Efficacy and Safety of K-877 (Pemafibrate), a Selective PPARα Modulator, in European Patients on Statin Therapy

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OBJECTIVE

High plasma triglyceride (TG) is an independent risk factor for cardiovascular disease. Fibrates lower TG levels through peroxisome proliferator–activated receptor α (PPARα) agonism. Currently available fibrates, however, have relatively low selectivity for PPARα. The aim of this trial was to assess the safety, tolerability, and efficacy of K-877 (pemafibrate), a selective PPARα modulator, in statin-treated European patients with hypertriglyceridemia.

RESEARCH DESIGN AND METHODS

A total of 408 statin-treated adults were recruited from 68 European sites for this phase 2, randomized, double-blind, placebo-controlled trial. They had fasting TG between 175 and 500 mg/dL and HDL-cholesterol (HDL-C) ≤50 mg/dL for men and ≤55 mg/dL for women. Participants were randomly assigned to receive placebo or one of six pemafibrate regimens: 0.05 mg twice a day, 0.1 mg twice a day, 0.2 mg twice a day, 0.1 mg once daily, 0.2 mg once daily, or 0.4 mg once daily. The primary end points were TG and non–HDL-C level lowering at week 12.

RESULTS

Pemafibrate reduced TG at all doses (adjusted *P* value <0.001), with the greatest placebo-corrected reduction from baseline to week 12 observed in the 0.2-mg twice a day treatment group (54.4%). Reductions in non–HDL-C did not reach statistical significance. Reductions in TG were associated with improvements in other markers for TG-rich lipoprotein metabolism, including reductions in apoB48, apoCIII, and remnant cholesterol and an increase in HDL-C levels. Pemafibrate increased LDL-cholesterol levels, whereas apoB100 was unchanged. Pemafibrate was safe and well-tolerated, with only minor increases in serum creatinine and homocysteine concentrations.

CONCLUSIONS

Pemafibrate is effective, safe, and well-tolerated for the reduction of TG in European populations with hypertriglyceridemia despite statin treatment.

Dyslipidemia is a major risk factor for cardiovascular disease (CVD), the leading cause of morbidity and mortality worldwide (1). Current treatment guidelines recommend lifestyle modification with or without pharmacotherapy (usually a statin) to lower plasma LDL-cholesterol (LDL-C) levels to specific targets (2,3). However,

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considerable residual risk remains even in patients who reach the recommended LDL-C levels (4,5). Hypertriglyceridemia, defined as triglyceride (TG) levels ≥150 mg/dL (1.7 mmol/L), is consistently and independently associated with increased CVD risk, especially when combined with low levels of HDL-cholesterol (HDL-C) (<40 mg/dL [1.0 mmol/L]) (6–8). TG-lowering therefore has potential value for the prevention of CVD.

Peroxisome proliferator–activated receptors (PPARs) are a group of ligand-activated nuclear hormone receptors comprising PPARα, PPARγ, and PPARβ/δ (9,10). PPARα agonists regulate TG concentrations by modifying the expression of genes that play important roles in TG metabolism. Depending on the specific ligand, the modulation (up- or downregulation) of gene expression induces changes in the levels of proteins that affect the regulation of HDL synthesis/metabolism, VLDL turnover, glucose homeostasis, endothelial inflammation, and thrombogenesis. Since these pathways may each contribute to cardiovascular risk, PPARα has been considered a potential therapeutic target for the reduction of CVD. This is especially true in patients with atherogenic dyslipidemia who have high TG concentrations combined with low HDL-C levels.

However, clinical studies with first-generation PPARα agonists (fibrates) have produced mixed results, with significant benefit observed in two studies with gemfibrozil (11,12), but negative results seen with bezafibrate (13) and fenofibrate (14,15). Furthermore, fibrates are contraindicated (even at low doses) in patients with severe renal and hepatic impairment, and their efficacy is limited by side effects, including elevations in serum creatinine (14,15) and homocysteine (15), both of which have been associated with risk for CVD.

K-877 (pemafibrate) is a novel, second-generation PPARα agonist approved for the treatment of dyslipidemia in Japan (10,16,17). Cell-based studies show that pemafibrate has several thousand-fold greater activity than first-generation PPARα agonists (Supplementary Table 1) and >5,000-fold greater specificity for PPARα versus PPARγ or δ (half-maximal effective concentrations for K-877 4.3 and 9.0 μmol/L, respectively) (10,18). The gene expression profile of pemafibrate differs from that of first-generation fibrates (18), and it is therefore considered to represent a new class of drugs, the selective PPARα modulators. Comparative data for pemafibrate versus older fibrates are presented in Supplementary Table 1. Studies conducted with pemafibrate support the efficacy and safety of this new PPARα agonist compared with placebo or fenofibrate (19–25). However, all of the efficacy studies were conducted in Japanese populations. The aim of this study was to evaluate the safety, tolerability, and efficacy of pemafibrate in European statin-treated patients with high TG concentrations.

RESEARCH DESIGN AND METHODS

Study Design and Participants

This randomized, placebo-controlled, double-blind, parallel-group phase 2 trial (Clinical trial reg. no. EudraCT 2013-001517-32, https://eudract.ema.europa.eu/) included statin-treated men and women, aged ≥18 years, with or without established CVD and/or type 2 diabetes mellitus (T2DM) from 68 sites across 9 European countries (Czech Republic, Denmark, Hungary, the Netherlands, Germany, Poland, Sweden, the U.K., and Russia). A list of investigators for each study site can be found in Supplementary Appendix A2. Patients were eligible for inclusion if their fasting TG levels were between 175 mg/dL (1.97 mmol/L) and 500 mg/dL (5.65 mmol/L) at screening, HDL-C concentrations ≤50 mg/dL (1.30 mmol/L) for men and ≤55 mg/dL (1.43 mmol/L) for women, and LDL-C concentrations no more than 10 mg/dL (0.259 mmol/L) above their recommended National Cholesterol Education Program Adult Treatment Panel III target (26). All patients were required to be on a stable dose of a statin (except pravastatin, lovastatin, or fluvastatin) for at least 12 weeks prior to screening, and patients were required to continue with the same statin at an unchanged dose/dosing regimen throughout the study. Full inclusion and exclusion criteria are listed in Supplementary Table 2.

Patients entered a screening period of up to 4 weeks following screening visit 1. Patients who failed to meet the eligibility criteria due only to their TG level were reassessed at screening visit 2. Patients were randomly assigned to placebo or one of the following pemafibrate dosing regimens: 0.05 mg twice a day, 0.1 mg twice a day, 0.2 mg twice a day, 0.1 mg once daily, 0.2 mg once daily, or 0.4 mg once daily (Supplementary Fig. 1). Stratification was based on country. Randomized patients received two tablets of study drug (0.05, 0.1, or 0.2 mg tablets) or matching placebo in the morning and two in the evening for 12 weeks. Blood sampling for clinical laboratory tests (chemistry, hematology, and endocrinology) was performed following an overnight fast of at least 10 h at screening visit 1 (week −4) and at every treatment visit (weeks 0, 2, 4, 8, and 12).

The trial was sponsored by Kowa Research Europe, Ltd. The study protocol was approved by the Independent Central/National Ethics Committee and local ethics committees if applicable, and Clinical Trial Authorization was granted by competent authorities for each center. The study was conducted according to the Declaration of Helsinki and the principles of Good Clinical Practice. Written informed consent was obtained from all participants.

Study End Points

The coprimary end point was the mean percentage change compared with placebo from baseline to week 12 in fasting TG and non–HDL-C levels. Secondary end points included changes from baseline to week 12 in fasting levels of total cholesterol, LDL-C, remnant cholesterol (cholesterol associated with VLDL and chylomicron remnants), HDL-C, apoAI, apoAII, total apoB, apoB100, apoB48, apoCII, apoCIII, and LDL and HDL subclasses. Exploratory measurements of fasting glucose and HOMA of insulin resistance were performed for the group treated with pemafibrate, 0.2 mg twice a day. Treatment-emergent adverse events (TEAEs), use of concomitant medications, physical examinations, clinical laboratory tests, vital signs, and electrocardiogram parameters were recorded to assess the safety of pemafibrate. Laboratory testing was performed at central laboratories coordinated by Medpace Reference Laboratories (Leuven, Belgium), and ion mobility analysis was performed at UCSF Benioff Children's Hospital (Oakland, CA) as described in Supplementary Appendix A3.

Statistical Analyses

The primary efficacy analyses of the coprimary end points, TG and non–HDL-C,

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were performed in a modified intent-to-treat population using a mixed model for repeated measures, including fixed categorical effects of treatment, week, treatment-by-week interaction, and country and a continuous covariate for baseline non–HDL-C or TG level. The superiority of each pemafibrate treatment group versus placebo was controlled by Dunnett test as a multiple-comparison method. Further primary end point analyses are described in Supplementary Appendix A4. Taking into account an expected withdrawal rate of up to 20%, we calculated that a total of 50 patients would need to be randomly assigned in every treatment group to detect a 42% reduction in TG and a 12% reduction in non–HDL-C with 90% power in patients receiving pemafibrate compared with placebo. The anticipated reductions in TG and non–HDL-C were based on results from a previous study (25). Secondary efficacy end points in the modified intent-to-treat population were analyzed using fixed-effects ANCOVA on the percentage change from baseline to week 12 using the last observation carried forward (LOCF) method for missing data. Pairwise comparisons between each treatment group versus placebo, based on least-squares mean contrasts with a two-tailed 95% CI, were determined, without Dunnett test. For the primary safety end points (serum creatinine and log homocysteine), the percentage change from baseline to week 12 was presented along with other descriptive statistics, and further analyses compared with placebo were performed using the same ANCOVA week 12 LOCF model. A summary overview of TEAEs was provided. Descriptive statistics for each laboratory parameter, vital signs, body weight, and 12-lead electrocardiogram measurements were presented. Abnormalities of liver function and muscle enzymes were reported as numbers and percentages of patients in each treatment group.

RESULTS

Baseline Characteristics

Between October 2013 and June 2014, 903 patients were screened, 408 of whom were eligible for the study and were randomly assigned to treatment (Supplementary Fig. 2). Of these, 407 (99.8%) received at least one dose of study drug, 375 (91.9%) completed the study, and 33 (8.1%) discontinued the study, including 10 (2.5%) patients who withdrew due to an adverse event, including one patient who withdrew before receiving any medication. Table 1 shows the baseline characteristics across all treatment groups. Almost all patients (99%) were Caucasian, mean age was 59 years, 69.1% of patients were male, mean BMI was 31.1, 91.7% had central obesity, and 89.5% had metabolic syndrome (both defined by International Diabetes Federation criteria [27]), and 39.0% had T2DM. Overall, 31.9% of the patients had suffered a CVD event prior to the study. Mean serum creatinine and homocysteine levels at baseline were 0.91 mg/dL and 14.33 μmol/L, respectively. The majority of patients (57.3%) had an LDL-C goal <100 mg/dL. The most commonly used statin was atorvastatin, followed by rosuvastatin and simvastatin. In addition to statins, 380 patients (93.4%) were using concomitant medication, including β-blockers (49.6%), platelet aggregation inhibitors (44.2%), and ACE inhibitors (33.4%). Mean lipid and lipoprotein concentrations at baseline are shown in Table 1. Mean baseline TG and non–HDL-C levels were 269.8 mg/dL and 137.6 mg/dL, respectively; mean HDL-C and LDL-C concentrations were 39.2 mg/dL and 88.4 mg/dL, respectively. The baseline data for TG and HDL-C levels were similar to those in the Bezafibrate Infarction Prevention (BIP), Fenofibrate Intervention and Event Lowering in Diabetes (FIELD), and Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid subgroups in whom fenofibrate treatment was associated with significant reductions in cardiovascular events (13,14,28). Mean compliance with the study drug (calculated from the number of returned tablets) was 97.9%.

Efficacy Results

Coprimary End Points

There were no changes in body weight or in waist circumference in any treatment group during the study. Pemafibrate resulted in dose-dependent, placebo-corrected reductions in fasting ser um TG concentrations of 36.1%, 45.8%, and 54.4%, with doses 0.05 mg, 0.1 mg, and 0.2 mg twice a day and 34.0%, 37.7%, and 42.7% with doses 0.1 mg, 0.2 mg, and 0.4 mg once daily (Table 2). The reductions were highly statistically significant for all treatment groups ($P < 0.001$ adjusted for multiplicity), with no significant differences between sexes (data not shown). The robustness of results was confirmed by ANCOVA repeated-measures analyses at weeks 4, 8, and 12 and by ANCOVA analysis at week 12 with LOCF ($P < 0.001$ for all treatment groups) (data not shown).

When administered twice daily, pemafibrate resulted in dose-dependent, placebo-adjusted reductions in fasting non–HDL-C concentrations of 6.8%, 7.4%, and 8.9% with doses 0.05 mg, 0.1 mg, and 0.2 mg twice a day (Table 2). Once-daily pemafibrate resulted in placebo-adjusted reductions in fasting non–HDL-C levels of 5.2% at 0.1 mg, 9.1% at 0.2 mg, and 7.8% at 0.4 mg. None of these changes were statistically significant after adjustment for multiplicity. Significant treatment differences relative to placebo for the 0.2 mg twice a day and 0.2 mg once daily treatment were demonstrated by the ANCOVA repeated-measures analyses at weeks 4, 8, and 12 and by the ANCOVA analysis at week 12 with LOCF.

An exploratory analysis was performed on the subgroup of participants who had T2DM; there was no interaction between treatment group and the presence of T2DM. Demographic characteristics and baseline plasma lipid levels in the subgroup with T2DM were similar to those of the total group, as were effects of pemafibrate on plasma TG and non–HDL-C (Supplementary Tables 3 and 4).

Secondary End Points

The placebo-adjusted changes from baseline to week 12 showed significant reductions, unadjusted for multiplicity, in all pemafibrate groups for remnant cholesterol, apoB48, and apoCIII concentrations. ApoCII concentrations significantly decreased in patients randomly assigned to pemafibrate 0.1 mg twice a day, 0.2 mg twice a day, and 0.2 mg once daily. Concentrations of apoAII significantly increased with all doses of pemafibrate, and there were significant increases in HDL-C, ranging from 7.4 to 12.9%, at all doses except 0.1 mg once daily. Significant increases in LDL-C, ranging from 9.2 to 20.5%, were observed at all doses except 0.05 mg twice a day. The placebo-adjusted change from baseline to week 12 was not significant in any pemafibrate treatment

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Table 1—Patient characteristics and lipid/lipoprotein levels at baseline (randomized set)

		Pemafibrate twice a day			Pemafibrate once daily			
	Placebo	0.05 mg	0.1 mg	0.2 mg	0.1 mg	0.2 mg	0.4 mg	Total
Number of patients	60	58	58	57	58	58	59	408
Age (years), mean (SD)	61 (10.3)	59 (9.8)	58 (12.3)	61 (8.9)	57 (9.7)	59 (11.7)	59 (9.7)	59 (10.4)
Female, *n* (%)	17 (28.3)	18 (31.0)	18 (31.0)	17 (29.8)	24 (41.4)	18 (31.0)	14 (23.7)	126 (30.9)
Race, *n* (%)								
Asian	0 (0.0)	0 (0.0)	1 (1.7)	1 (1.8)	0 (0.0)	1 (1.7)	0 (0.0)	3 (0.7)
Caucasian	59 (98.3)	58 (100.0)	57 (98.3)	56 (98.2)	58 (100.0)	57 (98.3)	59 (100.0)	404 (99.0)
CHD, *n* (%)	26 (43.3)	13 (22.0)	16 (27.6)	21 (36.8)	15 (25.9)	18 (31.0)	21 (35.6)	130 (31.9)
LDL-C treatment goal (mg/dL), *n* (%)								
<70	18 (30.0)	9 (15.3)	12 (20.7)	16 (28.1)	9 (15.5)	11 (19.0)	12 (20.3)	87 (21.3)
<100	42 (70.0)	30 (51.7)	33 (56.9)	36 (63.2)	29 (50.0)	33 (56.9)	31 (52.5)	234 (57.4)
<130	56 (93.3)	50 (86.2)	49 (84.5)	56 (98.3)	46 (79.3)	47 (81.0)	53 (89.8)	357 (87.5)
<160	60 (100.0)	58 (100.0)	58 (100.0)	57 (100.0)	58 (100.0)	58 (100.0)	59 (100.0)	408 (100.0)
BMI, kg/m^2	30.7	31.8	30.2	30.5	31.7	31.1	31.7	31.1
Central obesity, *n* (%)								
Yes	53 (88.3)	54 (93.1)	51 (87.9)	48 (84.2)	56 (96.6)	55 (94.8)	57 (96.6)	374 (91.7)
No	6 (10.0)	3 (5.2)	5 (8.6)	8 (14.0)	1 (1.7)	3 (5.2)	2 (3.4)	28 (6.9)
T2DM, *n* (%)	26 (43.3)	26 (44.8)	23 (39.7)	21 (36.8)	22 (37.9)	24 (41.4)	17 (28.8)	159 (39.0)
Metabolic syndrome								
Yes	52 (86.7)	54 (93.1)	51 (87.9)	47 (82.5)	55 (94.8)	52 (89.7)	54 (91.5)	365 (89.5)
No	7 (11.7)	3 (5.2)	5 (8.6)	9 (15.8)	2 (3.4)	6 (10.3)	5 (8.5)	37 (9.1)
Number of patients	58	55	53	55	56	57	58	392
Serum creatinine, mean (SD) mg/dL	0.89 (0.18)	0.90 (0.16)	0.94 (0.29)	0.90 (0.17)	0.88 (0.22)	0.90 (0.15)	0.94 (0.16)	0.91 (0.19)
Homocysteine, mean (SD) μmol/L	13.85 (3.33)	14.85 (5.02)	13.94 (3.90)	14.98 (6.00)	14.45 (5.16)	14.68 (6.44)	13.59 (3.96)	14.33 (4.03)
Number of patients	60	57	58	57	58	58	59	407
Statin, *n* (%)								
Atorvastatin	27 (45.0)	32 (56.1)	22 (37.9)	30 (52.6)	30 (51.7)	26 (44.8)	30 (50.8)	197 (48.4)
Rosuvastatin	22 (36.7)	11 (19.3)	24 (41.4)	17 (29.8)	16 (27.6)	20 (34.5)	21 (35.6)	131 (32.2)
Simvastatin	11 (18.3)	14 (24.6)	12 (20.7)	10 (17.5)	12 (20.7)	12 (20.7)	8 (13.6)	79 (19.4)
Patients taking concomitant medications, *n* (%)	56 (93.3)	56 (98.2)	50 (86.2)	55 (96.5)	55 (94.8)	52 (89.7)	56 (94.9)	380 (93.4)
Number of patients	60	58	58	57	58	58	59	408
Lipid parameters, mean (SD) mg/dL								
TG	254.4 (71.64)	272.7 (116.37)	286.9 (96.33)	267.9 (78.91)	251.5 (82.21)	255.2 (82.58)	297.1 (109.22)	269.8 (93.01)
Non–HDL-C	136.1 (40.19)	139.0 (33.58)	143.1 (34.65)	131.6 (32.04)	136.7 (38.81)	138.3 (37.97)	138.2 (35.00)	137.6 (36.05)
Remnant cholesterol	46.13 (21.42)	47.31 (26.99)	52.19 (25.62)	49.26 (22.89)	45.52 (21.28)	43.83 (15.75)	55.53 (27.49)	48.54 (23.52)

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Table 1—Continued

	Placebo	Pemafibrate twice a day			Pemafibrate once daily			Total
		0.05 mg	0.1 mg	0.2 mg	0.1 mg	0.2 mg	0.4 mg	
Number of patients	60	57	58	55	58	57	59	404
apoB48	1.267 (0.6780)	1.541 (1.1190)	1.670 (1.2254)	1.636 (1.2334)	1.475 (1.0903)	1.458 (0.9308)	2.034 (1.4813)	1.583 (1.1455)
apoCIII	14.89 (3.742)	14.37 (3.986)	14.66 (3.686)	14.72 (3.904)	13.41 (3.282)	14.42 (3.689)	15.78 (4.519)	14.61 (3.874)
apoCII	8.448 (1.9560)	8.026 (2.1880)	8.298 (2.1739)	8.548 (2.0943)	7.775 (2.4455)	8.195 (2.0350)	8.622 (1.8508)	8.274 (2.1151)
apoAII	29.9 (4.82)	30.8 (4.07)	30.4 (4.29)	29.9 (4.66)	30.6 (4.74)	31.2 (4.38)	30.3 (4.80)	30.4 (4.53)
Number of patients	60	58	58	57	58	58	59	408
HDL-C	39.0 (8.81)	40.0 (7.39)	37.4 (7.37)	39.2 (7.81)	40.0 (8.07)	40.8 (7.35)	38.3 (6.81)	39.2 (7.70)
LDL-C	89.3 (32.61)	91.2 (25.16)	90.3 (30.14)	82.0 (29.39)	91.3 (30.79)	92.2 (33.54)	82.7 (29.78)	88.4 (30.35)
Total cholesterol	175.1 (41.12)	179.0 (32.58)	180.5 (34.56)	170.7 (33.56)	176.7 (41.45)	179.1 (39.97)	176.5 (36.67)	176.8 (37.16)
Number of patients	60	57	58	55	58	57	59	404
apoB100	88.72 (24.93)	84.92 (20.92)	88.01 (22.13)	82.56 (19.62)	86.59 (22.35	86.57 (23.07)	84.57 (22.25)	86.03 (22.19)
apoB	90.0 (24.90)	86.5 (20.99)	89.7 (22.08)	84.3 (19.73)	88.1 (22.36)	88.1 (22.97)	86.6 (22.30)	87.7 (22.18)
apoAI	134.0 (23.32)	134.0 (19.26)	133.3 (20.44)	134.3 (23.19)	136.6 (20.78)	140.7 (18.98)	132.8 (20.10)	135.1 (20.93)

Baseline was defined as the day 1 value or, if the day 1 assessment was missing or from a nonfasted sample, the last value from screening. CHD, coronary heart disease.

group for total cholesterol, apoB100, total apoB, or apoA1 (Table 3).

Ion mobility analysis demonstrated reductions in small LDL subclasses and increases in larger LDL subclasses compared with placebo. The diameter of the major LDL particle subclass significantly increased in every treatment group compared with placebo, with dose-dependent increases ranging from 1.47 to 3.39 Angstroms. There were reductions in all sizes of VLDL particles, with the greatest changes in large particles. HDL 2b particles decreased modestly, with no changes in HDL 2a or HDL 3 (Supplementary Table 5).

Previous small studies over several decades have shown very modest or no effects of fibrates on measures of insulin resistance. Exploratory analyses in the current study indicated that fasting glucose increased 5.2% on placebo, while pemafibrate treatment at 0.2 mg twice a day was associated with a 2.6% reduction; HOMA of insulin resistance changes were 0.33% on placebo and −1.74% on pemafibrate 0.2 mg twice a day.

Safety Results

Pemafibrate was generally well-tolerated. The percentage of patients withdrawing from the study due to TEAEs was 2.2% and was similar across treatment groups (Supplementary Table 6). Rates of TEAEs and treatment-emergent serious adverse events were similar in patients randomly assigned to pemafibrate and placebo. Overall, 45 patients (11.1%) had a TEAE possibly related to the study drug, and most cases were mild in severity. Nine patients (2.2%) had treatment-emergent serious adverse events, one of which (drug-induced liver injury in a patient taking pemafibrate 0.1 mg once daily) was considered by the investigator to have a probable relationship with the study drug. The patient was also taking simvastatin and two drugs (co-dydramol and paracetamol), which together meant this individual was receiving 4 g/day of acetaminophen daily. γ-Glutamyl transferase and ALT both increased, and the latter continued to rise after discontinuation of the study drug. Liver function tests improved only after simvastatin was discontinued and the dose of co-dydramol halved.

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Table 2—Percent change and placebo-adjusted percent change (pemafibrate vs. placebo) in coprimary end points (TG and non–HDL-C levels) from baseline to week 12

	Change from baseline to week 12	Placebo (N = 56)	Pemafibrate twice a day			Pemafibrate once daily		
			0.05 mg (N = 56)	0.1 mg (N = 54)	0.2 mg (N = 54)	0.1 mg (N = 57)	0.2 mg (N = 58)	0.4 mg (N = 56)
TG	Percent	+15.0 (4.85); 95% CI +5.4, +24.5	−21.2 (4.96); 95% CI −30.9, −11.4	−30.8 (5.08); 95% CI −40.8, −20.8	−39.5 (5.11); 95% CI −49.5, −29.4	−19.1 (4.98); 95% CI −28.9, −9.3	−22.7 (4.88); 95% CI −32.3, −13.1	−27.7 (4.99); 95% CI −37.5, −17.9
	Placebo-adjusted		**−36.1 (6.72); P < 0.001*†**	**−45.8 (6.81); P < 0.001*†**	**−54.4 (6.83); P < 0.001*†**	**−34.0 (6.76); P < 0.001*†**	**−37.7 (6.72); P < 0.001*†**	**−42.7 (6.75); P < 0.001*†**
Non-HDL-C	Percent	+2.1 (2.90); 95% CI −3.60, +0.78	−4.8 (2.98); 95% CI −10.6, +1.1	−5.4 (3.04); 95% CI −11.4, +0.6	−6.8 (3.05); 95% CI −12.8, −0.8	−3.2 (2.96); 95% CI −9.0, +2.7	−7.1 (2.88); 95% CI −12.7, −1.4	−5.7 (2.99); 95% CI −11.6, +0.1
	Placebo-adjusted		−6.8 (3.87); P = 0.078*/P = 0.307†	−7.4 (3.91); P = 0.058*/P = 0.237†	−8.9 (3.91); P = 0.024*/P = 0.111†	−5.2 (3.88); P = 0.179*/0.582†	−9.1 (3.85); P = 0.018*/P = 0.086†	−7.8 (3.87); P = 0.044*/P = 0.187†

Data are least-squares means (SE) from MMRM analyses (MITT group), including fixed categorical effects of treatment, week, treatment-by-week interaction, and country, and a continuous covariate for baseline non-HDL-C or TG level. P values are shown for the superiority of each pemafibrate treatment group vs. placebo (*unadjusted; †adjusted for multiplicity, Dunnett test). Significant adjusted treatment differences ($P < 0.05$) are highlighted in bold. MITT, modified intent-to-treat; MMRM, mixed-model repeated-measures.

Bilirubin remained normal throughout, and no patient had a liver injury meeting Hy's Law criteria. Two patients (one taking placebo and one taking 0.2 mg once daily) had transient, asymptomatic increases in creatine kinase to >10 times the upper limit of normal, which resolved and allowed continuation of therapy. Changes in liver function tests and muscle enzymes are summarized in Supplementary Table 6.

Serum creatinine changes from baseline to week 12 were only significantly increased versus placebo in the 0.2 mg twice a day group (Table 4). Overall, six (1.5%) patients had creatinine increases above the upper limit of normal (1.3 mg/dL women, 1.5 mg/dL for men). After a 2-week washout from active drug, the mean rise in serum creatinine on 0.2 mg twice a day approximately halved, while the increases in serum creatinine at the lower twice a day doses remained about the same. Log-transformed mean homocysteine levels increased from baseline to week 12 in all treatment groups, with significant differences versus placebo in the 0.2-mg twice a day, 0.2-mg once daily, and 0.4-mg once daily groups.

CONCLUSIONS

In this 12-week, phase 2 trial, administration of pemafibrate, a selective PPARα modulator, was associated with significant dose-dependent reductions in plasma TG in European statin-treated patients with hypertriglyceridemia at baseline. Reductions emerged as early as week 2 and were sustained throughout the 12-week study. The effect on non–HDL-C was not significant in the primary analysis. Generally, the largest drug effects and most consistent dose responses were seen with twice-a-day rather than every-day dosing. The greatest placebo-corrected reductions from baseline to week 12 were observed in the 0.2-mg twice a day treatment group for TG (54.4%) and in the 0.2-mg twice a day and 0.2-mg once daily groups for non–HDL-C (8.9 and 9.1%, respectively). Overall, reductions were similar to those observed in earlier studies conducted in statin-treated patients in Japan, in which TG reductions ranged from 44.3 to 53.4% after 12 to 24 weeks of pemafibrate therapy (0.1–0.2 mg twice a day), and non–HDL-C reductions ranged from 8.0 to 13.1% (19,24,29).

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Table 3—Percent change and placebo-adjusted percent change (pemafibrate vs. placebo) in secondary end points (lipid and lipoprotein levels) from baseline to week 12

	Change from baseline to week 12	Placebo (*N* = 56)	Pemafibrate twice a day			Pemafibrate once daily		
			0.05 mg (*N* = 56)	0.1 mg (*N* = 54)	0.2 mg (*N* = 54)	0.1 mg (*N* = 57)	0.2 mg (*N* = 58)	0.4 mg (*N* = 56)
Remnant cholesterol	Percent	+22.25 (6.08); 95% CI +10.30, +34.21	−13.3 (6.16)	−26.6 (6.30)	−35.8 (6.29)	−17.6 (6.01)	−23.6 (5.87)	−23.2 (6.18)
	Placebo-adjusted		**−35.6 (7.89); *P* < 0.001**	**−48.8 (7.98); *P* < 0.001**	**−58.0 (7.97); *P* < 0.001**	**−39.9 (7.84); *P* < 0.001**	**−45.9 (7.82); *P* < 0.001**	**−45.5 (7.93); *P* < 0.001**
apoB48	Percent	+26.97 (9.97); 95% CI +7.38, +46.57	−13.8 (10.06)	−29.1 (10.28)	−36.4 (10.41)	−6.21 (9.81)	−20.2 (9.66)	−23.6 (10.16)
	Placebo-adjusted		**−40.8 (12.92); *P* = 0.002**	**−56.1 (13.07); *P* < 0.001**	**−63.4 (13.20); *P* < 0.001**	**−33.2 (12.83); *P* = 0.010**	**−47.2 (12.84); *P* < 0.001**	**−50.6 (13.11); *P* < 0.001**
apoCIII	Percent	+5.13 (3.85); 95% CI −2.44, +12.70	−10.3 (3.90)	−23.6 (3.98)	−30.8 (4.04)	−12.0 (3.82)	−19.2 (3.75)	−18.6 (3.92)
	Placebo-adjusted		**−15.5 (5.00); *P* = 0.002**	**−28.7 (5.05); *P* < 0.001**	**−36.0 (5.10); *P* < 0.001**	**−17.1 (4.99); *P* < 0.001**	**−24.3 (4.97); *P* < 0.001**	**−23.8 (5.01); *P* < 0.001**
apoCII	Percent	−0.07 (4.55); 95% CI −9.01, +8.87	−5.12 (4.62)	−18.2 (4.71)	−19.5 (4.77)	−2.04 (4.51)	−17.6 (4.43)	−11.5 (4.61)
	Placebo-adjusted		−5.05 (5.92); *P* = 0.394	**−18.1 (5.97); *P* = 0.003**	**−19.4 (6.02); *P* = 0.001**	−1.97 (5.89); *P* = 0.738	**−17.5 (5.88); *P* = 0.003**	−11.4 (5.91); *P* = 0.054
apoAII	Percent	+3.26 (2.52); 95% CI −1.69, +8.20	+17.24 (2.55)	+22.87 (2.60)	+34.64 (2.64)	+12.49 (2.49)	+19.41 (2.45)	+26.87 (2.55)
	Placebo-adjusted		**+13.98 (3.27); *P* < 0.001**	**+19.61 (3.30); *P* < 0.001**	**+31.38 (3.33); *P* < 0.001**	**+9.23 (3.25); *P* = 0.005**	**+16.15 (3.26); *P* < 0.001**	**+23.62 (3.27); *P* < 0.001**
HDL-C	Percent	−0.05 (2.69); 95% CI −5.34, 5.24	+7.59 (2.73)	+12.84 (2.80)	+10.89 (2.78)	+3.66 (2.66)	+10.32 (2.60)	+7.29 (2.73)
	Placebo-adjusted		**+7.65 (3.50); *P* = 0.029**	**+12.89 (3.53); *P* < 0.001**	**+10.95 (3.53); *P* = 0.002**	+3.71 (3.48); *P* = 0.286	**+10.37 (3.47); *P* = 0.003**	**+7.35 (3.50); *P* = 0.036**

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Table 3—Continued

	Change from baseline to week 12	Placebo (*N* = 56)	Pemafibrate twice a day			Pemafibrate once daily		
			0.05 mg (*N* = 56)	0.1 mg (*N* = 54)	0.2 mg (*N* = 54)	0.1 mg (*N* = 57)	0.2 mg (*N* = 58)	0.4 mg (*N* = 56)
LDL-C	Percent	−3.01 (3.56); 95% CI −10.0, +3.99	+5.00 (3.61)	+13.06 (3.68)	+17.49 (3.70)	+6.18 (3.52)	+8.21 (3.43)	+12.65 (3.62)
	Placebo-adjusted		+8.01 (4.62); *P* = 0.084	**+16.06 (4.67); *P* < 0.001**	**+20.49 (4.67); *P* < 0.001**	**+9.19 (4.59); *P* = 0.046**	**+11.21 (4.58); *P* = 0.015**	**+15.66 (4.63); *P* < 0.001**
Total cholesterol	Percent	+0.65 (2.10); 95% CI −3.47, +4.77	−1.42 (2.12)	−1.99 (2.17)	−3.13 (2.17)	−1.67 (2.07)	−2.12 (2.02)	−1.68 (2.12)
	Placebo-adjusted		−2.08 (2.72); *P* = 0.446	−2.64 (2.75); *P* = 0.338	−3.78 (2.75); *P* = 0.169	−2.32 (2.71); *P* = 0.392	−2.77 (2.70); *P* = 0.306	−2.33 (2.72); *P* = 0.393
apoB100	Percent	+0.21 (2.99); 95% CI −5.67, +6.08	+2.76 (3.03)	+0.42 (3.09)	−1.88 (3.14)	−1.30 (2.96)	+0.07 (2.91)	−0.14 (3.03)
	Placebo-adjusted		+2.56 (3.89); *P* = 0.511	+0.21 (3.92); *P* = 0.957	−2.09 (3.97); *P* = 0.599	−1.51 (3.86); *P* = 0.695	−0.14 (3.86); *P* = 0.971	−0.35 (3.89); *P* = 0.929
Total apoB	Percent	+0.48 (2.94); 95% CI −5.32, +6.27	+2.20 (2.99)	−0.23 (3.05)	−2.71 (3.10)	−1.62 (2.91)	−0.57 (2.87)	−0.89 (2.98)
	Placebo-adjusted		+1.72 (3.83); *P* = 0.653	−0.71 (3.86); *P* = 0.855	−3.19 (3.91); *P* = 0.415	−2.10 (3.80); *P* = 0.582	−1.05 (3.80); *P* = 0.783	−1.37 (3.83); *P* = 0.721
apoAI	Percent	+1.82 (1.90); 95% CI −1.92, +5.55	+6.25 (1.93)	+4.78 (1.97)	+2.23 (1.99)	+1.72 (1.88)	+3.71 (1.86)	+4.47 (1.93)
	Placebo-adjusted		+4.43 (2.47); *P* = 0.073	+2.97 (2.49); *P* = 0.234	+0.41 (2.51); *P* = 0.871	−0.10 (2.45); *P* = 0.969	+1.90 (2.46); *P* = 0.441	+2.65 (2.47); *P* = 0.284

Data are expressed as least-squares mean (SE) using the ANCOVA model (LOCF method for missing values) with fixed effects of treatment, country, and baseline (MITT Set). Pairwise comparisons between each treatment group and placebo are based on least-squares mean contrasts with a two-tailed 95% CI. Significant treatment differences ($P < 0.05$) are highlighted in bold. MITT, modified intent-to-treat.

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Table 4—Percent change and placebo-adjusted percent change from baseline to week 12 in primary safety outcomes

	Change from baseline to week 12	Placebo (*N* = 56)	Pemafibrate twice a day			Pemafibrate once daily		
			0.05 mg (*N* = 56)	0.1 mg (*N* = 54)	0.2 mg (*N* = 54)	0.1 mg (*N* = 57)	0.2 mg (*N* = 58)	0.4 mg (*N* = 56)
Serum creatinine	Percent change	+1.13 (1.41) (95% CI −1.64, +3.90)	+1.53 (1.43) (95% CI −1.28, +4.34)	+1.82 (1.46) (95% CI −1.05, +4.70)	+4.92 (1.46) (95% CI +2.06, +7.79)	+1.15 (1.40) (95% CI −1.59, +3.89)	+3.02 (1.36) (95% CI +0.35, +5.69)	+3.56 (1.43) (95% CI +0.75, +6.38)
	Placebo-adjusted		+0.41 (1.83); *P* = 0.824	+0.70 (1.85); *P* = 0.706	**+3.80 (1.85); *P* = 0.040**	+0.03 (1.82); *P* = 0.989	+1.89 (1.81); *P* = 0.297	+2.44 (1.84); *P* = 0.185
Log homocysteine	Percent change	+3.00 (1.14) (95% CI +0.76, +5.24)	+2.90 (1.16) (95% CI +0.63, +5.18)	+5.89 (1.18) (95% CI +3.57, +8.21)	+8.45 (1.18) (95% CI +6.13, +10.77)	+3.93 (1.13) (95% CI +1.71, +6.14)	+5.91 (1.10) (95% CI +3.76, +8.07)	+8.37 (1.15) (95% CI +6.10, +10.64)
	Placebo-adjusted		−0.10 (1.48); *P* = 0.948	+2.89 (1.49); *P* = 0.054	**+5.45 (1.49); *P* < 0.001**	+0.93 (1.47); *P* = 0.529	**+2.91 (1.47); *P* = 0.048**	**+5.37 (1.48); *P* < 0.001**

Data are least-squares mean (SE) (ANCOVA with LOCF [safety set]). Significant placebo-adjusted treatment differences ($P < 0.05$) are highlighted in bold.

Major limitations for first-generation PPARα agonists include typical dose-dependent increases in serum creatinine levels (which may be interpreted as indicating renal function decline) and increases in homocysteine levels (a biomarker for increased CVD risk) (14,15,28). These increases tend to occur within a few weeks of treatment initiation and remain stable over time. The addition of pemafibrate to statin therapy only led to a significant increase in serum concentrations of creatinine compared with placebo at a dose of 0.2 mg twice a day. Moreover, the greatest increase (3.8% vs. placebo) was considerably smaller than that reported for comparable doses of fenofibrate (5–22%) (30,31) and was similar to elevations observed in previous pemafibrate studies (19–21, 23–25), including one study conducted in people with reduced kidney function (29). Importantly, the effects of fenofibrate on estimated glomerular filtration rate in both the ACCORD and FIELD trials were fully reversible upon cessation of treatment, even after several years of active therapy (32,33).

Significant increases in homocysteine were observed in patients treated with pemafibrate 0.2 mg twice a day, 0.2 mg once daily, and 0.4 mg once daily; however, the observed increases (<20% vs. placebo) were considerably lower than those reported for fenofibrate (30–66%) (14,31). Since the effects of fibrates on creatinine and homocysteine are thought to be PPARα-mediated, the dissociation of the response curves for these effects from that of TG reduction differentiates pemafibrate from first-generation fibrates.

No clinically important changes in vital signs, physical examination findings, or electrocardiogram results were reported for pemafibrate, and no other safety concerns were identified. The incidence rates of TEAEs possibly reated to pemafibrate (11.1%) and TEAEs leading to study withdrawal (2.2%) were similar to those observed in previous pemafibrate studies after 12–24 weeks (20,21,23–25) and were lower than those reported for fenofibrate after 12 weeks (26.4% and 10.0%) (23). Our current results suggest that pemafibrate was safe and well-tolerated in statin-treated patients. However, the relatively short follow-up (12 weeks) precludes us from drawing conclusions about the long-term safety.

Elevated TG levels are thought to arise from the combination of increased production of TG-rich lipoproteins from the liver and the small intestine and reduced TG-rich lipoprotein fractional catabolism (34). The former is related to insulin resistance or T2DM and the latter to defective lipoprotein lipase-mediated lipolysis of TG-rich lipoprotein TG, possibly due to increased levels of apoCIII (a lipoprotein lipase inhibitor) (8). Reduced TG-rich lipoprotein fractional catabolism leads to the generation and accumulation of atherogenic remnant lipoproteins that have been shown to cross the epithelial barrier and enter the subintimal space, thereby contributing to the development/progression of atherosclerosis (35). Consistent with previous observations (20,21,23–25), pemafibrate-mediated changes in TG and non–HDL-C levels were accompanied by beneficial changes in other markers of TG-rich lipoprotein metabolism, including reductions in apoB48, apoCIII, and remnant cholesterol. Compared with placebo, apoCIII reductions from baseline to week 12 were greatest in patients treated with pemafibrate 0.2 mg twice a day (treatment difference −36.0%) and were considerably greater than those previously observed with fenofibrate (−1.44% to −21.20% vs. placebo after 2 to 12 weeks [36]). Although the effects of apoCIII-lowering on CVD risk have not been directly evaluated, Mendelian randomization studies have demonstrated that loss-of-function mutations in *APOC3* lead to low levels of TG and reduced CVD risk in humans (37).

Previous studies show that first-generation PPARα agonists, n-3 fatty acids, and pemafibrate increase levels of LDL-C, with the greatest increases in people with higher baseline TG and/or lower LDL-C (20,23–25,38,39). Consistent with those findings, levels of LDL-C increased up to 20.5% with pemafibrate in the current study compared with placebo after 12 weeks. However, similar to previous studies, no significant increases were observed in either total apoB or specifically measured apoB100 levels. This suggests that the increase in LDL-C levels was largely due to increased amounts of cholesterol per particle (particle size) rather than increased LDL particle

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number. This hypothesis is supported by results from our ion mobility analyses, which demonstrates pemafibrate-mediated increases in concentrations of large LDL particles, a significant increase in the diameter of the major LDL particle, and decreased concentrations of small dense LDL particles. The effect of the observed lowering of TG and small LDL-C concentrations and the increase in LDL particle size on CVD outcomes are currently being evaluated in the Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) trial (NCT03071692) (40). The trial has enrolled ~10,000 statin-treated patients with T2DM and diabetic dyslipidemia (hypertriglyceridemia and low levels of HDL-C), and the anticipated duration of this event-driven study is 5 years (mean 4 years). Results are expected in 2022.

The significant reductions in TG, remnant cholesterol, and apoB48 all suggest that treatment with pemafibrate may produce CVD benefits in the PROMINENT trial, in which all subjects are dyslipidemic (40). In contrast, the absence of a change in apoB100 in the current study suggests that a lack of benefit may be seen (41). The issue of how drugs with many effects, such as fibrates or fish oils, can reduce coronary artery disease/coronary heart disease is very important but unresolved (42,43); it is hoped that the results of the PROMINENT trial will shed light on this critical issue.

In previous studies, pemafibrate 0.1 to 0.2 mg twice a day increased HDL-C levels by 13% to 20% in statin-treated Japanese patients (24); similar increases (up to 13% at week 12) were demonstrated in this study, suggesting that the effect of pemafibrate on HDL-C levels is similar across ethnicities. Similar to results from fibrate trials (31,44,45), the increase in HDL-C levels was accompanied by significant increases in apoAII levels in all treatment groups, with no significant change in apoAI levels. Although the effects of pemafibrate on CVD were not investigated in this study, fenofibrate-mediated increases in HDL-C and apoAII were shown to correlate negatively with total CVD and CVD death in the 5-year FIELD study (46).

Several earlier studies demonstrated significant reductions of fibrinogen by fenofibrate, and the pooled analysis of the effects of pemafibrate by Yamashita et al. (47), confirmed significant reductions in fibrinogen in Japanese subjects. Fibrinogen levels in the current study were measured as a safety rather than outcome parameter, but did not change significantly.

Conclusion

This phase 2 trial shows that pemafibrate resulted in significant, dose-dependent reductions in plasma TG levels in European statin-treated patients with persistent hypertriglyceridemia and close to guideline-recommended LDL-C levels (2,3). Pemafibrate was generally well-tolerated, and elevations in serum creatinine and homocysteine levels were considerably lower than those observed in previous studies with fenofibrate. This observation is consistent with the selective modulation of gene effects at the PPARα receptor by pemafibrate. The results of this phase 2 dose-ranging study support the choice of 0.2-mg twice a day dosing in the ongoing PROMINENT study (40).

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The study sponsor had a role in the study design, data collection, data analysis, data interpretation, and writing of the report.

Author Contributions. H.N.G. designed the study, interpreted the data, and revised the manuscript. G.K.H. acquired data, interpreted the data, and revised the manuscript. N.J.H. and Y.S. oversaw acquisition of data and H.S. oversaw the analysis of data on behalf of the sponsor. P.B., R.C., A.K., R.A.L., and T.V.S. acquired data. All authors contributed to the development of the article and approved the final version prior to submission. N.J.H. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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