Effects of Pemafibrate, a Novel Selective PPARα Modulator, on Lipid and Glucose Metabolism in Patients With Type 2 Diabetes and Hypertriglyceridemia: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial

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OBJECTIVE

Type 2 diabetes is frequently complicated with atherogenic dyslipidemia. This study aimed to evaluate the efficacy and safety of pemafibrate (K-877) in patients with type 2 diabetes comorbid with hypertriglyceridemia.

RESEARCH DESIGN AND METHODS

Patients were randomly assigned to three groups and received placebo (*n* = 57), 0.2 mg/day pemafibrate (*n* = 54), or 0.4 mg/day pemafibrate (*n* = 55) for 24 weeks (treatment period 1). Subsequently, the patients received follow-up treatment for another 28 weeks (treatment period 2), in which the placebo was switched to 0.2 mg/day pemafibrate. This article presents the results of treatment period 1, which were the primary objectives.

RESULTS

The pemafibrate groups showed significantly reduced fasting serum triglyceride levels by ∼45% compared with the placebo group ($P < 0.001$). Additionally, the pemafibrate groups displayed significant decreases in non-HDL and remnant lipoprotein cholesterol, apolipoprotein (Apo) B100, ApoB48, and ApoCIII levels and significant increases in HDL cholesterol and ApoA-I levels. LDL cholesterol levels were not considerably altered in the pemafibrate groups. Furthermore, the 0.2 mg/day pemafibrate group showed a significantly reduced HOMA-insulin resistance score compared with the placebo group; however, no significant changes compared with placebo were found in fasting plasma glucose, fasting insulin, glycoalbumin, or HbA_{1c} levels. The pemafibrate groups also showed significantly increased fibroblast growth factor 21 levels compared with the placebo group. All groups displayed comparable rates of adverse events and drug reactions.

CONCLUSIONS

Pemafibrate significantly ameliorated lipid abnormalities and was well tolerated in patients with type 2 diabetes comorbid with hypertriglyceridemia.

The leading cause of death in patients with type 2 diabetes is atherosclerotic cardiovascular disease (ASCVD) (1). Cardiovascular events are more common in patients with diabetes than in those without (2,3). The increased ASCVD risk in patients with diabetes is attributed to abnormalities in both glucose and lipid metabolism. Lipid abnormalities are often comorbid with type 2 diabetes and are unique in terms of quantitative and qualitative lipid abnormalities that are associated with insulin resistance (IR) (4). The clinical features of these abnormalities include elevated triglyceride (TG) levels, reduced HDL cholesterol (HDL-C) levels, and delayed TG-rich lipoprotein catabolism, leading to elevated postprandial TG levels, remnant lipoprotein accumulation, and increased small dense LDL production.

A number of large-scale clinical trials have demonstrated that the management of dyslipidemia resulted in significantly reduced cardiovascular risk in patients with diabetes. The Collaborative Atorvastatin Diabetes Study (CARDS) (5) and Cholesterol Treatment Trialist (CTT) Collaboration meta-analysis (6) reported that LDL cholesterol (LDL-C)–lowering therapy with statins reduces cardiovascular risk in patients with type 2 diabetes. Additionally, the Japan Diabetes Complications Study (JDCS) identified both high LDL-C and TG levels as risk factors for the development of coronary artery disease (7). Furthermore, the UK Prospective Diabetes Study (UKPDS) revealed that both high LDL-C and low HDL-C levels were associated with elevated coronary artery disease risk (8). Therefore, research in recent decades has focused on interventions targeting diabetic lipid abnormalities other than high LDL-C levels. In particular, large-scale clinical trials have revealed that treatment with fibrates, which decrease TG levels and increase HDL-C levels, reduces ASCVD risk in patients with type 2 diabetes. For example, in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) and Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid studies, treatment with fenofibrate led to event reduction in subgroup patients with high TG and low HDL-C levels (9,10). Moreover, the post hoc analysis of the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) showed that treatment with gemfibrozil resulted in cardiovascular event reduction in a subgroup of patients with diabetes (11).

Pemafibrate (K-877) is a novel selective peroxisome proliferator–activated receptor α (PPARα) modulator approved for the treatment of dyslipidemia. A dose-finding phase 2 trial on pemafibrate conducted in patients with atherogenic dyslipidemia revealed that this drug exerted significant TG reduction and HDL-C increase, with comparable rates of adverse events (AEs) to placebo, such as serum creatinine and liver enzyme increases, which suggests that pemafibrate may have a better benefit/risk balance than fenofibrate (12)

Given that type 2 diabetes is frequently complicated with atherogenic dyslipidemia, a considerable proportion of patients treated with pemafibrate are anticipated to have type 2 diabetes. However, to date, the efficacy and safety of pemafibrate, specifically in patients with type 2 diabetes comorbid with hypertriglyceridemia, have not been investigated through a prospective randomized trial. Therefore, we conducted this phase 3 clinical trial to evaluate them through placebo-controlled treatment for 24 weeks (treatment period 1), followed by further long-term treatment for another 28 weeks, in which placebo was switched to pemafibrate (treatment period 2). This article is based on the clinical study report for treatment period 1, which was documented before the completion of a 52-week treatment period. The overall results throughout the 52 weeks will be separately documented in another article based on the other clinical study report that includes the results of treatment period 2.

RESEARCH DESIGN AND METHODS

Study Design

This multicenter, placebo-controlled, randomized, double-blind, parallel-group study was performed in 34 medical institutions in Japan from 20 February 2014 to 30 April 2015, denoted as treatment period 1.

The study protocol was approved by the Institutional Review Boards of the 34 medical institutions prior to the implementation of the study. Additional matters that needed to be approved, such as protocol amendments, were assessed and approved by the Institutional Review Boards as needed. The study was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice Ministerial Ordinance by the Ministry of Health, Labor and Welfare (of Japan). All patients provided written informed consent prior to their participation. This study is registered at Japan Pharmaceutical Information Center Clinical Trials Information (JapicCTI-142412).

Patients

The inclusion criteria were as follows: *1*) type 2 diabetes comorbid with hypertriglyceridemia ($\geq$6.2% [44.3 mmol/mol] HbA_{1c} and $\geq$150 mg/dL [1.7 mmol/L] fasting serum TG levels for two consecutive screening visits); *2*) age $\geq$20 years; *3*) men and postmenopausal women; and *4*) $\geq$12 weeks of dietary or exercise guidance before the first screening test.

The exclusion criteria were as follows: *1*) fasting serum TG levels $>$1,000 mg/dL (11.3 mmol/L); *2*) type 1 diabetes, inadequately controlled diabetes ($\geq$8.0% [63.9 mmol/mol] HbA_{1c}), diabetes requiring treatment with insulin, thiazolidinediones, biguanides, high-dose sulfonylureas ($\geq$4 mg/day glimepiride, $\geq$7.5 mg/day glibenclamide, and $\geq$120 mg/day gliclazide), sodium-glucose cotransporter-2 inhibitors, or combination therapy with three or more antidiabetic agents, and recent changes in the class and dosage of antidiabetic agents within 12 weeks prior to the first screening test; *3*) inadequately controlled thyroid disorders; *4*) inadequately controlled hypertension ($\geq$180/$\geq$110 mmHg systolic/diastolic blood pressure); *5*) $\geq$1.5 mg/dL serum creatinine levels for patients receiving statin treatment; *6*) a creatine kinase (CK) level that is more than five times the upper limit of normal (ULN) for patients on statin treatment; *7*) aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels that are more than three times the ULN, or serious hepatic disorders; *8*) gallstones or serious biliary disorders; *9*) occurrence of acute myocardial infarction or stroke within 3 months before providing informed consent; and *10*) heart failure with New York Heart Association class III or IV.

Procedures

Patients who provided their informed consent were assessed for eligibility as participants (Supplementary Fig. 1). Eligible patients were randomly and equally assigned to the placebo, 0.2 mg/day pemafibrate (twice daily), and 0.4 mg/day pemafibrate (twice daily) groups using the dynamic allocation method with the HbA_{1c} value ($\geq$7.4% [57.4 mmol/mol] or $<$7.4%) from the second screening test

and antidiabetic treatment (no agent, sulfonylurea, or the other antidiabetic agent) as adjustment factors. An independent third party generated the random allocation key codes, confirmed that placebo was indistinguishable from pemafibrate, and conducted the numbering and concealment of the study drugs. Another independent third party managed the dynamic allocation based on the screening test results. Investigators and participants were not provided with any information related to the randomization throughout the study period.

Patients were instructed to take the assigned study drug twice daily before or after a meal (fixed throughout the study period) in the morning and evening for 24 weeks. Throughout the study period, the following drugs were prohibited for concomitant medications: fibrates, bile acid sequestrants, adrenocorticosteroids (systemic use), and sodium-glucose cotransporter-2 inhibitors. In principle, initiation, discontinuation, or change in the dosage regimen was prohibited for any antidyslipidemic agent not mentioned as prohibited concomitant medication from 4 weeks before the screening tests. Such changes in the use of antidiabetic agents, protease inhibitors, anabolic steroid hormones, and progestogen were prohibited. However, changes in the class and dosage regimen of antidiabetic agents were permitted for the next hospital visit (from week 16 onward) to treat deterioration in glycemic control found after week 12. Patients with a drinking habit were instructed to limit alcohol intake to $<$25 g/day during the treatment period.

The fasting blood and urine samples were collected at least 10 h after the last meal. Apolipoproteins (Apos) were measured through immunoassay. ApoB100 levels were calculated by subtracting ApoB48 from ApoB. LDL-C, HDL-C, and remnant lipoprotein cholesterol (RemL-C) levels were measured using the homogenous assays Determiner L LDL-C, MetaboLead HDL-C, and MetaboLead RemL-C (Kyowa Medex Co., Ltd., Tokyo, Japan), respectively. Fibroblast growth factor 21 (FGF21) was analyzed through an ELISA with Human FGF21 ELISA (BioVendor, Brno, Czech Republic). Common laboratory tests were performed using standardized methods at LSI Medience Corporation, Tokyo, Japan. High-performance liquid chromatography analyses (LipoSEARCH; Skylight Biotech Inc., Akita, Japan) were performed after 12 weeks at Skylight Biotech to examine the lipoprotein profiles by subclass.

A meal tolerance test was performed at the study sites where this test was feasible at weeks 0 and 24 in patients who provided written informed consent for undergoing this test. Fasting blood samples were collected before the meal and study drug administration. The patients had the test meal within 15 min in principle and took the study drug at 30 min before or after starting the meal. Postprandial blood samples were collected 0.5, 1, 2, 2.5, 4.5, and 6.5 h after starting the meal. The test meal was Meal Test C (Saraya Co., Ltd., Osaka, Japan), which contained 592 kcal, 28.5 g fat (derived from butter), 75.0 g carbohydrates (derived from wheat starch and maltose), 8.0 g protein, 0.5–4.0 g dietary fiber, 125 mg sodium, and 0 g sucrose.

End Points

The primary efficacy end point was the percentage change in fasting serum TG level from the baseline at the final evaluation over 24 weeks. The secondary efficacy end points were the percentage changes or changes in the levels of fasting and postprandial lipid-related and glycemic parameters from baseline except for the primary efficacy end point.

The primary safety end points were the incidence rates of AEs and adverse drug reactions (ADRs) after the study drug administration. AEs were defined as any undesirable or unintended signs, symptoms, and disorders, including laboratory test abnormalities, regardless of their causal relationship with the study drug. AEs were regarded as ADRs if the causal relationship could not be ruled out.

Statistics

Pemafibrate exposure in at least 100 patients for 1 year was needed to satisfy the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use-E1 guidelines for the evaluation of drug safety. Assuming that 10% of the patients would discontinue participation in the study, 55 patients per group was the aim for enrollment, considering that the power of the primary efficacy analysis was $>$99%.

The primary efficacy analysis was performed based on the full analysis set through a last-observation-carried-forward (LOCF) method, imputing the last valid values to subsequent missing values. The safety analyses were based on the safety analysis set. The safety analysis set included all patients who received at least one dose of the study drug. The full analysis set included patients in the safety analysis set who had valid baseline and postbaseline efficacy measurements.

The primary efficacy analysis was conducted using ANCOVA with the baseline as a covariate. Multiplicity was adjusted using the Dunnett test for the comparison of the effect between the placebo group and each of the pemafibrate groups. The secondary efficacy end points were analyzed using a one-sample *t* test for the differences from the baseline and ANCOVA for the differences between groups. The primary safety end points were analyzed using the Fisher exact test. The significance level was 0.05 for a two-sided test. SAS version 9.3 (SAS Institute Inc., Cary, NC) was used for the analyses. All primary efficacy and safety end point analyses were performed based on a prespecified statistical analysis plan.

RESULTS

Supplementary Figure 2 shows the disposition of the patients. Among 306 patients who provided written consent, 167 patients were eligible and randomly assigned to the three groups. One patient discontinued participation in the study before study drug administration because of an AE. Thus, 57, 54, and 55 patients received the placebo, 0.2 mg/day pemafibrate, and 0.4 mg/day pemafibrate, respectively. After the study drug administration, the treatment was discontinued in six patients (two and four in the placebo and 0.4 mg/day pemafibrate groups, respectively). Therefore, 160 patients completed the treatment for 24 weeks. Table 1 shows the characteristics of the patients. No noteworthy differences were observed between the groups. Men accounted for 72.9% of the patients, the mean age of the participants was 60.5 years, and their mean BMI was 25.9 kg/m^2. Approximately 60% of them had drinking habits, and two-thirds had hypertension or fatty liver. The mean duration of diabetes was 5.7 years, and 44.6% of the patients were receiving one or two antidiabetic agents, with dipeptidyl peptidase-4 inhibitor being the most frequently used drug (34.3%). Additionally, 39.2% of the patients received statins (atorvastatin 23.1%; pitavastatin 27.7%; rosuvastatin 35.4%; and other statins 13.8%).

Table 1—Patient characteristics

	Placebo (n = 57)	Pemafibrate 0.2 mg/day (n = 54)	Pemafibrate 0.4 mg/day (n = 55)
Age (years)	61.2 ± 10.0	59.8 ± 11.6	60.6 ± 10.1
Age ≥65 years	35.1 (20)	35.2 (19)	34.5 (19)
Men	66.7 (38)	79.6 (43)	72.7 (40)
BMI (kg/m^2)	26.0 ± 3.3	26.5 ± 3.8	25.3 ± 3.4
BMI ≥25 kg/m^2	57.9 (33)	63.0 (34)	45.5 (25)
Drinking habit	57.9 (33)	66.7 (36)	58.2 (32)
Hypertension	64.9 (37)	59.3 (32)	60.0 (33)
Fatty liver	56.1 (32)	59.3 (32)	47.3 (26)
Duration of diabetes (years)	5.5 ± 4.5	4.9 ± 3.7	6.8 ± 5.9
No antidiabetic drug	54.4 (31)	55.6 (30)	56.4 (31)
One antidiabetic drug	22.8 (13)	25.9 (14)	23.6 (13)
Sulfonylurea		3.7 (2)	
DPP-4 inhibitor	19.3 (11)	18.5 (10)	14.5 (8)
α-glucosidase inhibitor			5.5 (3)
Glinide	3.5 (2)	1.9 (1)	1.8 (1)
GLP-1 receptor agonist		1.9 (1)	1.8 (1)
2 antidiabetic drugs	22.8 (13)	18.5 (10)	20.0 (11)
Sulfonylurea/DPP-4 inhibitor	19.3 (11)	11.1 (6)	5.5 (3)
Sulfonylurea/α-glucosidase inhibitor			3.6 (2)
Sulfonylurea/GLP-1 receptor agonist			3.6 (2)
DPP-4 inhibitor/α-glucosidase inhibitor	1.8 (1)	3.7 (2)	5.5 (3)
DPP-4 inhibitor/Glinide	1.8 (1)		1.8 (1)
α-glucosidase inhibitor/glinide		3.7 (2)	
Statin	40.4 (23)	33.3 (18)	43.6 (24)
TG (mmol/L)	3.2 ± 1.3	2.7 ± 1.1	2.9 ± 1.1
HDL-C (mmol/L)	1.2 ± 0.3	1.2 ± 0.3	1.3 ± 0.7
HDL-C category <1.0 (mmol/L)	28.1 (16)	25.9 (14)	20.0 (11)
FPG (mmol/L)	7.7 ± 1.1	7.7 ± 1.1	7.4 ± 1.1
Fasting insulin (pmol/L)	92.7 ± 56.6	83.7 ± 49.2	81.1 ± 40.5
HOMA-IR	4.6 ± 3.0	4.2 ± 2.5	3.8 ± 1.8
HbA_{1c} (%)	7.0 ± 0.5	6.9 ± 0.4	7.0 ± 0.4
HbA_{1c} (mmol/mol)	52.9 ± 5.0	52.4 ± 4.7	52.6 ± 4.7
Glycoalbumin (%)	16.9 ± 2.5	17.1 ± 2.0	17.1 ± 2.2
eGFR (mL/min/1.73 m^2)	73.6 ± 19.2	75.7 ± 14.7	73.3 ± 14.4

Data are presented as the mean ± SD for continuous parameters and % (n) for categorical parameters. DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide 1.

Fasting serum TG levels in the placebo, 0.2 mg/day pemafibrate, and 0.4 mg/day pemafibrate groups decreased from 284.3 ± 117.6 mg/dL (3.2 ± 1.3 mmol/L), 240.3 ± 93.5 mg/dL (2.7 ± 1.1 mmol/L), and 260.4 ± 95.9 mg/dL (2.9 ± 1.1 mmol/L), respectively, at baseline to 242.0 ± 92.2 mg/dL (2.7 ± 1.0 mmol/L), 129.0 ± 71.5 mg/dL (1.5 ± 0.8 mmol/L), and 135.8 ± 71.2 mg/dL (1.5 ± 0.8 mmol/L) at week 24 (LOCF). The percentage changes in fasting serum TG levels at week 24 (LOCF) were −10.8% (P < 0.01), −44.3% (P < 0.001), and −45.1% (P < 0.001), respectively (Fig. 1*A*). Moreover, both of the pemafibrate groups had statistically significant reductions in these levels compared with the placebo group (P < 0.001, multiplicity adjusted). These findings were similar even without imputation using the LOCF method. No sex differences were observed in the findings. In each pemafibrate group, TG was significantly reduced from week 4, and the significance remained until week 24 (Fig. 1*B*) (P < 0.001 for each point). The proportions of patients who achieved <150 mg/dL (1.7 mmol/L) fasting serum TG levels at week 24 (LOCF) were 15.8%, 81.5%, and 70.9% in the placebo, 0.2 mg/day pemafibrate, and 0.4 mg/day pemafibrate groups, respectively. The distances to this target level at week 24 (LOCF) were 92.0 ± 92.2 mg/dL (1.0 ± 1.0 mmol/L), −21.0 ± 71.5 mg/dL (−0.2 ± 0.8 mmol/L), and −14.2 ± 71.2 mg/dL (−0.2 ± 0.8 mmol/L), respectively.

With regard to other lipid-related parameters, the pemafibrate groups showed significant reductions in non–HDL-C, RemL-C, ApoB100, ApoB48, and ApoCIII levels and significant increases in HDL-C and ApoA-I levels (Supplementary Fig. 3). LDL-C levels were not considerably altered in these groups. As a result of the high-performance liquid chromatography analyses conducted at week 12, the cholesterol content decreased in small and very small LDL, whereas it increased in large LDL in the pemafibrate groups (Supplementary Fig. 4). On the other hand, the cholesterol content increased in medium, small, and very small HDL, whereas it decreased in large HDL in these groups.

The changes in glycemic parameters were unclear (Fig. 2*A*–*E*). The 0.2 mg/day pemafibrate group showed a significant decrease in HOMA-IR score

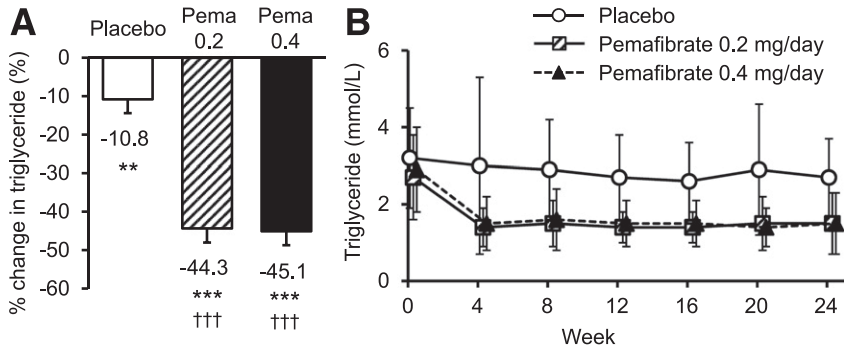

Figure 1—Percentage change in fasting serum TGs from baseline to week 24 (LOCF) (*A*), with values presented as the least squares mean ± SEM estimated using ANCOVA with baseline level as a covariate, and fasting serum TG levels over time (*B*), with values presented as the mean ± SD. $^{**}P < 0.01$, $^{***}P < 0.001$ vs. baseline by ANCOVA. $^{\dagger\dagger\dagger}P < 0.001$ vs. placebo by ANCOVA with Dunnett test for multiplicity adjustment. Pema 0.2, pemafibrate 0.2 mg/day; Pema 0.4, pemafibrate 0.4 mg/day.

compared with the placebo group. However, no significant changes in other glycemic parameters were found between these groups. Both of the pemafibrate groups showed a slight increase from the baseline in HbA_{1c} level at week 24, although this was not statistically significant when compared with the placebo group. The data were subjected to a post hoc repeated-measures ANCOVA at weeks 4–24, in which the pemafibrate groups displayed significant reductions in fasting plasma glucose (FPG), fasting insulin, and HOMA-IR levels compared with the placebo group (Fig. 2*F–H*). FGF21 levels significantly increased in the pemafibrate groups (Supplementary Fig. 5).

The results of the meal tolerance test showed that the pemafibrate groups displayed a significantly reduced the area under the curve of 0–6.5 hours for TG at week 24 compared with the placebo group, whereas the area under the curve of 0–6.5 hours for plasma glucose and insulin were not significantly altered (Supplementary Fig. 6).

The incidence rates of AEs and ADRs were similar across the pemafibrate and placebo groups without statistically significant differences (Table 2). Serious AEs were observed in three (5.3%), three (5.6%), and two (3.6%) patients, respectively, in the placebo, 0.2 mg/day pemafibrate, and 0.4 mg/day pemafibrate groups, and the causal relationship with the study treatment was ruled out for all groups. AEs leading to discontinuation of participation in the study were observed in four patients in the 0.4 mg/day pemafibrate group, and a causal relationship with acute kidney injury and liver function abnormality could not be ruled out. Abnormal elevations in levels of liver enzymes, serum creatinine, estimated glomerular filtration rate, and CK in the pemafibrate groups were limited and comparable to those in the placebo group. The liver enzyme levels decreased, and the renal function test results and CK levels were not significantly altered with pemafibrate treatment (Supplementary Table 1).

CONCLUSIONS

This study is the first to demonstrate the long-term efficacy and safety of pemafibrate treatment for over 24 weeks in patients with type 2 diabetes comorbid with hypertriglyceridemia. Treatment with pemafibrate for 24 weeks remarkably reduced the fasting serum TG levels by ~45%. The significant TG reduction was stably maintained over 24 weeks. The proportion of patients who achieved <150 mg/dL (1.7 mmol/L) TG levels at week 24 was >80% in the 0.2 mg/day pemafibrate group but ~70% in the 0.4 mg/day pemafibrate group. This finding may be attributed to the fact that the former group had lower baseline TG levels by ~20 mg/dL (0.2 mmol/L) than the latter group. Not only TG but also other markers of TG-rich lipoproteins were dramatically ameliorated. Additionally, HDL-C and ApoA-I levels increased. These changes were accompanied by favorable shifting in the LDL and HDL atherogenic profiles by subclasses. These comprehensive effects on lipoprotein profiles were similar to those observed in the previous studies including patients without diabetes as well as the incidence rates of AEs and ADRs, which were similar across the treatment groups (12,13).

The unique quantitative and qualitative lipid abnormalities frequently comorbid with type 2 diabetes based on IR involve the following mechanisms. First, impaired insulin action enhances adipocyte lipolysis by activating hormone-sensitive lipase, thereby liberating nonesterified fatty acids (NEFAs) into the circulation. NEFA, which is taken up by the liver, is re-esterified to form TGs, thereby stimulating the secretion of VLDLs (4). Hyperinsulinemia secondary to IR is also suggested to increase de novo lipogenesis through augmenting the expression of carbohydrate responsiveness element-binding protein and sterol regulatory element-binding protein-1c (4). Second, Niemann-Pick C1-like 1 (NPC1L1) and microsomal TG transfer protein mRNA expression was enhanced in the small intestine, leading to the increases in chylomicron production and postprandial TG levels (14). Third, lipoprotein lipase (LPL) activity was impaired, and the catabolism of increased chylomicrons and VLDLs was delayed, leading to remnant lipoprotein accumulation, HDL-C reduction, and small, dense LDL production (4).

PPARα agonists have been implicated to enhance hepatic NEFA uptake, NEFA β-oxidation, and concomitant decreases in de novo lipogenesis and VLDL production through which they modulate lipoprotein profiles (15). Pemafibrate was also shown to enhance β-oxidation–related gene expression in human hepatocytes, murine hepatocytes, and rat livers (16,17) and decrease de novo lipid synthesis (18), hepatic TG content (17), and VLDL secretion in rat livers (18). PPARα agonists are suggested to decrease intestinal cholesterol absorption, which may be mediated by decreases in NPC1L1, microsomal TG transfer protein, and ApoB mRNA (19,20). Pemafibrate also inhibited NPC1L1 mRNA expression along with increased fecal cholesterol excretion in LDL receptor knockout mice (21) and inhibited ApoB mRNA expression in apoE2/E2 knockin mice (22). In the current study, the levels of ApoB48, a major component of chylomicrons, were significantly reduced with pemafibrate treatment, which presumably reflects the reduction in intestine-derived chylomicron production and/or its stimulated catabolism. Furthermore, PPARα agonists

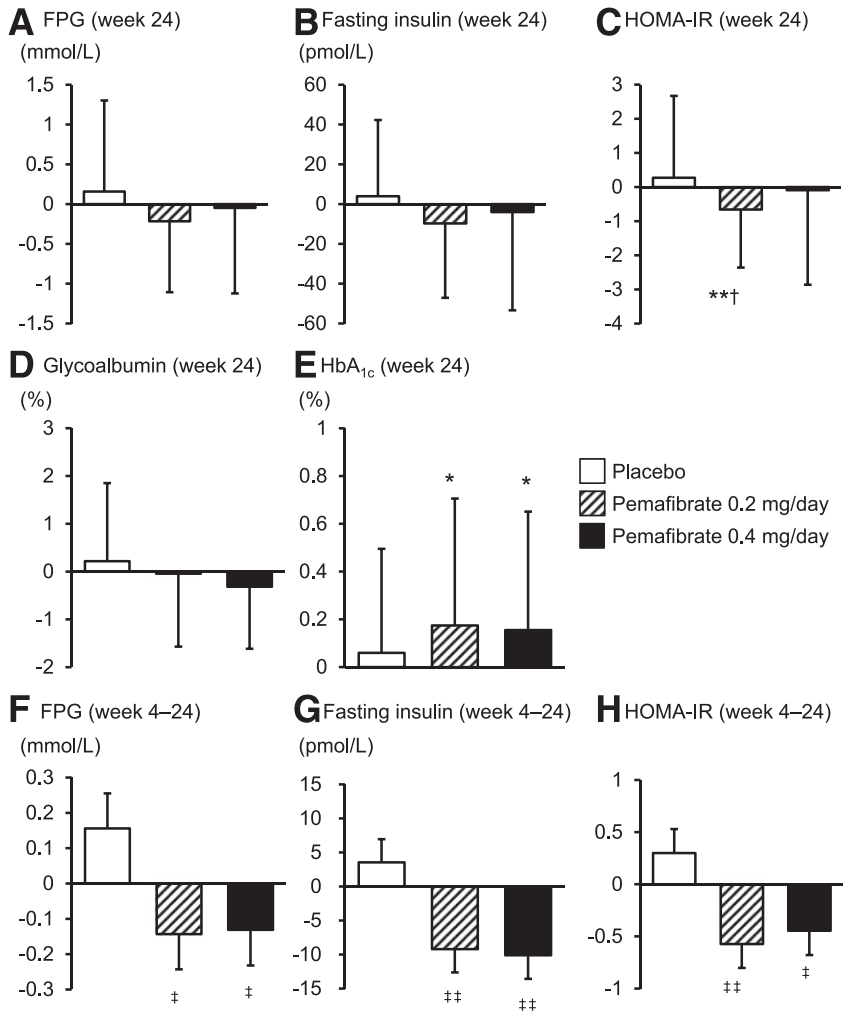

Figure 2—Change from baseline to week 24 (LOCF) in FPG (*A*), fasting insulin (*B*), HOMA-IR (*C*), glycoalbumin (*D*), and HbA_{1c} (*E*), with values presented as the mean ± SD, and the change from baseline to weeks 4–24 in FPG (*F*), fasting insulin (*G*), and HOMA-IR (*H*) estimated by post hoc repeated-measures ANCOVA for weeks 4–24, with values presented as the least squares mean ± SEM. *$P < 0.05$, **$P < 0.01$ vs. baseline by one-sample *t* test. †$P < 0.05$ vs. placebo by ANCOVA with baseline level as a covariate. ‡$P < 0.05$, ‡‡$P < 0.01$ vs. placebo by repeated-measures ANCOVA.

have been shown to increase the expression of LPL and inhibit that of ApoCIII, which inhibits LPL activity (15). Pemafibrate suppressed ApoC3 mRNA expression and enhanced postheparin plasma LPL activity in LDL receptor knockout mice (21). In fact, pemafibrate remarkably decreased the ApoCIII levels in the present and previous clinical studies. Through these mechanisms (i.e., suppressing the production and enhancing the catabolism of TG-rich lipoproteins), pemafibrate was suggested to increase levels of HDL-C and decrease levels of small, dense LDL, which has even higher atherogenicity (23).

The overall results of lipid profiles in the current study were similar to those observed in a dose-response study of another PPARα agonist, LY518674, comparing placebo and 200 mg/day fenofibrate (24). The baseline lipid profiles were similar in both studies, although only 14.6% of patients had diabetes in the latter study. The potential biphasic dose response of HDL-C increase and non–HDL-C reduction in the current study was similarly observed in the study of LY518674 (24). Such a dose response of HDL-C increase with LY518674 may be attributed to enhanced ApoA-I turnover, which was suggested by increased production and fractional catabolic rate of ApoA-I(25) and may be, at least in part, reflected to that of non–HDL-C reduction. ApoA-I turnover may be similarly enhanced with pemafibrate also, considering that very large and large HDL-C levels decreased in the 0.4 mg/day pemafibrate group more than in the 0.2 mg/day pemafibrate group, whereas medium, small, and very small HDL-C levels increased in both groups in the current study. The same trend has been observed in previous studies (12,13).

The effects of pemafibrate on cardiovascular outcomes are being assessed in a global large-scale trial in patients with type 2 diabetes comorbid with atherogenic dyslipidemia (PROMINENT; Clinical trial reg. no. NCT03071692) (26). The biphasic dose response, which was not clear in fenofibrate treatment to the best of our knowledge, may be related to the fact that LY518674 and pemafibrate are both more potent and selective PPARα agonists than fenofibrate (16,27). Pemafibrate is primarily eliminated via the liver, whereas fenofibrate and gemfibrozil are eliminated via kidneys (26,28). The above-mentioned differences may be, at least in part, associated with different responses in several clinical laboratory tests.

In the present and previous studies of pemafibrate compared with placebo and/or fenofibrate (12,13,29), the effects of pemafibrate on serum creatinine, ALT, γ-glutamyl transferase, and homocysteine levels appeared comparable to that of placebo or smaller than that of fenofibrate. Rather, pemafibrate even decreased the liver enzyme levels and affected the serum creatinine levels to a lesser extent than fenofibrate. Furthermore, these effects of pemafibrate monotherapy were similar to pemafibrate and statin combination therapy (13). Gemfibrozil shares similar adverse effects on the clinical laboratory tests and is associated with a relatively higher risk of rhabdomyolysis, which is even increased with statin combination therapy (28,30). In the study of LY518674 (24), the incidence rates of serum creatinine levels greater than the ULN and ALT levels >1.5× ULN were over three times higher in the 25–100 μg/day LY518674 and 200 mg/day fenofibrate groups than in the placebo group, whereas both of them in the pemafibrate groups were comparable or lower than those in the placebo group from post hoc analyses in the current study using similar cutoff levels (Supplementary Table 2). The differences in the safety profiles supported a good risk/benefit balance of pemafibrate.

Table 2—Summary of AEs and ADRs

	Placebo (*n* = 57)	Pemafibrate 0.2 mg/day (*n* = 54)	Pemafibrate 0.4 mg/day (*n* = 55)
Total AEs	41 (71.9)	36 (66.7)	33 (60.0)
vs.Placebo		*P* = 0.681	*P* = 0.232
Serious AEs	3 (5.3)	3 (5.6)	2 (3.6)
AEs leading to discontinuation	0	0	4 (7.3)
Total ADRs	7 (12.3)	6 (11.1)	9 (16.4)
vs. Placebo		*P* = 1.000	*P* = 0.597
Serious ADRs	0	0	0
ADRs leading to discontinuation	0	0	2 (3.6)
Laboratory tests			
AST >3× ULN	0	0	0
AST >5× ULN	0	0	0
ALT >3× ULN	1 (1.8)	0	0
ALT >5× ULN	0	0	0
GGT >3× ULN	4 (7.0)	2 (3.7)	0
GGT >5× ULN	4 (7.0)	0	0
CK >4× ULN	0	1 (1.9)	0
CK >5× ULN	0	1 (1.9)	0
CK >10× ULN	0	0	0
Serum creatinine >1.5 mg/dL	2 (3.5)	1 (1.9)	2 (3.6)
Serum creatinine >2.0 mg/dL	0	1 (1.9)	1 (1.8)

Data are presented as the number of patients (%). ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase. *P* values were estimated by Fisher exact test.

In terms of glycemic parameters, the post hoc repeated-measures ANCOVA showed that pemafibrate decreased the fasting glucose, insulin, and HOMA-IR levels, although the prespecified analyses did not show a clear trend. The results of previous studies on the effects of PPARα agonists other than pemafibrate on IR were inconsistent (31–35). Pemafibrate has been suggested to improve IR in the hyperinsulinemic-euglycemic–clamp study (36) and pooled analyses of previous studies (37). Moreover, markedly elevated FGF21 levels and reduced ApoCIII levels with pemafibrate treatment may positively impact the reduction of IR because an FGF21 analog ameliorated IR and glucose metabolism (38) and an ApoCIII antisense improved insulin sensitivity (39). The changes in fasting glycemic parameters were inconsistent with those in HbA_{1c} and glycoalbumin levels, which reflects the mean plasma glucose levels over the past 1–2 months and 2 weeks, respectively. Therefore, further investigation is needed to confirm the effects of pemafibrate on glucose metabolism.

The current study has the following limitations. First, it was not designed to investigate the effects of pemafibrate on vascular events. The effects of PPARα agonists on cardiovascular events in patients with type 2 diabetes were examined in the FIELD and ACCORD lipid studies (9,40). These studies demonstrated that cardiovascular events were significantly suppressed in the subgroup of patients with high TG and low HDL-C levels and suggested that diabetic microangiopathy might be prevented. Further large-scale studies on the effect of pemafibrate on diabetic complications and cardiovascular outcomes are necessary. Second, all patients were Japanese, many patients had relatively mild type 2 diabetes, many antidiabetic agents were prohibited, and changes in the class and dosage regimen of antidiabetic agents were restricted even for nonprohibited drugs. Therefore, further investigation is needed to clarify whether the findings of the current study can be generalized to other races or patients with more severe diabetes.

Conclusion

Pemafibrate, a novel selective PPARα modulator, demonstrated excellent efficacy in the amelioration of lipid abnormalities and was well tolerated in patients with type 2 diabetes. The good risk/benefit balance of pemafibrate was confirmed in this population, which was similar to that in previous studies in patients with hypertriglyceridemia with or without diabetes, over a long period of 24 weeks. These findings provide significant information on the management of lipid abnormalities in patients with type 2 diabetes comorbid with hypertriglyceridemia.

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Appendix

The study sites and their principal investigators are as follows: NTT-East Sapporo Hospital (So Nagai), Iwate Medical University Hospital (Noriko Takebe), Juntendo University Hospital (Fuki Ikeda), Aichi Medical University Hospital (Jiro Nakamura), Shiga University of Medical Science Hospital (Hiroshi Maegawa), Yamaguchi University Hospital (Yasuharu Ohta), Kyushu University Hospital (Toyoshi Inoguchi), Kumamoto University Hospital (Takeshi Matsumura), Chiba University Hospital (Minoru Takemoto), Sugiura Clinic (Toshiyuki Sugiura), Musashi Fujisawa Central Clinic (Seiki Wada), Nakayama Clinic (Mikihiro Nakayama), Goshi Hospital (Takeo Naito), Tao Internal Medicine Clinic (Tsuyoshi Tao), BOOCS Clinic Fukuoka (Kazuyuki Saito), Diabetes Center, Shin-Koga Hospital (Shoichi Akazawa and Eiji Kawasaki), Kurihara Diabetic Care Clinic (Yoshio Kurihara), Okuguchi Clinic of Internal Medicine (Fuminobu Okuguchi), Naka Kinen Clinic (Takeshi Osonoi), Tomonaga Clinic (Osamu Tomonaga), Kurashiki Central Hospital (Takashi Matsuoka), Kanauchi Medical Clinic (Rie Wada), Osaka Gyoumeikan Hospital (Shinya Makino), Osaka Ekisaikai Hospital (Haruyuki Taguchi), Tohoku Medical and Pharmaceutical University Wakabayashi Hospital, formerly NTT-East Tohoku Hospital (Kazumi Yamato), Tokyo-Eki Center-building Clinic (Arihiro Kiyosue), Sakakibara Sapia Tower Clinic (Makiko Abe), Chikamori Hospital (Yoshitaka Kumon), Ayame Medical Clinic (Hideo Ayame), Ehime Rosai Hospital (Kazuaki Nakai), Saiseikai Matsuyama Hospital (Hiroaki Miyaoka), Matsuyama Red Cross Hospital (Shiori Kondo), Matsuba Clinic (Ikuro Matsuba), and Manda Memorial Hospital (Shinji Taneda).

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