six deaths in the muraglitazar group were classified as cardiovascular or cerebrovascular events: three sudden deaths occurred in subjects with known histories of atherosclerosis and multiple cardiac risk factors, with two of the three having histories of heart failure, and two deaths from stroke occurred in subjects with multiple risk factors for cerebrovascular accident. The remaining death in the muraglitazar group was caused by pancreatic cancer. The one death in the pioglitazone group was caused by a perforated duodenal ulcer. In the muraglitazar group, investigators reported the relationship of study medication and five of the deaths as "not related," whereas the death caused by pancreatic cancer was reported as "not likely related."

Discontinuations. Of the 1,159 randomized patients, 1,004 completed the initial 24-week period, with 155 patients discontinuing (65 in the muraglitazar group and 90 in the pioglitazone group) (Table 1). At week 24, adverse events resulted in study discontinuation in 15 (2.6%) and 8 (1.4%) patients treated with muraglitazar and with pioglitazone, respectively. A total of 18 patients in the muraglitazar group and 36 patients in the pioglitazone group discontinued the study because of lack of glycemic efficacy at week 24. A total of 762 (66%) patients (muraglitazar group, $n = 396$; pioglitazone group, $n = 366$) completed the 50-week treatment period. Reasons for discontinuation in the muraglitazar and pioglitazone groups included lack of glycemic efficacy (12 vs. 17%), withdrawal of consent (8 and 9%), adverse events (5 and 3%), sponsor-related administrative reason/lost to follow-up (6 and 4%), and protocol violation/compliance problem/pregnancy/other (3 and 2%).

CONCLUSIONS — The current study is the first to compare the effect of muraglitazar, a dual (α/γ) PPAR activator in the

new glitazar class, with pioglitazone, a PPARγ activator, on glycemic control and lipid abnormalities in individuals with type 2 diabetes inadequately controlled with metformin monotherapy. Results of this 24-week, double-blind trial showed that muraglitazar lowered A1C levels to a greater extent than pioglitazone therapy (mean difference of −0.29%, $P < 0.0001$) when added to stable doses of metformin. In addition, the proportion of patients achieving target A1C levels was significantly greater in the muraglitazar treatment group (at week 24) than in the pioglitazone group for each of the A1C goals evaluated (<7.0, <6.5, and <6.0%; $P \leq 0.0004$ vs. pioglitazone). Muraglitazar's insulin-sensitizing effects were demonstrated by reductions in plasma insulin levels, decreases in HOMA-IR values, and lower circulating FFA levels. Between-group differences for all three parameters statistically favored muraglitazar.

Compared with pioglitazone, muraglitazar resulted in a statistically significant improvement in plasma triglyceride, HDL cholesterol, apoB, and non-HDL cholesterol concentrations at week 12, which was time on treatment before any additional modifications in lipid-lowering therapies could be made. Muraglitazar reduced triglyceride concentrations to a larger extent than pioglitazone, regardless of baseline triglyceride levels. Muraglitazar and pioglitazone treatment was associated with slight (3–4%) increases in LDL cholesterol. However, muraglitazar resulted in significantly larger reductions in apoB levels than pioglitazone. Reductions in apoB levels were accompanied by minimal effects on LDL cholesterol levels, suggesting a shift in LDL cholesterol particle size from small dense LDL particles to larger, more buoyant ones. Specific measurement of LDL cholesterol particle size and concentration was not performed.

It should be noted that the maximally effective dose of pioglitazone is 45 mg/day. Therefore, caution should be used in evaluating the clinical significance of the differences in A1C and plasma lipid levels between the muraglitazar (5 mg/day) and pioglitazone (30 mg/day) groups in the present study.

Significant reductions in levels of high-sensitivity CRP and the prothrombotic plasma marker PAI-1 were observed in the muraglitazar-treated group. Interventions that decrease high-sensitivity CRP levels have been shown to reduce the risk of macrovascular complications in patients with atherosclerosis (6). However, it is unknown whether the effects of muraglitazar to decrease high-sensitivity CRP and PAI-1, coupled with the lipid effects (i.e., decreases in triglycerides and increases in HDL cholesterol), will translate into a difference in CVD risk. The effects of PPARγ activation (7) and PPARα activation (8) in long-term trials should provide more insight into the potential impact of dual PPAR activators on CVD outcomes.

Weight gain has been widely observed in clinical trials involving thiazolidinediones (9–12), and the magnitude of weight gain is generally correlated with the degree of improvement in glycemic control (10–12). In addition to the weight gain associated with improved glycemic control, several other mechanisms may also contribute to weight gain, including fluid retention and an increase in overall adipogenesis. Stimulation of PPARγ receptors on adipocytes initiates cell division, leading to an increase in the number of small fat cells in subcutaneous fat depots (13). In addition, activation of PPARγ receptors induces numerous genes involved in lipogenesis and the inhibition of lipolysis (11,14). These effects lead to an increase in subcutaneous fat mass and are responsible, in part, for the reduction in plasma FFA concentration. Hence, a reduction in plasma FFA concentration and an increase in body weight reflects improved insulin action, which correlates with improvements in glycemic control (10,11).

Fluid retention leading to the development of peripheral edema is a well-known effect of current PPARγ activators. Edema has been reported in up to 16% of patients treated with thiazolidinedione monotherapy (9,12,15–18). Both muraglitazar and pioglitazone therapy were associated with edema (11.8 and 8.9%, respectively, at week 50) in the present study. PPARγ activators can cause fluid retention by promoting solute and water retention in the renal collecting duct (19,20). PPARγ agonists also possess calcium channel–blocking activity (21) and stimulate the release of nitric oxide (22), both of which are associated with edema formation in ~5–10% of individuals (23,24). PPARγ agonists have also been shown to cause vascular leak in animals (25). Finally, it has been suggested that PPARγ agonists enhance insulin-mediated sodium reabsorption by the kidney (26).

It is important to differentiate the presence of edema in patients treated with PPARγ therapy from the development of conjestive heart failure (CHF). Although the development of edema is relatively common, the development of heart failure is infrequent and is reported in 1–3% of patients receiving thiazolidinediones either alone or in combination with insulin (15,16,27). Prior studies suggest that PPARγ agonists can reduce peripheral vascular resistance and improve cardiac output (28). A recent observational study examined the characteristics of fluid retention in a large cohort of patients with diabetes and impaired left ventricular function (29). Results of this study showed that pulmonary edema was much more common in individuals treated with a nonthiazolidinedione antidiabetic agent than with a thiazolidinedione (80 vs. 11%, respectively) (29). In the current study, a small number of patients developed clinical heart failure: five muraglitazar-treated patients and two pioglitazone-treated patients. Given this low incidence, it is difficult to attribute any clinical significance to this observation. Nonetheless, thiazolidinediones are contraindicated in diabetic patients with class III–IV CHF, and in the present study, CHF occurred in asymptomatic individuals with either known histories of class I or II CHF and/or with significant risk factors for CHF. Therefore, all diabetic patients who are treated with a PPARγ activator should be monitored closely for evidence of edema and symptoms of CHF.

A total of 22 patients (12 muraglitazar and 10 pioglitazone) experienced a coronary or cerebral event during the 50-week period. A total of seven deaths occurred during the course of this study. Five of the deaths in the muragltiazar group appeared to be associated with either cardiovascular or cerebrovascular events. A recent publication (30) suggested that muraglitazar was associated with an increased number of cardiovascular events. However, this analysis (30) did not take into account the patient years of exposure in the various study groups, and it combined with placebo an active comparator (pioglitazone) to constitute the control group. Based on the recently published PROactive study (7), which demonstrated that the combined end point of death/myocardial infarction/stroke was significantly decreased in pioglitazone-treated diabetic patients, it is essential that the calculation of event rates (i.e., cardiovascular events and cardiovascular deaths)

be based on patient exposure years for each individual group (i.e., muraglitazar, pioglitazone, placebo). This is a major tenet of all cardiovascular outcome studies, and an analysis using these factors is currently in development. In summary, it is difficult to conclude either that any cardiovascular risk or cardiovascular benefit of muraglitazar exists, given the small number of events which accrued over a relatively short period of time. In addition, in the muraglitazar clinical trials programs, outcome events were not adjudicated, nor was there long-term follow-up of patients who discontinued therapy. Accurate assessment of benefit or risk for cardiovascular outcomes only can be determined by larger long-term trials.

Although results of the present study show that muraglitazar improved A1C values and lipid parameters to a larger extent than pioglitazone, the dose of pioglitazone used was less than the maximally approved dose of this agent. During development of the study protocol, the maximum pioglitazone dose approved for use in combination with metformin was 30 mg, which is the highest recommended dose for initiating combination treatment with metformin in the current pioglitazone prescribing information (15). Thus, any comparisons between the efficacy and safety of 5 mg muraglitazar and 30 mg pioglitazone should take into account that the pioglitazone dose was submaximal. Whether the incidence of edema and heart failure or the extent of weight gain would have been greater with 45 mg pioglitazone is not known. Any comparison between the two groups would require a much larger sample size and a comparison of the full range of muraglitazar and pioglitazone doses.

In summary, muraglitazar, a dual (α/γ) PPAR activator in the new glitazar class, significantly improved blood glucose control in patients with type 2 diabetes inadequately controlled with use of metformin monotherapy. Compared with a submaximal dose of 30 mg pioglitazone, 5 mg muraglitazar resulted in greater decreases in A1C, triglyceride, apoB, and non-HDL cholesterol and a larger increase in HDL cholesterol. The use of dual (α/γ) PPAR activators, with their glucose-lowering, insulin-sensitizing, and lipid-altering properties, supports the potential clinical benefits of muraglitazar in the treatment of patients with type 2 diabetes.

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