Long-Term Effects of Troglitazone

Open-label extension studies in type 2 diabetic patients

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OBJECTIVE — To determine the long-term effects of troglitazone as monotherapy or in combination with sulfonylureas or insulin regarding glycemic and lipid measures.

RESEARCH DESIGN AND METHODS — Patients who completed one of three double-blind studies (a 6-month troglitazone monotherapy study, a 52-week study of troglitazone in combination with micronized glyburide, or a 6-month study of troglitazone in combination with insulin) were allowed to enter open-label extensions of their respective double-blind studies. Troglitazone dose titrations were allowed to a maximum of 600 mg in response to inadequate glycemic control during the open-label phases of troglitazone monotherapy or sulfonylurea combination therapy but not with insulin combination therapy. This article focuses on the effectiveness of the highest dose of troglitazone used in these studies (600 mg daily). Safety data from all patients studied at all doses are also presented.

RESULTS — For patients who received a fixed dose of 600 mg troglitazone, mean changes in fasting serum glucose and HbA_{1c} levels from baseline to the end of the open-label phase were −57 mg/dl and −0.4%, respectively (monotherapy); −49 mg/dl and −1.8%, respectively (sulfonylurea combination); and −31 mg/dl and −1.0%, respectively (insulin combination). The proportion of patients achieving an HbA_{1c} level of ≤8% from the combined cohort of all three studies was 54% versus only 19% at baseline. The mean decrease in triglycerides from baseline to the end of the open-label phase was 18% among all patients in the three studies who received a fixed dose of 600 mg troglitazone. Troglitazone was well tolerated in these three open-label studies; a total of 758 patients completed a total exposure of 16,264 patient-months to troglitazone in these three studies with minimal adverse events.

CONCLUSIONS — Long-term use of troglitazone alone or in combination with sulfonylureas or insulin is safe and effective in sustaining glycemic control and in reducing hypertriglyceridemia in type 2 diabetic patients.

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The progression of diabetes involves multiple stages from impaired glucose tolerance (IGT) to advanced diabetes (1). The standard treatment of type 2 diabetes, therefore, progresses with the disease from diet and exercise only, to oral antidiabetic medications, to combination therapy of different classes of antidiabetic agents, and eventually to the use of insulin. Thiazolidinedione derivatives, a new class of antidiabetic agents, sensitize peripheral tissues to the action of endogenous insulin, a process that reduces the need for exogenous insulin (2). These agents, unlike other antidiabetic agents such as sulfonylureas, may be less likely to lead to pancreatic β-cell exhaustion after long-term use (3). Troglitazone, the first of the thiazolidinediones approved by the U.S. Food and Drug Administration, has been shown to have beneficial metabolic effects on hyperglycemia, hyperinsulinemia, hypertriglyceridemia, and HDL cholesterol levels and may help to manage type 2 diabetes more effectively (4–6).

As evidenced by the results from the Diabetes Control and Complications Trial (DCCT) (6) and the U.K. Prospective Diabetes Study (7), strict glycemic control is important in preventing microvascular complications and may also be important in preventing the cardiovascular complications of diabetes (8). Troglitazone, which exerts its therapeutic effects by reducing insulin resistance, reverses many cardiovascular risk factors (4,9–11). One of the problems in clinical practice is the long-term maintenance of strict glycemic control, which tends to deteriorate over time with sulfonylureas, biguanides, and insulin (7). Therefore, the purpose of these long-term studies with troglitazone was to examine whether the initial glycemic and lipidemic benefits observed in the double-blind studies could be maintained in a clinical practice setting.

RESEARCH DESIGN AND METHODS

This article presents the long-term extension of three previously reported double-blind studies (3,12,13). Each of these three studies had a unique design and different schemes for dose titrations. This article focuses on the effectiveness data collected from patients who received a fixed troglitazone dose of 600 mg in each of the three studies. We restricted the analysis to this subgroup of patients for two reasons: *1*) 600 mg is the most effective dose, and *2*) many patients taking lower doses were titrated up to 600 mg and therefore were not on a fixed dose for the long-term duration of the study. Thus, the patients described received the same dose of study medication throughout the double-blind and open-label phases. Safety data are presented for all patients at all doses in these three studies. All protocols were reviewed by institutional review

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Abbreviations: ADA, American Diabetes Association; DCCT, Diabetes Control and Complications Trial; FFA, free fatty acid; FSG, fasting serum glucose; IGT, impaired glucose tolerance; LOCF, last observation carried forward; SAE, serious adverse event.

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

Table 1—*Summary of patient retention rates in the studies*

	Total patients			Total patients taking 600 mg troglitazone		
	Study 1	Study 2	Study 3	Study 1	Study 2	Study 3
Patients at the beginning of the double-blind phase	402	552	350	80	82	116
Patients at the end of the double-blind phase	286	318	314	65	70	100
Patients entering the open-label extension	231	241	286	47	58	93
Patients completing the open-label extension	126	174	229	42	44	77

Data are *n*.

boards, and all patients gave written informed consent.

All patients who completed the double-blind portion of one of these three studies were invited to continue into the open-label extensions. Of the 918 eligible patients who completed the double-blind portion, 758 patients (83%) entered the open-label extension; of these 758 patients, 529 (70%) completed the open-label extension. The most common reasons for withdrawal were lack of effectiveness (monotherapy and sulfonylurea combination studies), which was highest at the lowest doses of troglitazone (range 45–55%) and lowest at the 600-mg troglitazone dose (range 4–20%), and voluntary withdrawal (insulin combination study). Overall dropout rates for the three studies and the 600-mg subgroup appear in Table 1.

Study design and patient sample

Study 1 was a 24-month open-label extension of a previously reported 6-month double-blind placebo-controlled troglitazone monotherapy study (12). On entering the open-label phase, patients originally randomized to troglitazone continued into the open-label phase with their originally assigned doses, and patients originally assigned to placebo were converted to a dose of troglitazone of 200 mg. Dose titration up to 600 mg was allowed as deemed necessary by the investigator. Median treatment duration was 24 months.

Study 2 was a 72-week open-label extension of a previously reported 52-week double-blind placebo-controlled study in type 2 diabetic patients who were inadequately controlled on maximum doses of sulfonylureas (13). Patients originally randomized to a fixed dose of 12 mg glyburide/600 mg troglitazone continued into the open-label phase with that dose. All other patients with poor glycemic control (fasting serum glucose [FSG] >160 mg/dl, HbA_{1c} >8%) were switched to a dose of 12 mg glyburide/400 mg troglitazone during the open-label phase. These patients were allowed to have the troglitazone dose further titrated to 600 mg. Median treatment duration was 29 months.

Study 3 was a 24-month open-label extension of a 6-month double-blind placebo-controlled study of troglitazone in type 2 diabetic patients who were inadequately controlled on insulin (3). During the open-label extension, patients who were randomized to either 200 or 600 mg troglitazone during the double-blind phase took the same dose; patients who had originally been randomized to placebo were converted to 400 mg troglitazone. Doses of troglitazone were not changed during the open-label study. Adjustments in insulin dose were at the investigator's discretion. Median treatment duration was 22 months.

Statistical analyses

The statistical methods used for the three double-blind studies have been described previously (3,12,13). Summary statistics were performed for all three open-label studies to capture the means ± SEM of changes from baseline to the end of the open-label study for all parameters. Paired *t* tests were performed to analyze the end of open-label treatment and baseline values for all glycemic lipid parameters. Proportions of patients who achieved glycemic control according to HbA_{1c} levels were summarized for all three studies; one sample *t* test was performed on the proportion at the open-label phase compared with the nominal proportion at baseline. A last observation carried forward (LOCF) technique was used to input missing observations for patients who did not complete the studies.

Measurement of glycemic and lipid parameters

All biochemical measurements were conducted at the Medical Research Laboratories (Highland Heights, KY) and at Corning Nichols Institute (San Juan Capistrano, CA). FSG levels were measured using the hexokinase procedure (Hitachi 747, Indianapolis, IN), HbA_{1c} levels were measured using high-performance liquid chromatography (Bio-Rad Variant, Richmond, CA), and insulin and C-peptide levels were measured using radioimmunoassay. Free fatty acid (FFA) levels were determined enzymatically (NEFA C-Test, WACO Chemicals, Richmond, VA). Triglyceride levels were measured using the standard lipase, glycerokinase, glycerol-3-phosphate oxidase, and peroxidase method, and HDL cholesterol was measured by using the precipitation and enzymatic method of lipoprotein (Hitachi 704). LDL cholesterol levels were calculated from the measurements of total cholesterol, HDL cholesterol, and triglycerides.

Safety measurements

Physical examination, adverse events, and standard clinical laboratory measurements including blood chemistry, hematology, and urinalysis were conducted periodically during all studies.

RESULTS

FSG and HbA_{1c}

Study 1. For the 47 patients taking a fixed dose of 600 mg troglitazone monotherapy, FSG levels decreased from a baseline mean of 238 to 181 mg/dl at the end of the open-label phase (Fig. 1). During the 24-month open-label phase, 600 mg troglitazone decreased the HbA_{1c} level by a mean of 0.8 ± 8.4%. At the end of the open-label phase, the proportions of patients who achieved the American Diabetes Association (ADA)-recommended action limit of ≤8% (14) and the ADA treatment target goal of ≤7% (51 and 40%, respectively) were greater than both proportions at baseline (30 and 13%, respectively; $P < 0.005$ and $P < 0.0001$, respectively) and proportions at the end of the double-blind phase (40 and 21%, respectively) (Table 2).

Study 2. For the 55 patients taking a fixed dose of 600 mg troglitazone/micronized gly-

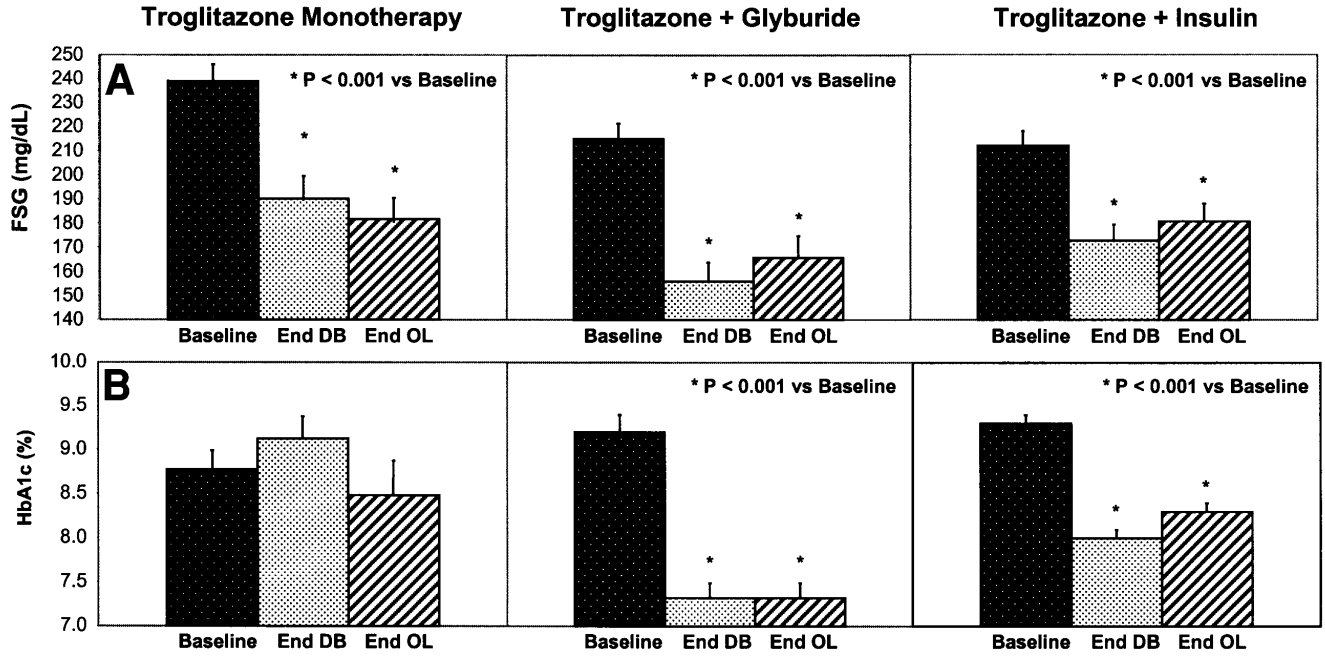

Figure 1—*FSG (*A*) and HbA$_{1c}$ (*B*) levels at baseline, at the end of the double-blind (DB) phase, and at the end of the open-label (OL) phase of each study. The error bars represent the SEM.*

buride, FSG levels decreased from a baseline mean of 215 to 166 mg/dl, and HbA$_{1c}$ levels decreased from a baseline mean of 9.2 to 7.4% ($P < 0.0001$) (Fig. 1). The proportions of patients achieving HbA$_{1c}$ levels ≤8 and ≤7% at the end of the open-label phase (69 and 51%, respectively) were comparable with those at the end of double-blind phase (71 and 44%, respectively) and were markedly higher than those at baseline (24 and 9%, respectively; $P < 0.0001$ and $P < 0.0001$, respectively) (Table 2).

Study 3. For the 93 patients taking a fixed dose of 600 mg troglitazone in combination with insulin, mean FSG levels decreased from a baseline mean of 212 to 173 mg/dl, and HbA$_{1c}$ levels decreased from a baseline mean of 9.3 to 8.0% during the double-blind phase (Fig. 1). During the 24-month open-label phase, the mean FSG level increased slightly to 181 mg/dl at the end of the open-label phase, and the HbA$_{1c}$ level increased slightly to 8.3%. However, these differences were not statistically significant and may be related to maintenance of the lower insulin dose achieved during the double-blind phase. Although fewer patients achieved the targets of HbA$_{1c}$ ≤8 and ≤7% at the end of the open-label phase (47 and 11%, respectively) than at the end of the double-blind phase (61 and 27%, respectively), these proportions are still improved from baseline (12 and 6%, respectively; $P < 0.0001$ and $P < 0.07$, respectively) (Table 2).

Total insulin, C-peptide, and daily insulin requirement

Study 1 and study 2 showed that, during the double-blind phase, with 600-mg troglitazone monotherapy or troglitazone in combination with 12 mg glyburide, total insulin levels and C-peptide levels showed statistically significant decreases; these decreases were maintained during the open-label extensions. During the double-blind phase of study 3, 600 mg troglitazone had markedly reduced the mean daily insulin dose by 25 U, and this reduction was maintained throughout the 24-month open-label period.

Lipid parameters

Results from all three studies showed that triglyceride levels decreased by means of 24% (study 1), 23% (study 2), and 11% (study 3) by the end of the open-label phase relative to baseline (Fig. 2). FFA levels decreased by means of 33% (study 1) and 14% (study 2) by the end of the open-label phase relative to baseline. HDL cholesterol levels increased by 15% (study 1), 24% (study 2), and 17%

Table 2—*Percentage of patients achieving selected HbA$_{1c}$ levels*

HbA$_{1c}$ level	Study 1	Study 2	Study 3	Combined cohort
n	47	55	93	195
HbA$_{1c}$ ≤8%				
Baseline	30	24	12	19
End of double-blind phase	40	71	61	59
End of open-label phase	51	69	47	54
HbA$_{1c}$ ≤7%				
Baseline	13	9	6	9
End of double-blind phase	21	44	27	30
End of open-label phase	40	51	11	29

Data are *n* or %. Study 1, 600 mg troglitazone; study 2, 600 mg troglitazone/12 mg glyburide; study 3, 600 mg troglitazone/insulin; combined cohort, all troglitazone treatments.

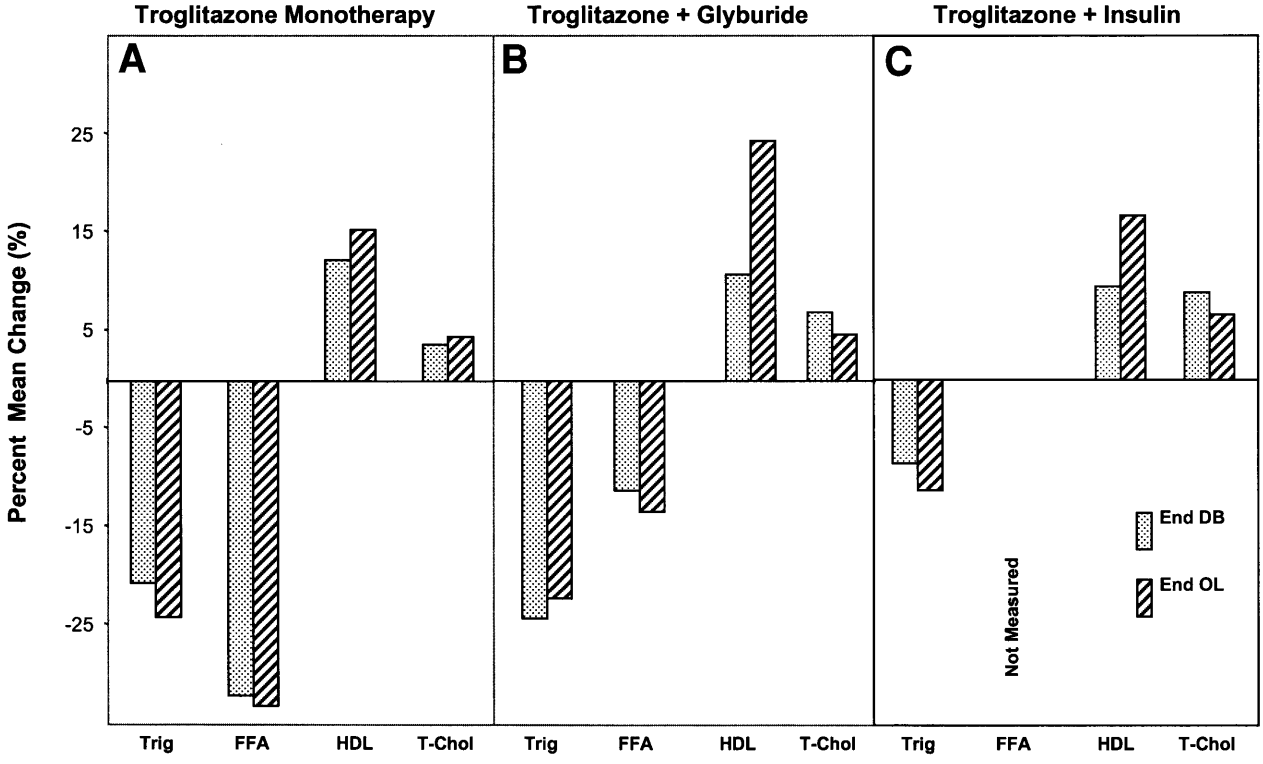

Figure 2—A, B, *and* C *present the change in levels of triglycerides (Trig), FFA, HDL cholesterol, and total cholesterol (T-Chol) at the end of the double-blind (DB) phase and the end of the open-label (OL) phase relative to baseline of study 1, study 2, and study 3, respectively.*

(study 3) by the end of the open-label phase relative to baseline. Total cholesterol levels increased by means of 4% (study 1), 5% (study 2), and 6% (study 3) by the end of the open-label phase relative to baseline.

Safety

Troglitazone was well tolerated in these three open-label studies in which a total of 758 patients completed a total exposure of 16,264 patient-months. A total of 23 (10%), 35 (15%), and 54 (19%) patients experienced serious adverse events (SAEs) in study 1, study 2, and study 3, respectively. The SAE rates were comparable with those observed with placebo or active control treatments during the double-blind phases of the three studies. Most of these SAEs were considered by the investigator to be unrelated to study treatment except for two cardiovascular events and one death from liver cirrhosis. A patient with liver cirrhosis from study 2 had pancreatic adenocarcinoma, and the cirrhosis was believed to have been present before the patient entered the study. The cardiovascular adverse event rates during the open-label phases, when normalized for the same length of exposure as the double-blind phases, were 6% (study 1), 18% (study 2), and 21% (study 3), which are comparable with the rates for the control groups (placebo or glyburide alone) in the double-blind phases.

A total of 8 patients (3 patients in study 1, 2 patients in study 2, and 3 patients in study 3) out of a total of 758 patients who entered the open-label phases of the three studies experienced elevations in alanine aminotransferase and/or aspartate aminotransferase at least three times the upper limit of normal. Most of these patients were asymptomatic, and only one (taking 600 mg troglitazone) developed jaundice. All of these elevations returned to the baseline value or were within the normal reference range once troglitazone treatment was discontinued except for the one patient who died.

Weight gain (which correlated with improved glycemic control) was observed during the double-blind phases of study 2 and study 3 but not during troglitazone monotherapy (study 1). An integrated analysis of weight change in the double-blind phase of these three studies showed that weight changes in patients treated with troglitazone monotherapy at all doses (mean −0.9 kg, median −1.1 kg) were comparable with those in placebo-treated patients (mean −1.1 kg, median −0.5 kg). However, a mean increase in weight was observed in patients taking combination therapy involving various doses of troglitazone with sulfonylureas or with insulin (mean 2.8 kg, median 2.5 kg). Weight gain among these patients correlated significantly with the improvement in HbA_{1c} levels (1.0–1.2 kg weight gain/1% decrease in HbA_{1c}; $P = 0.0001$). Moreover, weight stabilized within 12–20 weeks and remained unchanged after that time; the time course for this increase in weight correlated with that seen for the decrease in HbA_{1c}. A similar correlation was observed during the open-label phases of these three studies.

CONCLUSIONS — Thiazolidinediones, a new class of antidiabetic agents, have demonstrated effectiveness in improving hyperglycemia and hyperinsulinemia via mechanisms independent of those in other classes of antidiabetic agents and thereby offer an alternative for patients who have not had success with other therapies. The short-term effectiveness of troglitazone in improving glycemic control in type 2 diabetic patients has been demonstrated in previous double-blind placebo-controlled studies (3,12,13,15,16).

This article presents the long-term effects of troglitazone in type 2 diabetic patients at various stages of disease progression. Specifically, the results from the open-label extension of three double-blind studies are presented herein, including the use of troglitazone as monotherapy or the use of troglitazone in combination with sulfonylureas or insulin. This article focuses on the effectiveness of the highest dose of troglitazone used in these studies (600 mg daily). The results show that long-term treatment with 600 mg troglitazone alone or in combination with glyburide or insulin sustained or even improved the glycemic and triglyceridemic benefits observed with short-term troglitazone treatment.

The open-label studies presented herein were based on the LOCF statistical technique. Analysis of the data for patients who completed these three studies confirmed the results based on the LOCF analysis in that the completer subsets showed even greater improvements in long-term glycemic control and lipid profiles (data not shown).

Hyperglycemia in type 2 diabetes is thought to result from a combination of peripheral insulin resistance and a defective β-cell insulin secretory response to glucose. In the troglitazone monotherapy study (study 1), despite the deteriorated β-cell function at baseline (as evidenced by the prior failure to respond to sulfonylureas), glycemic control was significantly improved with troglitazone during both the double-blind and open-label phases, which suggests that troglitazone increased peripheral insulin sensitivity among these patients. Interestingly, further improvements in glycemic control with long-term troglitazone treatment were accompanied by stabilizing levels of total insulin and C-peptide, which suggests that long-term troglitazone treatment may also have prevented further deterioration of β-cell function. Similar results obtained from study 2 and study 3 confirmed this possibility. Because the action of troglitazone requires insulin, the sustained action of troglitazone accompanied by maintenance of improved glycemic control during long-term treatment thus suggests a preservation of β-cell function and raises the possibility that troglitazone may play a role in maintaining β-cell function. Indeed, studies have demonstrated troglitazone's ability to restore the oscillatory secretion pattern in β-cells and to improve β-cell responses to glucose among patients with IGT (17,18).

The use of insulin injections is resisted by both patients and physicians and is usually regarded as a last resort for the standard treatment of type 2 diabetes. Therefore, using oral agents may be preferable to reduce the need for exogenous insulin while achieving adequate glycemic control. Combination therapy of troglitazone with insulin successfully achieved the ADA-recommended standards for adequate glycemic control in 47% of patients in study 3 while markedly reducing exogenous insulin requirements. This decreased insulin requirement was effectively maintained for >2 years after the initial reduction, even in those patients who were able to discontinue insulin entirely. Although the proportion of patients achieving HbA_{1c} levels ≤7% at the end of the open-label phase in study 3 was noticeably smaller compared with the proportions in study 1 and study 2, this may be related to the confounding effects of insulin withdrawal during the study. These data support the results of another recent study of insulin-treated patients that also demonstrated sustained glycemic control with long-term troglitazone and insulin combination therapy (16).

The few adverse events observed during the large number of patient-months in these three studies demonstrate the safety of long-term use of troglitazone. Long-term troglitazone treatment was associated with modest weight gain; however, the magnitude of weight gain was comparable with that seen with intensive therapy in the DCCT (6), and the correlation analysis of weight gain versus the decrease in HbA_{1c} levels across all three studies suggests that weight gain is closely associated with improvements in glycemic control and not with troglitazone per se. Although some increases in liver function tests were observed, the frequency of such abnormalities was low, and liver function tests returned to baseline with or without the discontinuation of troglitazone.

Open-label extension trials such as those reported herein have several obvious potential limitations (19,20). These include a smaller sample size than the original controlled trial, patient selection bias, less strict protocol adherence, and the possibility of dose titration bias. In addition, the potential exists for carry-over bias based on the need to analyze data according to an LOCF analysis. However, these limitations have been minimized in this analysis because of the large number of patients. Because the LOCF analysis includes patients who withdrew early because of lack of effectiveness, these results reflect lesser improvements in glycemic control than an analysis of more complete subsets would show. In this sense, the LOCF analysis is actually more likely to produce a bias against the effectiveness of the treatment. Consequently, these data are useful in confirming and corroborating observations from controlled studies and in providing insights into the long-term benefits and safety of troglitazone on glycemic and lipidemic measures. Such data are important because diabetes is a lifelong disease, but data on most therapies are derived from short-term clinical trials.

In summary, these three open-label extension studies demonstrate that the acute improvements in glycemic control and lipid profiles observed with short-term troglitazone treatment as monotherapy or in combination with sulfonylureas or insulin are sustained with long-term treatments. We therefore anticipate that the risks for microvascular and macrovascular complications will be reduced with these prolonged improvements in glycemic and lipid control.

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APPENDIX: INVESTIGATORS FOR THE TROGLITAZONE STUDY GROUPS

Study 1

T. Blevins, Austin, TX; J. Cohen, Washington, DC; K. Dawson, Vancouver, BC, Canada; N. Friedman, Albuquerque, NM; H. Gerstein, Hamilton, ON, Canada; B. Goldstein, Philadelphia, PA; B. Gumbiner, Rochester, NY; J. Hone, Wheatridge, CO; W. Hsueh, Los Angeles, CA; D. Kelly, Pittsburgh, PA; K.J. Lucas, Atlanta, GA; F. Maggiacomo, Providence, RI; W. Mitchell, Albuquerque, NM; J. Olefsky, San Diego,

CA; A. Peters, Los Angeles, CA; S. Plevin, Palm Harbor, FL; K. Polonsky, Chicago, IL; S. Ross, Calgary, AB, Canada; S. Schwartz, San Antonio, TX; G. Shulman, New Haven, CT; R. Sims, Birmingham, AL; J. Snyder, Las Vegas, NV; R. Suwannasri, St. Louis, MO.

Study 2

J. Angelo, New Orleans, LA; S. Berger, Chicago, IL; P. Dandona, Buffalo, NY; M. Doyle, Ferndale, MI; B. Draznin, Denver, CO; E. Fineberg, Indianapolis, IN; W. Fowler, Kansas City, MO; A. Garber, Houston, TX; R. Guthrie, New Orleans, LA; J. Harp, Atlanta, GA; B. Hagg, Springfield, MA; F. Hofeldt and E. Havranek, Denver, CO; E.S. Horton, Boston, MA; C. Kilo, St. Louis, MO; T. Littlejohn, Winston-Salem, NC; M.S. Magee, Appleton, WI; R. Montoro, Coral Gables, FL; M. Nolte, San Francisco, CA; K. Osei, Columbus, OH; S. Pek, Ann Arbor, MI; M. Rendell, Omaha, NE; S. Rosenblatt, Irvine, CA; S. Schwartz, San Antonio, TX; D. Simonson, Boston, MA; M. Sperling, Fountain Valley, CA; M. Stjernholm, Boulder, CO; T. Wahl, Omaha, NE; B. Warner, Mobile, AL; E. Wedell, Cheyenne, WY; S. Weiss, San Diego, CA; F. Whitehouse, Detroit, MI.

Study 3

T. Blevins, Austin, TX; J. Blodgett, San Antonio, TX; P. Dandona, Buffalo, NY; B. Draznin, Denver, CO; L. Fish, Minneapolis, MN; V. Fonseca, New Orleans, LA; B. Francis, Seattle, WA; R. Guthrie, New Orleans, LA; B. Haag, Springfield, MA; B. Henson, Kansas City, MO; J. Levine, Nashville, TN; W. Mitchell, Albuquerque, NM; W. Nicholas, Jackson, MS; M. Nolte, San Francisco, CA; S. Pek, Ann Arbor, MI; A. Peters and M. Davidson, Los Angeles, CA; S. Plevin, Palm Harbor, FL; P. Raskin, Dallas, TX; P. Ross, Fairfax, VA; S. Schwartz, San Antonio, TX; R. Suwannasri, St. Louis, MO; R. Teague, Birmingham, AL.

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