

Efficacy and Safety of Pemafibrate, a Novel Selective PPAR α Modulator in Chinese Patients with Dyslipidemia: A Double-Masked, Randomized, Placebo- and Active-Controlled Comparison Trial

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Aims: Pemafibrate substantially lowers serum triglyceride (TG) levels and increases high-density lipoprotein cholesterol (HDL-C) levels primarily in Japan, but it has not been evaluated in China. We aimed to confirm the efficacy and safety of pemafibrate in Chinese patients with hypertriglyceridemia and low HDL-C levels by comparing placebo and fenofibrate.

Methods: A multicenter, double-masked trial was conducted in China involving 344 patients with high TG and low HDL-C levels randomly assigned to one of four groups: pemafibrate 0.2 mg/d, pemafibrate 0.4 mg/d, fenofibrate 200 mg/d, or placebo for 12 weeks. The primary endpoint was the percentage change in fasting TG levels.

Results: The percentage change in TG levels from baseline was -34.1%, -44.0%, -30.5%, and 6.5% in the pemafibrate 0.2 mg/d, pemafibrate 0.4 mg/d, fenofibrate 200 mg/d, and placebo groups, respectively. Pemafibrate 0.4 mg/d significantly reduced TG levels compared with that in both placebo ($p < 0.0001$) and fenofibrate groups ($p = 0.0083$). Significant improvements in HDL-C, remnant cholesterol, and apolipoprotein A1 levels were also observed with both doses of pemafibrate than with the placebo. Pemafibrate showed significantly smaller changes in alanine aminotransferase, aspartate aminotransferase, and serum creatinine levels than those with fenofibrate.

Conclusions: In Chinese patients, pemafibrate exhibited superior efficacy in improving TG levels and enhanced hepatic and renal safety compared to fenofibrate. Thus, pemafibrate may represent a promising therapeutic option for dyslipidemia in Chinese patients.

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Key words: Pemafibrate, Selective PPAR α modulator, Clinical trial, Dyslipidemia, Triglyceride

Introduction

Hypertriglyceridemia is a risk factor for

atherosclerotic cardiovascular disease¹⁾. Mendelian randomization analyses have suggested that elevated triglyceride (TG) levels causally contribute to

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cardiovascular disease risk²). Despite statins being the first-line lipid-lowering therapy, a residual risk associated with hypertriglyceridemia remains³). Pemafibrate, a selective peroxisome proliferator-activated receptor alpha (PPAR α) modulator (SPPARM α), has demonstrated high potency and selectivity against PPAR α when compared to those with fibrates^{4, 5}). Clinical trials in Japan showed that pemafibrate considerably reduced TG levels by approximately 50%, while also exhibiting a superior safety profile, especially for the liver and kidney, in comparison to that with fenofibrate⁶⁻⁸). Pemafibrate also maintains stable blood concentration in patients with moderate to severe renal impairment⁹). However, clinical experience with pemafibrate outside Japan is limited.

Aim

This study aims to confirm the efficacy and safety of pemafibrate in Chinese patients with hypertriglyceridemia and low high-density lipoprotein cholesterol (HDL-C) levels by comparing the use of a placebo and fenofibrate.

Methods

Trial Design

This study was a phase 3, 12-week, multicenter, placebo- and active-controlled, randomized, double-masked trial (registered at chinadrugtrials.org.cn as CTR20211983). It was conducted at 31 sites in China in compliance with the latest version of the Declaration of Helsinki and Good Clinical Practice. [Supplementary Table 1](#) lists all 31 sites. Ethical approval was obtained from the Institutional Review Board of Beijing Anzhen Hospital. Patients received complete information regarding the trial protocol, and written informed consent was obtained prior to study enrollment.

The original protocol, dated November 2019, was amended in October 2020, before the first subject was enrolled. The statistical analysis plan, dated December 2019, was amended in March 2023 to include an analysis of the modified per-protocol set. As these changes were made before unmasking, they had no implications for the interpretation of the study data.

Patients

Men and postmenopausal women aged 18 years or older were eligible for inclusion if they had fasting serum TG levels of 2.26 mmol/L or higher and HDL-C levels less than 1.30 mmol/L (men) or 1.42

mmol/L (women) at screening despite following diet and lifestyle recommendations for at least 12 weeks prior to the treatment period. Patients receiving statins and ezetimibe were included in the trial if their dosages remained consistent during the study period. Major exclusion criteria were as follows: ongoing or planned use of any lipid-modifying medications other than statins and ezetimibe; type 1 diabetes or poorly controlled type 2 diabetes defined by HbA1c of 8.0% or higher; uncontrolled hypertension defined by seated systolic blood pressure of 160 mmHg or more and/or diastolic blood pressure of 100 mmHg or more; uncontrolled thyroid disorder; serum creatinine (sCr) of 1.5 mg/dL or more; severe hepatic disorder defined as cirrhosis of Child-Pugh class B or C, or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) more than two times the upper limit of normal (ULN); unexplained creatine kinase (CK) more than five times the ULN; myocardial infarction or stroke (including transient ischemic attack) within three months prior to the informed consent; class III or IV heart failure as per the New York Heart Association functional classification. The ULN were 37 U/L for AST, 41 U/L for ALT, 129 U/L for alkaline phosphatase (ALP), 61 U/L for gamma-glutamyltransferase (GT), 1.17 mg/dL for sCr, 308 U/L for CK in men, 31 U/L for AST, 33 U/L for ALT, 104 U/L for ALP, 36 U/L for gamma-GT, 0.95 mg/dL for sCr, and 192 U/L for CK in women. [Supplementary Table 2](#) describes the inclusion and exclusion criteria.

Study Procedures and Measurements

Eligible patients were randomly assigned to the placebo, pemafibrate 0.1 mg twice daily, pemafibrate 0.2 mg twice daily (0.2 and 0.4 mg/d), or fenofibrate (LIPANTHYL®) 200 mg once daily groups in a 1:2:2:2 ratio ([Supplementary Fig. 1](#)). Randomization was performed using a dynamic allocation method, that is, minimization, with site and current statin therapies used as stratifiers. The study medication was masked using pemafibrate 0.1 mg tablet or matching placebo, or LIPANTHYL® 200 mg capsule marketed in China or matching placebo. To ensure study masking, tablets and capsules were indistinguishable. The patients took two tablets and one capsule in the morning and two tablets in the evening orally from week 0 to 12. Patients took the tablets orally in either a fed or fasted state (before or after meals) and the capsule during a meal. However, at all sites, patients were instructed to try and remain consistent with the fed/fasted state for the tablets and the timing of dosing for all doses throughout the study. Physiological, fasting blood, and urine tests were performed at

screening visits and at weeks 0, 4, 8, and 12.

Endpoints and Assessments

The primary efficacy endpoint was the percentage change in fasting TG levels from baseline to weeks 8 and 12. The secondary efficacy endpoints included the percentage changes in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C, direct method), HDL-C (direct method), non-HDL-C (calculated), remnant cholesterol (calculated), apolipoprotein A1, and apolipoprotein B from baseline to weeks 8 and 12. The safety endpoints included the incidence of adverse events and adverse drug reactions, as defined by the Medical Dictionary for Regulatory Activities version 25.1; changes in laboratory test values; and the number and percentage of patients who experienced abnormalities in laboratory values after the administration of the study drug.

Sample Size and Statistical Analysis

This trial was designed in compliance with the Drug Registration Regulation in China, which requires randomized controlled clinical trials involving a minimum of 100 pairs of participants, and adhered to guidelines for clinical trials addressing the treatment of lipid metabolic disorders, which require an active-controlled study with 3-to-12-month duration. The number of participants provided sufficient power for the primary efficacy analysis.

Patients who took the study drugs at least once were included in the safety analysis. Those with available baseline data and at least one post-baseline TG measurement were included in the full analysis set. The efficacy and safety analyses were conducted using the full analysis and safety analysis sets, respectively. To confirm the primary and key secondary efficacy endpoints, these endpoints were analyzed in the per-protocol set, including patients from the full analysis set who completed the treatment period without any major deviations and had TG measurements at baseline and weeks 8 or 12. To account for disruptions caused by the COVID-19 pandemic in China, a modified per-protocol set was also prepared, comprising patients who discontinued the study treatment owing to the lockdown but had at least a week 8 TG measurement in addition to the per-protocol set of patients.

The primary efficacy endpoint was analyzed using a mixed-effect model, incorporating treatment, visits at weeks 8 and 12, current statin therapy use, and sites as fixed effects. Baseline TG value was included as a covariate, and the subject was considered a random effect, assuming heteroscedasticity between

the placebo and active treatments. The least-squares mean was calculated for each treatment and compared between treatments. To control for family-wise Type I errors at the 5% level, a fixed sequential testing procedure was implemented. This hierarchical step-down procedure comprised four steps that could proceed only when each previous step was achieved: (1) to test the superiority of pemafibrate 0.4 mg/d to placebo; (2) to test the non-inferiority of pemafibrate 0.4 mg/d to fenofibrate 200 mg/d; (3) to test the superiority of pemafibrate 0.2 mg/d to placebo; (4) to test the non-inferiority of pemafibrate 0.2 mg/d to fenofibrate 200 mg/d. If step 4 was successfully confirmed, key secondary efficacy analyses were performed using the same model as the primary efficacy analysis following the hierarchical step-down method: (5) to test the superiority of pemafibrate 0.4 mg/d to fenofibrate (200 mg/d), and (6) to test the superiority of pemafibrate 0.2 mg/d to fenofibrate (200 mg/d). Each test was conducted at the 5% level, and the non-inferiority margin was set at 15%. The secondary efficacy endpoints were analyzed using a model similar to the primary efficacy endpoint for the percentage changes from baseline for TC, LDL-C, HDL-C, non-HDL-C, and remnant cholesterol levels. A post-hoc analysis of the laboratory values was conducted. Changes (least square means and 95% confidence intervals [CIs]) were calculated for each treatment group for subjects above and below the ULN of the laboratory parameters at baseline.

Unless otherwise stated, Fisher's exact test was used to compare binary variables, with 95% CIs calculated for differences. Analysis of variance was used to compare continuous variables among the four groups. Changes from baseline at each visit in the clinical safety laboratory tests were compared between pre-baseline and post-baseline using the Wilcoxon signed-rank test. The proportion of patients with abnormal test results above or below the cutoff values (e.g., three times the ULN) was calculated. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) with a significance level of 5% ($p < 0.05$).

Results

Baseline Characteristics

The clinical trial was conducted from September 2021 to January 2023. Written informed consent was obtained from 618 patients, 353 of whom met the eligibility criteria and were randomly assigned to one of the four treatment groups (51, 100, 100, or 102 patients in the placebo, pemafibrate 0.2 mg/d, pemafibrate 0.4 mg/d, and fenofibrate 200 mg/d

Table 1. Baseline characteristics of patients

	Placebo	Pemafibrate		Fenofibrate	Total
<i>n</i>	50	0.2 mg/d 99	0.4 mg/d 97	200 mg/d 98	344
Men, <i>n</i> (%)	35 (70.0)	69 (69.7)	69 (71.1)	78 (79.6)	251 (73.0)
Asian, <i>n</i> (%)	50 (100)	99 (100)	97 (100)	98 (100)	344 (100)
Age, year	51.2 ± 12.6	51.6 ± 10.3	51.3 ± 11.5	50.6 ± 10.5	51.2 ± 11.0
BMI, kg/m ²	26.1 ± 3.3	26.6 ± 3.5	26.7 ± 3.6	25.9 ± 3.0	26.4 ± 3.3
TG, mmol/L	3.20 (2.82–3.78)	3.53 (2.83–4.53)	3.29 (2.69–3.92)	3.35 (2.76–4.53)	3.35 (2.75–4.19)
LDL-C, mmol/L	2.77 (2.02–3.10)	2.65 (2.08–3.34)	2.75 (1.94–3.28)	2.58 (1.94–3.17)	2.68 (1.98–3.26)
HDL-C, mmol/L	0.96 (0.84–1.05)	0.93 (0.85–1.02)	0.94 (0.83–1.05)	0.90 (0.79–1.02)	0.93 (0.83–1.03)
Statin medication, <i>n</i> (%)	8 (16.0)	12 (12.1)	14 (14.4)	14 (14.3)	48 (14.0)
Atorvastatin	5 (10.0)	8 (8.1)	9 (9.3)	10 (10.2)	32 (9.3)
Fluvastatin	1 (2.0)	2 (2.0)	2 (2.1)	0	5 (1.5)
Pitavastatin	0	1 (1.0)	0	1 (1.0)	2 (0.6)
Rosuvastatin	2 (4.0)	1 (1.0)	3 (3.1)	3 (3.1)	9 (2.6)
Type 2 Diabetes, <i>n</i> (%)	10 (20.0)	18 (18.2)	22 (22.7)	15 (15.3)	65 (18.9)
Hypertension, <i>n</i> (%)	24 (48.0)	56 (56.6)	56 (57.7)	45 (45.9)	181 (52.6)
Alcohol Use, <i>n</i> (%)					
Never	29 (58.0)	57 (57.6)	66 (68.0)	54 (55.1)	206 (59.9)
Current	19 (38.0)	37 (37.4)	28 (28.9)	33 (33.7)	117 (34.0)
Former	2 (4.0)	5 (5.1)	3 (3.1)	11 (11.2)	21 (6.1)

Data are presented as mean ± SD for age and BMI, median (interquartile range) for TG, LDL-C, and HDL-C, and the number of patients (%) for categorical parameters. BMI, body mass index; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol

groups, respectively) (**Supplementary Fig. 2**). Three patients in the fenofibrate group discontinued their participation prior to the administration of the trial drug, and 350 patients were administered the trial drug and included in the safety analysis set. A total of 344 patients were administered the trial drugs, and their TG levels were measured at least once after administration and included in the full analysis set. Of these, 290 patients were included in the per-protocol set, and 302 patients were included in the modified per-protocol set, considering the COVID-19 lockdown.

The baseline patient demographics were similar in all groups (**Table 1**). In this trial, 73% of patients were men. The mean (SD) age was 51.2 (11.0) years; 14% of patients were taking statins, and the median (interquartile range) values of TG, LDL-C, and HDL-C levels at baseline were 3.35 (2.75–4.19) mmol/L, 2.68 (1.98–3.26) mmol/L, and 0.93 (0.83–1.03) mmol/L, respectively.

Efficacy

In the mixed-effect model, the percentage change in TG levels from baseline was -34.1% (95% CI: -43.1, -25.2) and -44.0% (95% CI: -52.9, -35.2) in the pemafibrate 0.2 and 0.4 mg/d groups in the full analysis set, respectively (**Fig. 1**). We conducted

primary and secondary efficacy analyses to evaluate the TG-lowering effects of the predefined procedure. Significant results up to step 5 were confirmed. Pemafibrate 0.2 and 0.4 mg/d significantly lowered TG levels compared with the placebo (least square mean of treatment effect of pemafibrate 0.2 mg/d: -40.7% [95% CI: -57.4, -23.9], $p < 0.0001$; least square mean of treatment effect of pemafibrate 0.4 mg/d: -50.6% [95% CI: -67.3, -33.9], $p < 0.0001$). The non-inferiority of pemafibrate 0.2 mg/d to fenofibrate (200 mg/d) was confirmed (least square mean of difference: -3.6% [95% CI: -13.5, 6.2], p for non-inferiority: 0.0002). The non-inferiority and superiority of pemafibrate 0.4 mg/d over fenofibrate (200 mg/d) were also confirmed (least square mean of difference: -13.5% [95% CI: -23.6, -3.5], p for non-inferiority < 0.0001 , p for superiority: 0.0083). To confirm the robustness of the primary efficacy outcomes, we performed the same analyses in the per-protocol and modified per-protocol sets (minimizing the effects of disruption in China due to COVID-19; **Supplementary Table 3**). The results of these analyses are in accordance with those obtained from the full analysis set.

The results for the other lipid profiles are summarized in **Table 2**. HDL-C and apolipoprotein A1 levels significantly increased compared to placebo

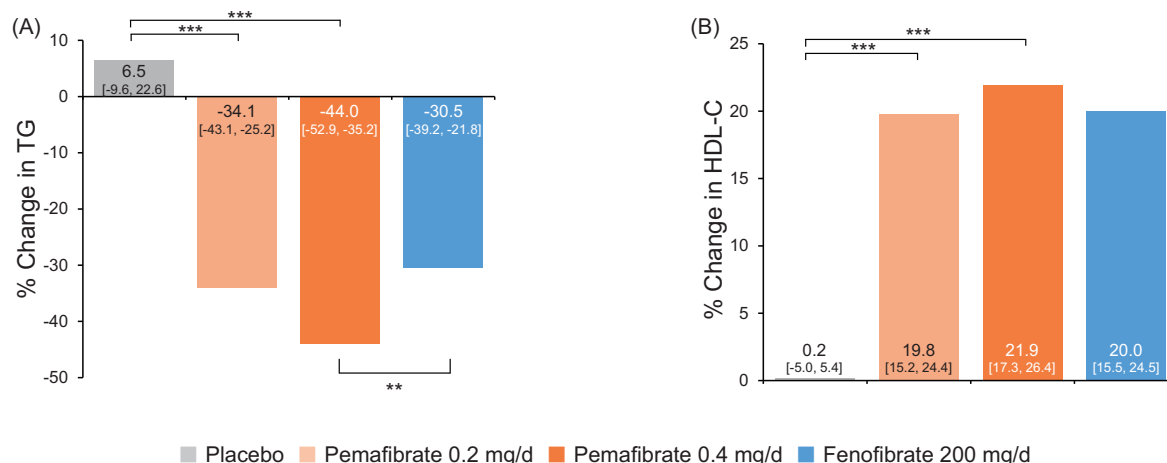


Fig. 1. Percentage changes in (A) TG and (B) HDL-C levels from baseline to week 8 and 12

Data are least square means [95% CI]. **p* < 0.05, ***p* < 0.01, ****p* < 0.001. TG, triglyceride; HDL-C, high-density lipoprotein cholesterol

Table 2. Percentage change of lipid parameters from baseline

				Placebo	Pemafibrate		Fenofibrate
					0.2 mg/d	0.4 mg/d	200 mg/d
TG	mmol/L	week 0	Mean	3.55 ± 1.53	3.76 ± 1.13	3.42 ± 0.99	3.65 ± 1.23
			Median	3.20 (2.82–3.78)	3.53 (2.83–4.53)	3.29 (2.69–3.92)	3.35 (2.76–4.53)
		% change		6.5 [-9.6, 22.6]	-34.1 [-43.1, -25.2]***	-44.0 [-52.9, -35.2]***††	-30.5 [-39.2, -21.8]
TC	mmol/L	week 0	Mean	4.98 ± 1.02	5.24 ± 1.16	5.07 ± 1.04	5.05 ± 1.09
			Median	5.02 (4.32–5.74)	5.21 (4.43–5.69)	4.98 (4.28–5.70)	5.00 (4.18–5.74)
		% change		5.8 [-2.2, 13.9]	2.9 [-1.2, 7.0]	3.0 [-1.0, 7.1]	2.1 [-1.9, 6.1]
LDL-C	mmol/L	week 0	Mean	2.65 ± 0.83	2.69 ± 0.87	2.73 ± 1.00	2.66 ± 1.01
			Median	2.77 (2.02–3.10)	2.65 (2.08–3.34)	2.75 (1.94–3.28)	2.58 (1.94–3.17)
		% change		13.0 [-4.7, 30.6]	22.0 [12.0, 32.0]	25.8 [16.0, 35.5]	19.3 [9.6, 28.9]
HDL-C	mmol/L	week 0	Mean	0.94 ± 0.15	0.93 ± 0.15	0.94 ± 0.16	0.91 ± 0.16
			Median	0.96 (0.84–1.05)	0.93 (0.85–1.02)	0.94 (0.83–1.05)	0.90 (0.79–1.02)
		% change		0.2 [-5.0, 5.4]	19.8 [15.2, 24.4]***	21.9 [17.3, 26.4]***	20.0 [15.5, 24.5]
non-HDL-C	mmol/L	week 0	Mean	4.04 ± 0.98	4.31 ± 1.11	4.13 ± 1.01	4.14 ± 1.06
			Median	4.08 (3.44–4.72)	4.24 (3.53–4.77)	4.03 (3.45–4.60)	3.98 (3.32–4.78)
		% change		9.5 [-3.2, 22.2]	0.1 [-5.2, 5.4]	-0.7 [-6.0, 4.5]	-1.2 [-6.4, 4.0]
Remnant-C	mmol/L	week 0	Mean	1.38 ± 0.55	1.62 ± 0.88	1.38 ± 0.56	1.48 ± 0.66
			Median	1.20 (1.03–1.60)	1.44 (1.07–1.86)	1.24 (0.97–1.69)	1.32 (1.01–1.85)
		% change		3.4 [-13.8, 20.5]	-30.2 [-38.9, -21.4]***	-36.4 [-45.0, -27.8]***	-26.7 [-35.2, -18.2]
ApoA1	mg/dL	week 0	Mean	131.6 ± 17.58	132.0 ± 16.69	134.1 ± 16.59	128.9 ± 17.30
			Median	134.0 (124.0–143.0)	130.0 (120.0–139.0)	133.0 (124.0–145.0)	129.5 (119.0–138.0)
		% change		2.0 [-1.7, 5.7]	9.5 [6.1, 12.9]***	9.0 [5.7, 12.4]**	9.8 [6.4, 13.2]
ApoB	mg/dL	week 0	Mean	104.7 ± 20.35	106.2 ± 22.87	107.8 ± 25.54	105.6 ± 25.70
			Median	108.0 (89.0–118.0)	106.0 (90.0–120.0)	107.0 (88.0–122.0)	105.0 (87.0–119.0)
		% change		6.0 [-1.6, 13.6]	4.5 [-1.0, 10.0]	3.8 [-1.6, 9.1]	0.7 [-4.7, 6.2]

Lipid parameters at baseline are presented as mean ± SD and median (interquartile range); % change from baseline are presented as least square mean [95% confidence interval]. For TG, TC, LDL-C, HDL-C, non-HDL-C, and remnant cholesterol, baseline is defined as the mean of valid values at week 0 and the last measurement prior to week 0, and least square means, confidence interval, and *p* value for % change from baseline to week 8 and 12 were calculated from the mixed-effect model. For Apolipoprotein A1 and Apolipoprotein B, baseline is defined as the valid value at week 0, and least square means, confidence interval, and *p* value for % change from baseline to the end of the treatment period were calculated from the fixed effect model. TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

p* < 0.05, *p* < 0.01, ****p* < 0.001 vs. placebo †*p* < 0.05, ††*p* < 0.01, †††*p* < 0.001 vs. fenofibrate

Table 3. Summary of adverse events

	Placebo (N = 51)	Pemafibrate		Fenofibrate 200 mg/d (N = 99)
		0.2 mg/d (N = 100)	0.4 mg/d (N = 100)	
Subjects with any AE	31 (60.8)	61 (61.0)	53 (53.0)	59 (59.6)
Maximum severity of AE				
Mild	25 (49.0)	53 (53.0)	45 (45.0)	50 (50.5)
Moderate	4 (7.8)	7 (7.0)	7 (7.0)	7 (7.1)
Severe	2 (3.9)	1 (1.0)	1 (1.0)	2 (2.0)
Subjects with any drug-related AE	13 (25.5)	21 (21.0)	28 (28.0)	30 (30.3)
Subjects with any AE leading to drug withdrawal	1 (2.0)	0	0	3 (3.0)
Subjects with any serious AE	2 (3.9)	2 (2.0)	1 (1.0)	3 (3.0)
Subjects with any serious AE leading to death	0	0	0	0
Hepatobiliary disorders*	4 (7.8)	1 (1.0)	2 (2.0)	5 (5.1)
Hepatic function abnormal	2 (3.9)	1 (1.0)	2 (2.0)	2 (2.0)
Hepatic failure	0	0	0	2 (2.0)
Musculoskeletal and connective tissue disorders*	2 (3.9)	6 (6.0)	3 (3.0)	5 (5.1)
Arthralgia	1 (2.0)	1 (1.0)	0	1 (1.0)
Myalgia	0	1 (1.0)	2 (2.0)	0
Intervertebral disc protrusion	0	0	0	2 (2.0)
Periarthritis	0	2 (2.0)	0	0
Renal and urinary disorders*	3 (5.9)	5 (5.0)	9 (9.0)	10 (10.1)
Renal impairment	0	0	2 (2.0)	3 (3.0)
Chronic kidney disease	0	1 (1.0)	1 (1.0)	1 (1.0)
Microalbuminuria	0	2 (2.0)	1 (1.0)	0
Proteinuria	0	1 (1.0)	1 (1.0)	1 (1.0)
Renal failure	0	0	1 (1.0)	2 (2.0)
Albuminuria	0	0	2 (2.0)	0
Nephrolithiasis	1 (2.0)	0	0	1 (1.0)
Renal injury	0	0	1 (1.0)	1 (1.0)
Ureterolithiasis	1 (2.0)	0	0	1 (1.0)

Data are presented as number (%). *Hepatic, renal, and muscle AEs with a total of at least two counts for each AE are listed. AE, adverse events.

group (both $p < 0.0001$ for pemafibrate 0.2 mg/d and 0.4 mg/d in HDL-C, and $p = 0.0006$ and $p = 0.0013$ for pemafibrate 0.2 mg/d and 0.4 mg/d in apolipoprotein A1, respectively) and remnant cholesterol significantly decreased in all pemafibrate groups ($p = 0.0004$ and $p < 0.0001$ for pemafibrate 0.2 mg/d and 0.4 mg/d, respectively). Non-HDL-C levels slightly increased in the placebo group but remained unchanged in other groups. Although LDL-C levels increased in the pemafibrate group, no significant difference was observed in the percentage change from baseline LDL-C or apolipoprotein B levels between the groups.

Safety

The incidence of adverse events was 31 patients (60.8%) in the placebo group, 61 patients (61.0%) in the pemafibrate 0.2 mg/d group, 53 patients (53.0%)

in the pemafibrate 0.4 mg/d group, and 59 patients (59.6%) in the fenofibrate 200 mg/d group (Table 3). No significant difference was observed between the pemafibrate and fenofibrate groups ($p = 0.1128$ and $p = 0.0735$ for pemafibrate 0.2 mg/d and 0.4 mg/d vs. fenofibrate 200 mg/d) or the placebo group ($p = 0.1397$ and $p = 0.0917$ for pemafibrate 0.2 mg/d and 0.4 mg/d vs. placebo).

After 12 weeks of treatment, a reduction in ALT levels was observed in the pemafibrate group, whereas a significant increase was observed in the fenofibrate group compared with that in the pemafibrate 0.2 and 0.4 mg/d groups ($p = 0.0003$ and $p = 0.0003$, respectively) (Fig. 2). In the fenofibrate group, elevations in ALT over three- and five-fold ULN were observed in five (5.1%) and one (1.0%) patient, respectively; however, this was not observed in patients in the pemafibrate group (Table 4). No change in

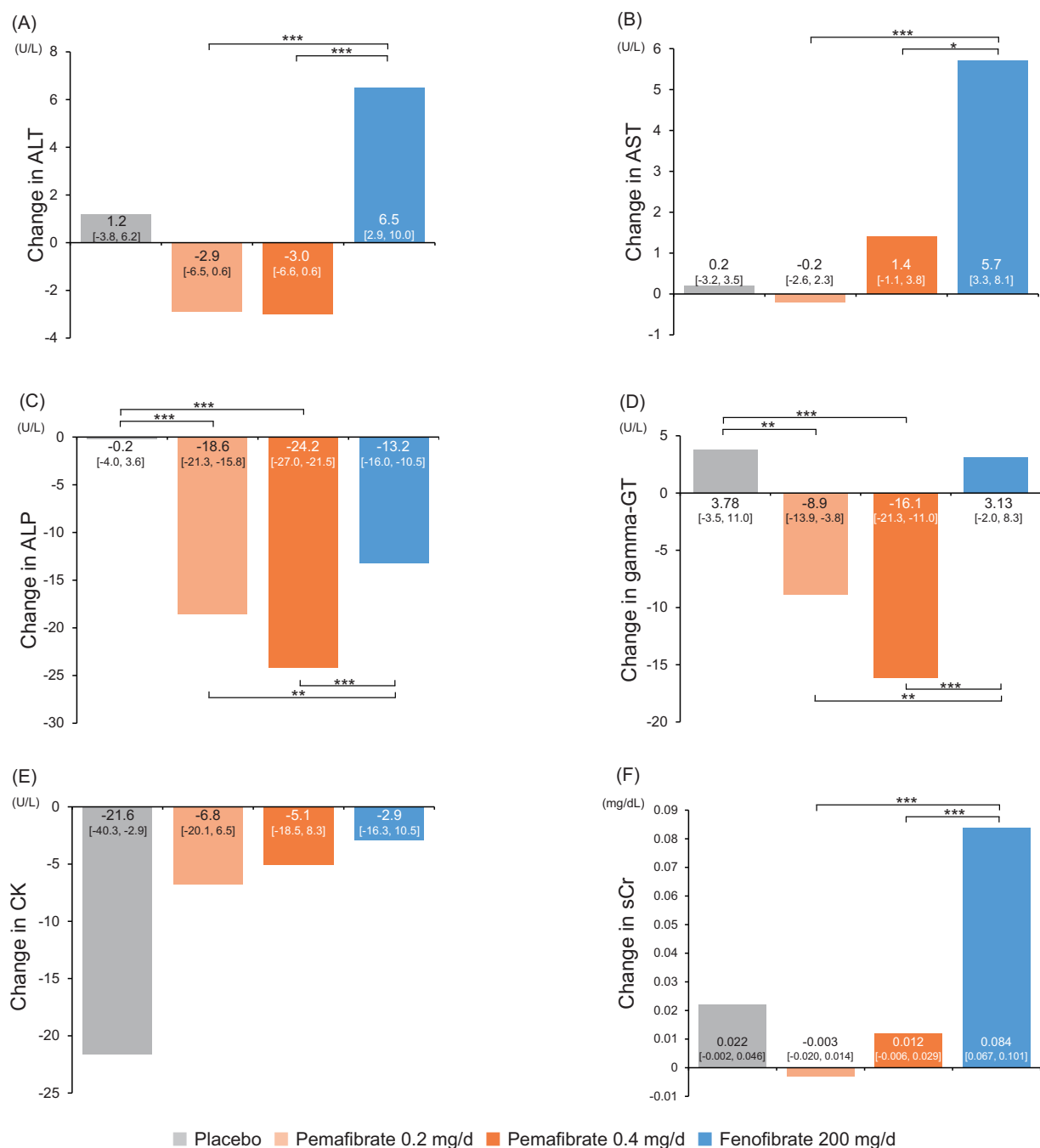


Fig. 2. Changes in (A) ALT, (B) AST, (C) ALP, (D) gamma-GT, (E) CK, and (F) sCr from baseline to last observation value. Data are least square means [95% CI]. ** $p < 0.01$, *** $p < 0.001$. ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; CK, creatine kinase; gamma-GT, gamma-glutamyltransferase; sCr, serum creatinine.

AST levels was observed in the placebo and pemafibrate groups, whereas a significant increase was observed in the fenofibrate group compared with that in the pemafibrate 0.2 and 0.4 mg/d groups ($p=0.0008$ and $p=0.0140$, respectively; **Fig. 2**). In the fenofibrate group, elevations in AST over three- and

five-fold ULN were observed in three (3.0%) and one (1.0%) patients, respectively; nonetheless, this was not observed in patients in the pemafibrate group (**Table 4**). Greater reductions in ALP and gamma-GT levels were also observed in the pemafibrate 0.2 mg/d and 0.4 mg/d group than those in the fenofibrate group

Table 4. Number of patients with laboratory parameter abnormal

	Placebo	Pemafibrate		Fenofibrate
	(N=51)	0.2 mg/d (N=100)	0.4 mg/d (N=100)	200 mg/d (N=99)
ALT >3*ULN	0	0	0	5 (5.1)
ALT >5*ULN	0	0	0	1 (1.0)
AST >3*ULN	0	0	0	3 (3.0)
AST >5*ULN	0	0	0	1 (1.0)
ALP >2.5*ULN	0	0	0	0
CK >2.5*ULN	0	0	2 (2.0)	0
CK >5*ULN	0	0	0	0
sCr >1.5 mg/dL	0	0	1 (1.0)	5 (5.1)
sCr >2.0 mg/dL	0	0	0	1 (1.0)

Data are presented as number (%).

The ULN were 41 U/L for ALT, 37 U/L for AST, 129 U/L for ALP, 1.17 mg/dL for sCr, 308 U/L for CK in men, 33 U/L for ALT, 31 U/L for AST, 104 U/L for ALP, 36 U/L for gamma-GT, 0.95 mg/dL for sCr, and 192 U/L for CK in women.

ALT, alanine aminotransaminase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; CK, creatine kinase; sCr, serum creatinine; ULN, upper limit of normal.

($p=0.0069$ and $p<0.0001$ in ALP, and $p=0.001$ and $p<0.001$ in gamma-GT, respectively) (Fig. 2).

No significant changes were observed in CK and sCr levels in the pemafibrate group; however, an increase in sCr levels was observed in the fenofibrate group (Fig. 2). In the pemafibrate 0.4 mg/d group, two (2.0%) patients had an elevation over 2.5 times the ULN in CK. In the pemafibrate 0.4 mg/d and fenofibrate 200 mg/d groups, one (1.0%) and five (5.1%) patients experienced an increase in sCr >1.5 mg/dL, and one (1.0%) patient in the fenofibrate 200 mg/d group experienced an increase in sCr >2.0 mg/dL (Table 4).

In the post-hoc analysis, reductions in AST, ALT, ALP, and gamma-GT levels were observed in patients with baseline laboratory values above the ULN in the pemafibrate group compared to those in the fenofibrate group. In these patients, there was a tendency for pemafibrate 0.4 mg/d to show greater reductions in ALP and gamma-GT levels than pemafibrate 0.2 mg/d and the fenofibrate group. sCr level increased only in the fenofibrate group (Supplementary Fig. 3).

Discussion

This clinical trial was designed to confirm the TG-lowering effect of pemafibrate in Chinese patients with high TG and low HDL-C levels. Pemafibrate treatment significantly reduced TG levels with acceptable adverse effects. TG reduction by pemafibrate 0.2 mg/d was comparable to that of fenofibrate (200 mg/d). Moreover, treatment with

pemafibrate 0.4 mg/d significantly reduced TG levels compared to fenofibrate (200 mg/d). However, this significant reduction was not observed in previous trials conducted in Japan, which may be attributed to the differences in race and lifestyle between the two countries⁶.

In this study, LDL-C levels showed an increase in both the pemafibrate and fenofibrate groups; however, this increase was not significant when compared to the increase in the placebo group. It is possible that relatively low baseline LDL-C and high TG levels are contributing to this response. In these patients, TG-rich lipoproteins account for a relatively high proportion of apolipoprotein B-containing lipoproteins, and LDL-C levels may increase because TG-rich lipoprotein catabolism is enhanced by pemafibrate. In a previous trial, pemafibrate led to an elevation in LDL-C. Nevertheless, high-performance liquid chromatography subfractionation revealed that pemafibrate increased the less atherogenic large and medium LDL subfractions, but concurrently reduced the more atherogenic small and very small LDL subfractions⁸.

Non-HDL-C is an additional target for treating dyslipidemia¹⁰, and non-HDL-C and remnants are the independent risk factors of cardiovascular outcome¹¹. In the current study, although not statistically significant, the percentage change in non-HDL-C levels after treatment was lower in the pemafibrate group than in the placebo group. This trend is similar to the results of the pooled analysis¹² of the studies conducted in Japan, showing that pemafibrate decreased both lipid parameters. In the

PROMINENT trial, however, remnant-like particle cholesterol decreased but non-HDL-C did not change in the pemafibrate group. These heterogeneous changes in non-HDL-C may be due to patients' profiles, such as the baseline lipid levels and concomitant treatments like statin. Appropriate patient populations that would benefit more from pemafibrate need to be investigated.

The occurrence of liver-related adverse events raises concerns regarding the use of conventional fibrates, such as fenofibrate and gemfibrozil^{6, 13}). In this trial, some patients experienced liver-related laboratory parameter abnormalities with fenofibrate, but not with pemafibrate. In addition, pemafibrate reduced ALT and ALP levels. Furthermore, in the post-hoc analysis of this study, pemafibrate reduced AST, ALT, ALP, and gamma-GT levels in patients above the ULN for each laboratory value at baseline. These findings are consistent with those of previous clinical trials, including a pooled analysis of six randomized, double-masked, placebo-controlled trials¹⁴). In the PROMINENT trial, significantly fewer total hepatic events and investigator-reported cases of nonalcoholic fatty liver disease were observed¹⁵). Furthermore, significant improvements in liver biomarkers and liver stiffness were observed in patients with nonalcoholic fatty liver disease¹⁶). Currently, a trial is underway to evaluate the improvement in disease activity and liver fibrosis by using a combination of pemafibrate and tofogliflozin¹⁷).

The safety profile of pemafibrate with respect to kidney function was confirmed in this study. The number of patients in the fenofibrate group with sCr level abnormalities was higher than that in the pemafibrate group, and fenofibrate substantially increased sCr compared to pemafibrate. In another trial, fenofibrate considerably increased sCr and decreased eGFR, whereas pemafibrate did not affect these parameters to the same extent as fenofibrate⁶). A post-hoc phase 3 study revealed that pemafibrate showed a good efficacy and safety profile in patients with chronic kidney disease⁹), possibly because pemafibrate is excreted mainly through bile¹⁸). Based on these data, pemafibrate was not contraindicated in patients with renal impairment¹⁹).

This study had several limitations. The treatment period was relatively short, and the sample size was insufficient to detect true outcomes, such as the occurrence of cardiovascular disease. The PROMINENT trial was terminated early due to futility, and the observed treatment effect on TG levels was smaller than that observed in this study. Additional long-term data are needed, especially for

patients who are anticipated to experience substantial decreases in TG levels when using pemafibrate. The number of patients receiving concomitant statin therapy was relatively small. Guidelines recommend statins as first-line pharmacotherapy for the treatment of dyslipidemia²⁰⁻²²). Additional investigation conducted in a real-world setting is necessary to obtain more insights.

Conclusion

This study demonstrated that pemafibrate therapy improves lipid profiles with an acceptable safety profile in Chinese patients with high TG and low HDL-C levels. Pemafibrate has been confirmed to have superior TG-lowering effects compared to fenofibrate, as well as a favorable safety profile for the liver and kidneys. Pemafibrate may be a potent option for treating dyslipidemia for Chinese patients.

Financial Support

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Conflicts of Interest

R. T., K. K., H. S., and R. K. are the employees of Kowa Company, Ltd. W. D., Qiang L, Qingling L., L. F., Yawei Z., Yumin Z., L. L., and C. M. have no Conflict of Interest to disclosure.

Acknowledgments

We thank the investigators and patients who participated in this study. The sponsor played a role in the study design, data collection, data analysis, data interpretation, and writing of the report.

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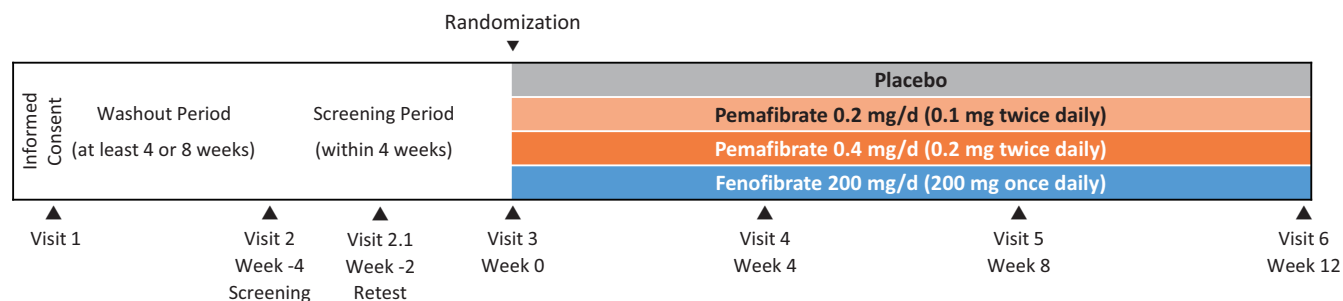
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Supplementary Table 1. Full list of sites and principal investigators

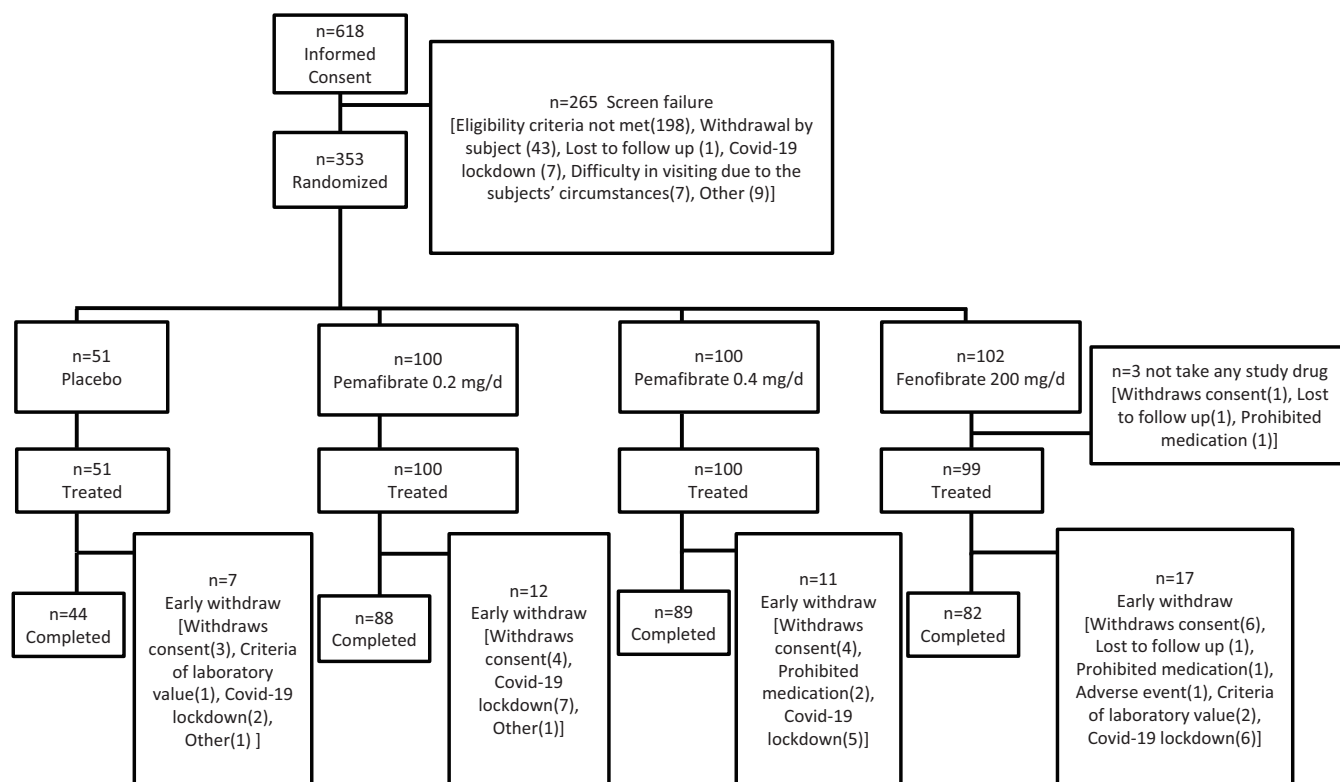
Site Name	Principal Investigator
Beijing Anzhen Hospital, Capital Medical University	Changsheng Ma
The People's Hospital of Guangxi Zhuang Autonomous Region	Ling Liu
Chengdu Xinhua Hospital	Qingling Li
The First Affiliated Hospital of Fujian Medical University	Jinxu Lin
The Third Xiangya Hospital of Central South University	Weihong Jiang
Nanjing Jiangning Hospital	Yuqing Zhang
Huainan First People's Hospital	Lijun Liu
Sir Run Run Hospital Nanjing Medical University	Xiang Lu
The First Affiliated Hospital of Nanchang University	Zeqi Zheng
The First Hospital of Nanchang	Shunhui Li
Peking Union Medical College Hospital	Lihua Zhang
People's Hospital of Wenzhou City	Xiaoshu Chen
Tongji Hospital, Tongji Medical College of HUST	Xiaomei Guo
Beijing Tongren Hospital, Capital Medical University	Guohong Wang
People's Hospital of Deyang City	Xiaojian Deng
The First Affiliated Hospital, Sun Yat-sen University	Yugang Dong
Shanghai Tongren Hospital	Zhaohui Qiu
Union Hospital, Tongji Medical College of Huazhong University of Science & technology	Cheng Xiang
Shaanxi Provincial People's Hospital	Junkui Wang
The First Affiliated Hospital of Harbin Medical University	Lu Fu
The Affiliated Hospital of Hangzhou Normal University	Zhao Xu
Tianjin Union Medical Center	Zhuhua Yao
The Second Hospital of Hebei Medical University	Jidong Zhang
Beijing Hospital	Fang Wang
Hainan General Hospital	Ping Qiao
Affiliated Hospital of Jiangsu University	Wei Yuan
The Third Hospital of Changsha	Yumin Zhang
Jiu Jiang No. 1 People's Hospital	Ling Chen
Pingxiang People's Hospital	Yawei Zhang
Jiangxi Provincial People's Hospital	Lang Hong
China-Japan Union Hospital of Jilin University	Ping Yang

Supplementary Table 2. Full inclusion and exclusion criteria

Inclusion Criteria
Participants were eligible to be included in the study if all of the following criteria were met: 1. Ability to understand and comply with study procedures and give written informed consent 2. Following the diet and lifestyle recommendations at least 12 weeks prior to the treatment period 3. Men or post-menopausal women 4. Aged ≥ 18 years at the time of informed consent 5. Fasting serum TG levels ≥ 200 mg/dl (≥ 2.26 mmol/L) and ≤ 500 mg/dl (5.65 mmol/L) at screening 6. Serum HDL-C < 1.30 mmol/L (men) or < 1.42 mmol/L (women) at screening
Exclusion criteria
Participants were excluded from the study if any of the following criteria were met: 1. Ongoing or planned use of any lipid-altering medications other than the study drugs, statins, or ezetimibe during the study i. Participants on statins or ezetimibe must be at high risk for atherosclerotic cardiovascular diseases, and the dose(s) must be stable for at least four weeks prior to screening ii. For participants currently on lipid-altering medications other than statins or ezetimibe, at least four-week washout period (or for participants currently on probucol at least 8-week washout period) was required prior to the first fasting blood sampling at screening visit 2. Type 1 diabetes mellitus or poorly controlled type 2 diabetes mellitus defined by HbA1c (NGSP level) $\geq 8.0\%$ at screening 3. Uncontrolled hypertension defined by seated systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg at screening 4. Uncontrolled thyroid disorder 5. Creatinine ≥ 1.5 mg/dl at screening 6. Severe hepatic disorder defined as cirrhosis of Child–Pugh class B or C, or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $> 2 \times$ upper limit of normal (ULN) at screening 7. History of pancreatitis 8. Gallbladder disorder, history of cholelithiasis, primary biliary cirrhosis, or history of disease or surgery that might affect the absorption, distribution, metabolism and excretion of drugs or the metabolism of bile salts 9. Unexplained creatine kinase (CK) $> 5 \times$ ULN at screening 10. Myocardial infarction or stroke (including transient ischemic attack) within three months prior to the informed consent 11. New York Heart Association Class III or IV heart failure 12. History of malignancy within five years 13. Participation in another clinical study at the time of informed consent or administration of an investigational drug other than placebo within 16 weeks prior to the informed consent for this study 14. Blood donation ≥ 200 mL within one month before the administration of the study drug, or ≥ 400 mL within 4 months before the administration of the study drug 15. History of drug or alcohol abuse 16. Drinking habit with an excessive amount of alcohol (eg, an average of > 25 g per day as consumed in the course of a week) or alcohol positive at screening 17. History of serious drug allergies (such as anaphylactic shock) or known sensitivity to PPARα agonists 18. Current or anticipated chronic use of cyclosporine, rifampicin, or other inhibitors of organic anion transporting polypeptides (OATP) 1B1, or OATP1B3 19. History of chronic active hepatitis B or hepatitis C, or known infection with human immunodeficiency virus (HIV) 20. Previous use of pemafibrate 21. Any condition or therapy which, in the opinion of the investigator, might be inappropriate for the participation in the study



Supplementary Fig. 1. Study period



Supplementary Fig. 2. Patient disposition flowchart

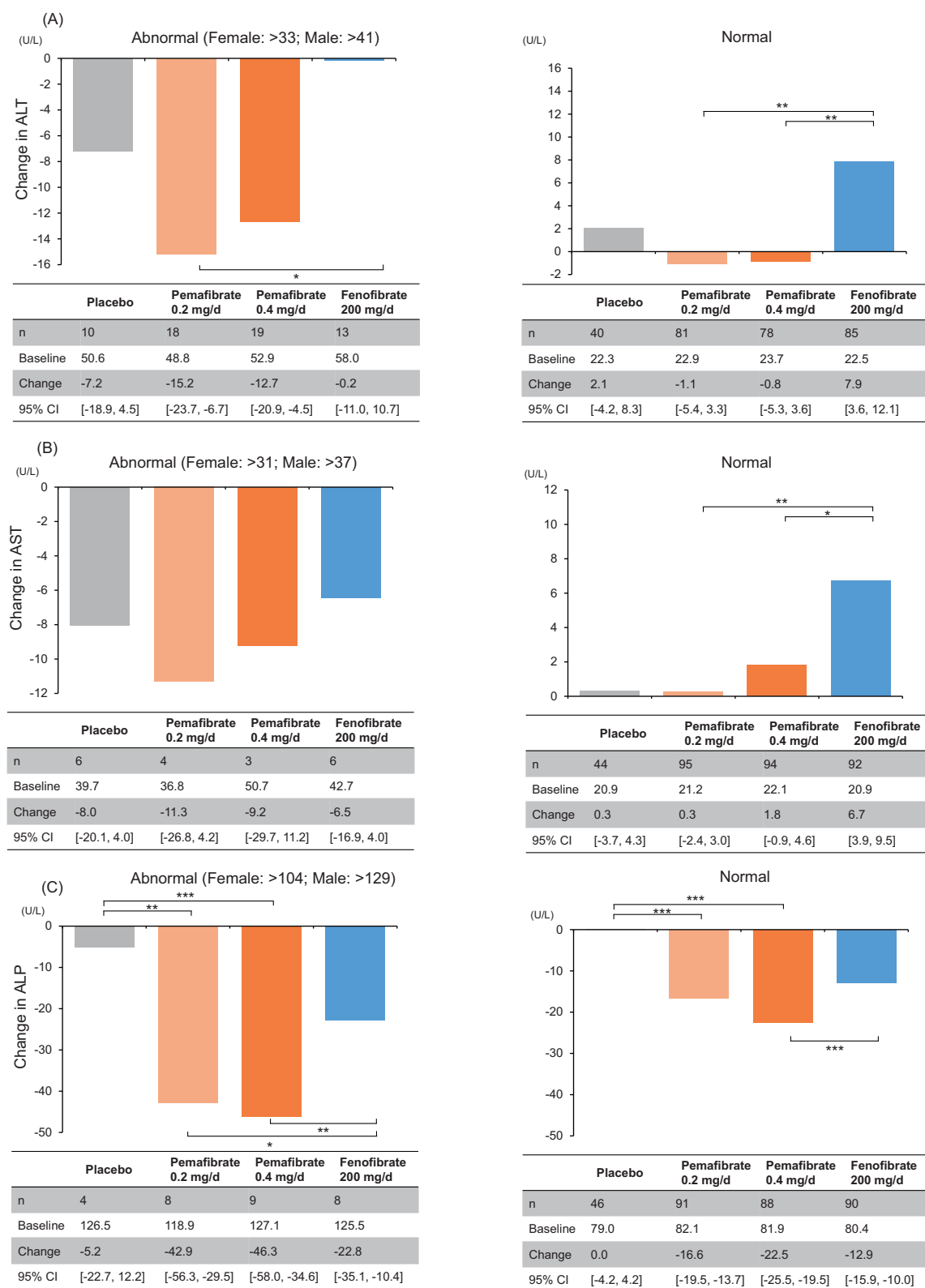
Supplementary Table 3. Percentage change in triglyceride level from baseline to weeks 8 and 12 in mixed effect model calculated from per-protocol set and modified per-protocol set

Per-protocol Set						
Statistics or category		Placebo (N=50)	Pemafibrate		Fenofibrate	
			0.2 mg/day (N=99)	0.4 mg/day (N=97)	200 mg/day (N=98)	
% change from baseline :	LS Mean (95% CI)	4.4 (-13.4 to 22.1)	-33.5 (-43.2 to -23.9)	-46.2 (-55.8 to -36.6)	-29.0 (-38.5 to -19.4)	
Superiority:	Difference		-37.9 (-56.4 to -19.5)	-50.5 (-68.9 to -32.2)		
pemafibrate vs. placebo	P-value		0.0001	<0.0001		
Non-inferiority:	Difference		-4.6 (-15.2 to 6.0)	-17.2 (-28.0 to -6.3)		
pemafibrate vs. fenofibrate	P-value		0.0003	<0.0001		
Superiority:	Difference		-4.6 (-15.2 to 6.0)	-17.2 (-28.0 to -6.3)		
pemafibrate vs. fenofibrate	P-value		0.3976	0.002		
Modified Per-protocol Set						
Statistics or category		Placebo (N=50)	Pemafibrate		Fenofibrate	
			0.2 mg/day (N=99)	0.4 mg/day (N=97)	200 mg/day (N=98)	
% change from baseline	LS Mean (95% CI)	3.9 (-13.4 to 21.3)	-34.3 (-43.7 to -24.8)	-45.4 (-54.9 to -35.8)	-29.2 (-38.6 to -19.8)	
Superiority:	Difference		-38.2 (-56.2 to -20.3)	-49.3 (-67.3 to -31.4)		
pemafibrate vs. placebo	P-value		0.0001	<0.0001		
Non-inferiority:	Difference		-5.1 (-15.4 to 5.3)	-16.2 (-26.8 to -5.5)		
pemafibrate vs. fenofibrate	P-value		0.0002	<0.0001		
Superiority:	Difference		-5.1 (-15.4 to 5.3)	-16.2 (-26.8 to -5.5)		
pemafibrate vs. fenofibrate	P-value		0.3362	0.0032		

Least square (LS) means, confidence interval (CI), and *P*-value were from the mixed effect model with treatment, visit (weeks 8 and 12), and current statin therapy use (not on statin therapy versus currently receiving statin therapy) and site as fixed effects, baseline triglyceride value as a covariate, and participant as a random effect.

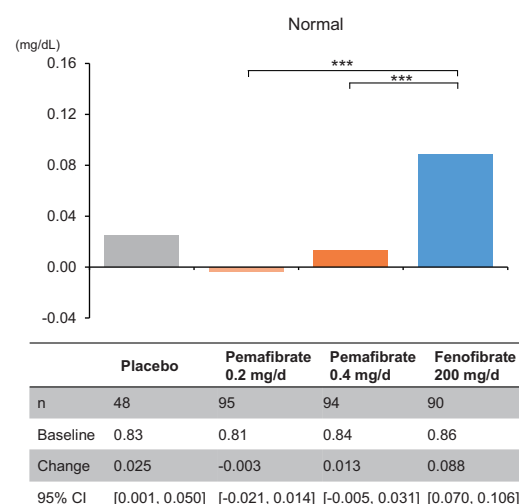
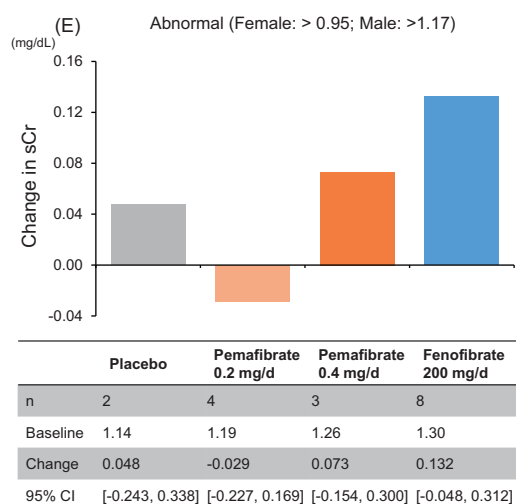
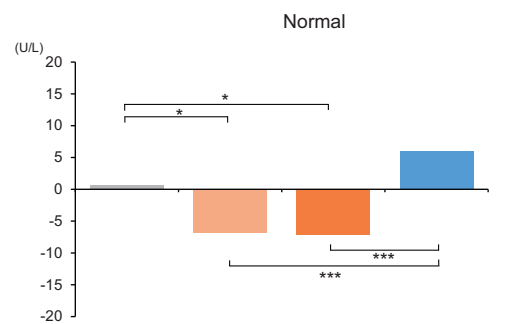
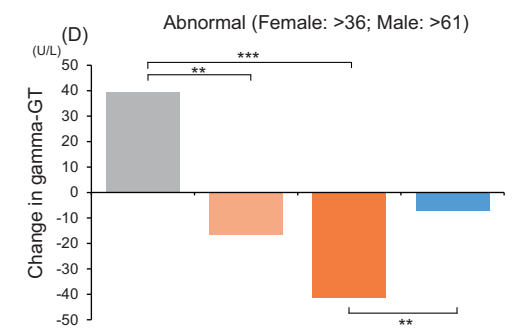
Type I error was set at 0.05 level.

For the non-inferiority test, the non-inferiority margin was set at 15%.



Supplementary Fig. 3. Changes in (A) ALT, (B) AST, (C) ALP, (D) gamma-GT, and (E) sCr for patients with baseline values above or below the upper limit of normal

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. ALT, Alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; gamma-GT, gamma-glutamyltransferase; sCr, serum creatinine.



■ Placebo ■ Pemaifibrate 0.2 mg/day ■ Pemaifibrate 0.4 mg/day ■ Fenofibrate 200 mg

(Cont. Supplementary Fig. 3)