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Effects of K-877, a novel selective PPARα modulator (SPPARMα), in dyslipidaemic patients: A randomized, double blind, active- and placebo-controlled, phase 2 trial

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ABSTRACT

Background and aims: To assess the efficacy and safety of K-877 (Pemafibrate), a novel selective peroxisome proliferator-activated receptor α modulator (SPPARMα) that possesses unique PPARα activity and selectivity, compared with placebo and fenofibrate in dyslipidaemic patients with high triglyceride (TG) and low high-density lipoprotein cholesterol (HDL-C) levels.
Methods and results: This study was a double blind, placebo-controlled, parallel-group 12-week clinical trial. The study randomized 224 patients to K-877 0.025, 0.05, 0.1, 0.2 mg BID, fenofibrate 100 mg QD, or placebo (1:1:1:1:1:1) groups. Least squares mean percent changes from the baseline TG levels were −30.9%, −36.4%, −42.6%, −42.7% for the K-877 0.025, 0.05, 0.1, 0.2 mg BID respectively ($p < 0.001$), which were greater than that of the fenofibrate 100 mg QD (−29.7%, $p < 0.001$) group. Statistically significant improvements from the baseline HDL-C, very-low-density lipoprotein cholesterol, chylomicron cholesterol, remnant lipoprotein cholesterol, apolipoprotein (apo) B (apoB), and apoC-III were also observed in the K-877 groups. The incidence of adverse events (AEs) in the K-877 groups (32.4–56.8%) was comparable to those in placebo (47.2%) and fenofibrate 100 mg QD (56.8%); adverse drug reactions (ADRs) in the K-877 groups (2.7–5.4%) were less than those in placebo (8.3%) and fenofibrate 100 mg QD (10.8%) groups.
Conclusion: In dyslipidaemic patients with high TG and low HDL-C, K-877 improved TG, HDL-C, and other lipid parameters without increasing AEs or ADRs, compared to placebo and fenofibrate. K-877 can be expected to improve atherogenicity and to be a new beneficial treatment for dyslipidaemic patients.
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1. Introduction

Cardiovascular diseases (CVDs) are the leading cause of mortality and morbidity, accounting for 31% of all deaths worldwide [1]. Of all deaths due to CVD, approximately 80% were due to coronary heart disease (CHD) or stroke. Dyslipidaemia is one of the major

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risk factors for CHD, along with hypertension, diabetes, smoking, and obesity [1].

Numerous studies show that blood cholesterol-lowering therapy reduces the occurrence of atherosclerotic cardiovascular disease (ASCVD) [2]. Meta-analysis of large clinical trials revealed that statins reduce the risk of ASCVD by approximately 20–30% [3]. This suggests that 70% of risk remains even after treatment of high low-density lipoprotein-cholesterol (LDL-C) by statins [4]. To further reduce this risk, other lipid risk factors such as high levels of triglycerides (TG), low high-density lipoprotein cholesterol (HDL-C), and high non-HDL-C are potential viable targets for non-statin treatment. Many guidelines recommend treatment with bile acid sequestrants, nicotinic acids, fibrates, and n-3 (omega-3) fatty acids to manage these factors [5]. Fibrates or nicotinic acids are particularly recommended to manage elevated TG and low HDL-C levels. According to sub-analyses of recent trials, the use of fibrate resulted in favourable cardiovascular outcomes in patients with high TG and low HDL-C levels [6]. Moreover, a meta-analysis revealed that fibrates could reduce CV risks [7].

Peroxisome proliferator-activated receptors (PPARs) are a superfamily of nuclear hormone receptors that form complexes with the retinoid X receptor (RXR) and bind to PPAR response elements (PPRE) on DNA. There are three different types of PPAR (α, δ, and γ) [8]. In general, the activation of PPARα is associated with the attenuation of lipid and/or glucose metabolic dysfunction, inflammation, atherosclerosis, and vascular dysfunction. With regard to TG metabolism, PPARα targets genes that express proteins such as apolipoprotein (apo) CIII, apoAV and lipoprotein lipase (LPL), thereby reducing the amount of free fatty acids utilized for the synthesis and secretion of apoB-containing lipoproteins. With regard to HDL metabolism, PPARα targets apoAI, apoAII, scavenger receptor-BI (SR-BI), and ATP-binding cassette transporter A1 (ABCA1), thereby increasing HDL production and stimulating reverse cholesterol transport [9].

K-877 (Pemafibrate) is a novel member of the selective PPARα modulator (SPPARMα) family [10] that was designed to have a higher PPARα agonistic activity and selectivity than existing PPARα agonists (such as fibrates) [11]. In the present study, we report the results of a K-877 phase 2 study in dyslipidaemic patients with high TG and low HDL-C levels.

2. Methods

2.1. Patients/study design and participants

We undertook this randomized, double blind, active- and placebo-controlled phase 2 trial at 19 sites in Japan. The study took place between November 22, 2010, and July 7, 2011.

Men and postmenopausal women aged 20–74 years who had a history of documented dyslipidaemia and plasma TG of 200 mg/dL or higher as well as HDL-C less than 50 mg/dL in men or 55 mg/dL in women, during two consecutive evaluations were eligible. Major exclusion criteria were as follows: TG of 500 mg/dL or more during two consecutive evaluations; patients who needed additional drug treatment for dyslipidaemia during the study period; type 1 diabetes or poorly controlled type 2 diabetes (HbA1c of 8.4% or more); poorly controlled hypertension (systolic blood pressure of 160 mmHg or more or diastolic blood pressure of 100 mmHg or more); poorly controlled thyroid disorder; mild or more severe renal disorder (serum creatinine of 1.5 mg/dL or more); current or past history of hepatic impairment; aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels more than 2-fold higher than the upper limit of the reference range; current gallbladder disease or a history of cholelithiasis; fibrinogen level less than the lower limit of the reference range; alcohol or drug addiction; habitual excessive alcohol consumption (γ-glutamyl transferase (γ-GT) levels 2.5-fold higher than the upper limit of reference range). The concomitant use of drug treatment for dyslipidaemia was prohibited. Patients were ineligible, if they received these drugs within four weeks prior to the first screening visit. Thiazolidinediones, insulin products and derivatives, adrenal corticosteroids, protease inhibitors, protein anabolic hormones, and luteum hormones were also prohibited during the study period owing to their potential effects on dyslipidaemia. Patients were instructed to maintain their diet, exercise, and pharmacological therapy during the study period.

The study protocol and amendment were approved by the independent ethic committee or institutional review board before the commencement of study. The study was conducted in accordance with the principle of the Declaration of Helsinki, and under the guidelines of Good Clinical Practice and the International Conference on Harmonization. All study participants provided written informed consent prior to involvement. This trial is registered with JAPIC Clinical Trials Information, number Japic CTI-101331.

2.2. Procedures

Fig. S1 shows the study design, depicting the duration of each period and timing of study visits. Fig. S2 shows the disposition of the patients. Patient demographics were assessed or recorded during the screening period. After randomization (week 0), patients were randomly assigned, in a 1:1:1:1:1:1 ratio, to treatment with either K-877 at a dose of 0.025, 0.05, 0.1, or 0.2 mg BID (twice daily; 0.05, 0.1, 0.2, and 0.4 mg/day, respectively), fenofibrate (LIPIDIL®) at a dose of 100 mg QD (once daily), or matching placebo. LIPIDIL® 100 mg micronized capsule had been marketed as equivalent to the LIPIDIL® 80 mg tablet. Randomization was done with a central computer-controlled system with stratification according to the HDL-C value at the first screening visit to avoid imbalance. This study comprised a screening period of a maximum of eight weeks before the commencement of the treatment, and then a 12-week, double-blind treatment period followed by a 4-week follow-up period. During the screening and treatment period, patients visited the site for at least two screening visits, and at baseline (randomization visit i.e. week 0), week 2, 4, 8, and 12, at which fasting ($\geq$10 h) blood and urine samples were collected for the assessment of clinical laboratory findings, including lipids. Study eligibility was determined by the laboratory data sampled at two screening visits. Following the treatment period, patients stopped taking the study drug and a follow-up visit was performed after four weeks (at week 16) for safety assessment.

At each treatment visit, patients received press-through-packages of the study drug except at week 12, and were instructed to take one tablet and one capsule after breakfast and one tablet after dinner.

2.3. Clinical laboratory and lipoprotein analysis

Lipoprotein level was measured by the direct enzymatic method; apolipoprotein level was measured by the immunoassay method. Other laboratory parameters were analysed by a standardized laboratory method (all measurements were done by LSI Medience Corporation, Japan, or its affiliates). Fibroblast growth factor 21 (FGF21) level was measured by enzyme-linked immunosorbent assay (ELISA) (Bio Vendor HUMAN FGF-21 ELISA). The concentration of TG and cholesterol, phospholipid, and free cholesterol contained in lipoprotein fractions were measured by the high-performance liquid chromatography (HPLC) (LipoSEARCH©, Skylight Biothech, Japan) method. HPLC measured TG,

cholesterol, phospholipid, and free cholesterol peaks of a total of 20 lipoprotein subfractions divided by particle diameters: two chylomicron (CM); five very-low-density lipoprotein (VLDL) (comprising large, medium, and small VLDL subclasses); six LDL (comprising large, medium, small and very small subclasses); seven HDL (comprising very large, large, medium, small, and very small subclasses) [12].

2.4. Statistical analysis

A sample size of 192 patients, with 32 patients in each group, ensured at least 90% power to detect a 30% reduction in TG levels from the baseline to week 12 using a Dunnett's test with an alpha level of 0.05. In this calculation, we assumed a standard deviation of 30 for percent change of TG reduction and a dropout rate of 10%. SAS (version 9.2) was used for analysis. The primary efficacy analysis was performed according to the per-protocol-set on data from all patients who were randomized to the treatment group and had at least one study treatment, both values of baseline, and at least one post-baseline visit without deviations, which affect efficacy evaluation. The primary safety analysis was performed according to safety-analysis-set on data from all patients who were randomized to the treatment group and had at least one study drug. All analyses of primary efficacy and safety parameters were performed according to pre-specified statistical analysis plan.

We analysed the primary endpoint using an ANCOVA model with the baseline value as a covariate. The primary efficacy endpoint was the percent change of TG at the end of the treatment period from baseline. Primary analysis of the primary endpoint was an evaluation of the dose-dependent relationship of all K-877 groups, including the placebo group, using the maximum contrast method. Secondary analysis of the primary endpoint was investigation of the superiority of the K-877 group compared to placebo by Dunnett's test, only if statistical significance was confirmed during primary analysis. Exploratory analysis of the primary endpoint was the difference of K-877 in each group and fenofibrate using the ANCOVA model. The primary safety endpoint was the event ratio of adverse events and adverse reactions. One sample *t*-test or Wilcoxon signed rank test was used to assess the difference from baseline to week 12, and the two sample *t*-test or Wilcoxon rank sum test were used to assess a group difference.

3. Result

A total of 224 patients were randomly assigned to treatment. Table 1 shows the demographics and clinical characteristics of patients at baseline. Of 224 patients, 10 patients were excluded from the per-protocol-population owing to concomitant use of prohibited treatment, missing TG baselines or last evaluation points; thus, per-protocol-population comprised 214 patients. One patient who received fenofibrate 100 mg QD discontinued the study owing to liver function abnormalities; thus, a total of 213 patients completed the study. Including TG and HDL-C, demographics and baseline clinical characteristics were similar across all dosing groups.

All treatments except placebo reduced the TG level (Fig. 1A, Fig. S3A). TG levels in the K-877 group decreased in a dose-dependent manner, with TG reduction plateauing at 0.1 mg BID, although a marked reduction was observed at higher doses. Compared to fenofibrate, all K-877 dosing groups demonstrated greater TG reduction, although the differences were not statistically significant.

All treatments except the placebo increased HDL-C level (Fig. 1B, Fig. S3B). There was a dose-dependent increase in the K-877 group, with the HDL-C increase plateauing at 0.05 mg BID, although 0.2 mg BID increased HDL-C the most in all groups. Compared to fenofibrate, the increase in HDL-C was larger in K-877 0.05, 0.1, and 0.2 mg BID, but the difference was not statistically significant.

The percent changes or changes from baseline of other key parameters are summarized in Table 2 and Table S1. The reductions of non HDL-C, VLDL-C, remnant lipoprotein cholesterol (RemL-C), apoB48, and apoCIII were statistically significant in the K-877 groups and fenofibrate, compared to placebo. The reduction of VLDL-C was statistically significant in K-877 0.1 and 0.2 mg BID groups compared to fenofibrate. All doses of K-877 and fenofibrate significantly increased levels of apoAI and apoAII. Compared to fenofibrate, K-877 0.2 mg BID showed greater increases of apoAI and apoAII levels. A slight increase from baseline in LDL-C was observed in the K-877 groups and fenofibrate group, with the change in both groups being comparable. As part of the post hoc analysis, we evaluated the relationship between the baseline levels of TG or LDL-C and the change in LDL-C (Figs. S4 and S5). The magnitude of change of LDL-C from baseline positively correlated with baseline TG and negatively correlated with baseline LDL-C.

The subclasses of lipoproteins were analysed by HPLC (Fig. 2, Table S2). Dose-related reductions from baseline were observed in the small and very small LDL categories in the K-877 groups while dose-dependent increases from baseline were observed in the small and very-small HDL categories in the K-877 groups.

FGF21, a hormonal regulator, significantly increased from

Table 1
Demographics and clinical characteristics at baseline (Per-protocol-set).

		K-877				Fenofibrate
	Placebo	0.025 mg BID	0.05 mg BID	0.1 mg BID	0.2 mg BID	100 mg QD
n	35	34	37	36	36	36
Age, years	48.7 (9.0)	50.9 (9.9)	50.0 (12.4)	48.8 (10.7)	47.8 (12.8)	51.1 (11.5)
Sex, male n (%)[a]	34 (97.1)	29 (85.3)	36 (97.3)	33 (91.7)	34 (94.4)	33 (91.7)
Weight, kg	77.02 (9.38)	75.95 (11.84)	76.01 (13.53)	80.76 (14.07)	75.08 (11.52)	75.47 (10.96)
BMI, kg/m^2	26.86 (2.66)	26.45 (3.26)	26.80 (3.82)	27.84 (3.72)	26.51 (3.56)	26.63 (3.01)
Type 2 DM, n (%)[a]	4 (11.4)	5 (14.7)	5 (13.5)	4 (11.1)	5 (13.9)	4 (11.1)
Hypertension, n (%)[a]	9 (25.7)	10 (29.4)	11 (29.7)	10 (27.8)	7 (19.4)	8 (22.2)
Fatty liver, n (%)[a]	8 (22.9)	8 (23.5)	4 (10.8)	6 (16.7)	8 (22.2)	10 (27.8)
TG, mmol/L	3.49 (1.47)	3.77 (2.49)	3.33 (1.25)	3.29 (1.35)	3.42 (2.36)	3.68 (2.31)
HDL-C, mmol/L	1.04 (0.16)	1.05 (0.21)	1.06 (0.18)	1.06 (0.19)	1.07 (0.18)	1.04 (0.19)
LDL-C,[b] mmol/L	3.32 (0.76)	3.30 (0.85)	3.16 (0.95)	3.39 (0.98)	3.76 (0.93)	3.47 (0.91)
Non HDL-C, mmol/L	4.78 (0.77)	4.70 (0.93)	4.56 (0.95)	4.75 (0.94)	5.13 (0.98)	4.96 (1.01)

Mean (SD).
[a] The number (percentage) of patients.
[b] Ultracentrifugation.

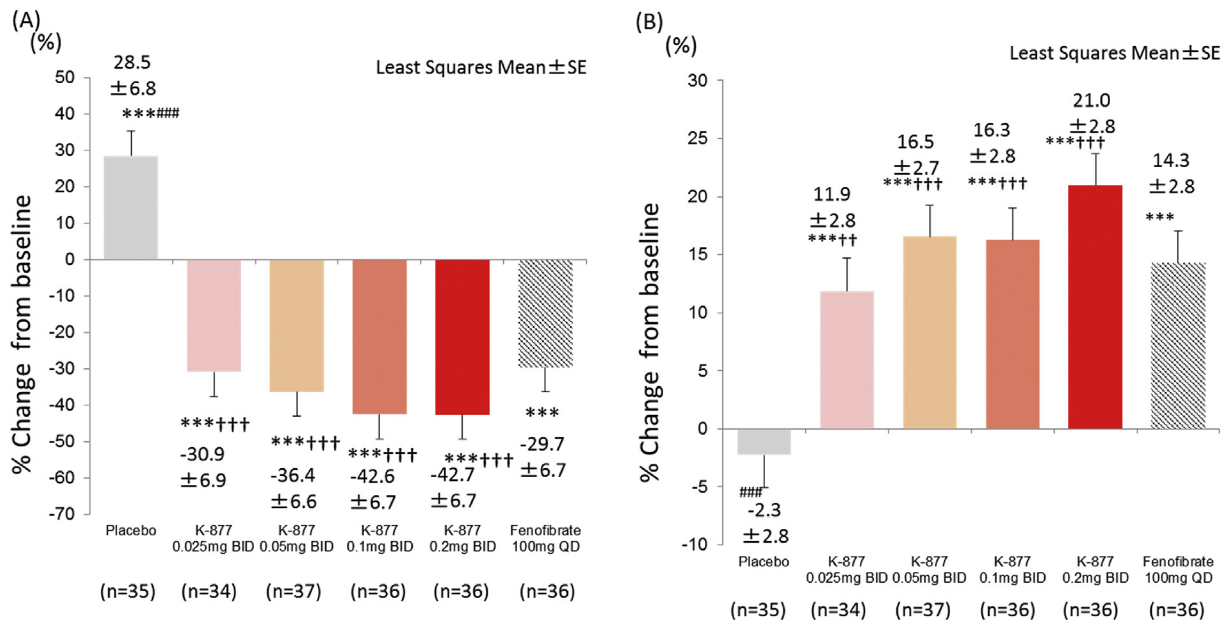

Fig. 1. Percent change from baseline at 12 weeks (A) TG, (B) HDL-C. Least Squares Mean. Error bars represent standard error (SE). $^{***}p < 0.001$ vs baseline, $^{††}p < 0.01$, $^{†††}p < 0.001$ vs Placebo (Dunnett), $^{\#\#\#}p < 0.001$ vs Fenofibrate.

baseline in the placebo, K-877 0.05, 0.1, and 0.2 mg BID groups. Statistically significant increases were observed in K-877 0.05, 0.1, and 0.2 mg BID compared to that of placebo and fenofibrate groups.

The overall frequency of adverse events was comparable across all groups. The most frequently observed adverse events included seasonal allergy and nasopharyngitis (n = 16 for both). In total, there was no dose-dependent increase of adverse events or adverse drug reactions in the K-877 groups. The fenofibrate and placebo groups were associated with a slightly higher frequency of adverse drug reactions than the K-877 groups. The most frequently observed adverse drug reactions with fenofibrate were clinical laboratory abnormalities. Adverse events and laboratory abnormalities with respect to liver and muscle enzymes are summarized in Table 3. The rate of elevated AST levels in the K-877 groups was similar to that of placebo, while fenofibrate group had higher levels of AST than the other groups. The rate of elevated ALT levels in the K-877 groups was lower than that of the placebo or fenofibrate group. One patient, who was assigned to fenofibrate group, discontinued the study owing to liver function abnormalities (liver enzyme increase). There was no case of elevated CK more than two times higher the upper limit of the reference range.

4. Discussion

In the present study, we first report that K-877 significantly reduced TG and increased HDL-C levels compared with the placebo.

The effects of K-877 in reducing TG and increasing HDL-C appear to be the most potent among this class of drugs with PPARα agonistic activity. Its relative efficacy is superior to fenofibrate by three orders of magnitude, almost completely corroborating its relative potency as a PPARα agonist evaluated in *in vitro* assays [10]. The TG reduction produced by 100 mg QD fenofibrate was as potent as that of 0.025 and 0.05 mg BID K-877, while the HDL-C-raising effects of 100 mg QD fenofibrate was as potent as 0.05 and 0.1 mg BID K-877. Therefore, K-877 may affect TG metabolism more favourably than HDL metabolism, although these differences were not statistically significant. In parallel, lipid parameters closely related to TG metabolism, such as VLDL-C, apoB48, RemL-C, and apoCIII, were more favourably affected than lipid parameters closely related to HDL metabolism such as apoAI and apoAII. Recent human genetic discoveries implicate the role of triglycerides and triglyceride-rich lipoproteins in the development of cardiovascular risk [13] and show that ApoCIII and ApoAV have a significant influence on the risk of CAD. Together with the results of longitudinal studies showing that remnant lipoproteins are strong risk factors for CHD [14], the preferential effects of K-877 on RemL-C, which reflects the combination of VLDL and chylomicron remnants, and apoB48, a marker for chylomicron remnants, may suggest that K-877 has anti-atherogenic potential. As reported previously, the transactivation of genes such as LPL, apoAI, apoAII, ABCA1, ABCG1, and SR-BI, as well as the transrepression of genes such as apoCIII, which antagonizes LPL action, may underlie these effects [9]. It is plausible that K-877 more preferentially affects genes governing TG metabolism than those governing HDL metabolism. These phenomena of differential effects between K-877 and fenofibrate were reported for other hepatic genes in mice and humans [15].

K-877 appears to increase LDL-C, albeit weakly, in the present study. However, this LDL-C raising effect was not accompanied by increases in apoB or non-HDL-C levels, suggesting that K-877 increases LDL-C not by increasing the particle number of LDL, but rather by increasing the cholesterol content of LDL. It is important to note that LDL consists of multiple classes with different atherogenic potentials. It is well known that an increase in small, dense LDL is associated with an increased risk for developing CHD. The results of the subfractionation of LDL by HPLC show that the large and medium LDL subfractions increased in the current study, which are conceivably less atherogenic. On the other hand, the more atherogenic small and very small LDL decreased. A similar increase in LDL-C was reported for LY518674, which is also a potent and selective PPARα agonist, in patients with atherogenic dyslipidaemia [16]. As in the case with LY518674, the increase in LDL-C with K-877 positively correlated with baseline TG. This relationship can be largely explained by the precursor-product relationship between VLDL and LDL; LDL is produced as an ultimate product of the lipolytic conversion of VLDL [17]. Further studies are warranted to define the mechanisms underlying the variability of the effects of

Table 2
Change fromWeek 0 of key secondary endpoint (Per-protocol-set).

				K-877								Fenofibrate	
		Placebo		0.025 mg BID		0.05 mg BID		0.1 mg BID		0.2 mg BID		100 mg QD	
		n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
TC, mmol/L	Week 0	35	5.82 (0.79)	34	5.74 (0.95)	37	5.61 (1.01)	36	5.81 (1.03)	36	6.20 (1.00)	36	6.00 (1.08)
	% Change		0.1 (9.8)[#]		–2.7 (11.4)		–6.5 (11.9)[**†]		–7.0 (11.3)[***†]		–5.3 (12.9)[*]		–6.0 (11.8)[**†]
non HDL-C, mmol/L	Week 0	35	4.78 (0.77)	34	4.70 (0.93)	37	4.56 (0.95)	36	4.75 (0.94)	36	5.13 (0.98)	36	4.96 (1.01)
	% Change		0.7 (12.8)[##]		–5.8 (12.4)[*]		–11.8 (14.0)[***†††]		–12.2 (13.8)[***†††]		–10.5 (14.2)[***†††]		–10.1 (14.2)[***††]
VLDL-C,[a] mmol/L	Week 0	35	0.98 (0.30)	34	0.92 (0.22)	37	0.97 (0.33)	36	0.96 (0.34)	36	1.00 (0.34)	36	0.96 (0.21)
	% Change		13.3 (38.9)[###]		–24.3 (24.0)[***†††]		–37.3 (26.7)[***†††]		–43.8 (24.0)[***†††##]		–48.4 (27.5)[***†††##]		–25.8 (29.7)[***†††]
LDL-C,[a] mmol/L	Week 0	35	3.32 (0.76)	34	3.30 (0.85)	37	3.16 (0.95)	36	3.39 (0.98)	36	3.76 (0.93)	36	3.47 (0.91)
	% Change		–6.3 (16.2)[*#]		8.9 (21.3)[*†]		8.3 (29.4)[†]		5.0 (28.0)		7.4 (26.5)[†]		5.3 (23.4)[†]
RemL-C, mmol/L	Week 0	35	0.56 (0.30)	34	0.54 (0.32)	37	0.53 (0.24)	36	0.50 (0.24)	36	0.54 (0.35)	36	0.55 (0.27)
	% Change		38.7 (75.7)[**###]		–32.3 (33.8)[***†††]		–42.8 (29.4)[***†††]		–48.3 (28.1)[***†††]		–50.1 (31.8)[***†††]		–31.8 (35.0)[***†††]
apoAI, mg/dL	Week 0	35	127.3 (13.9)	34	128.6 (13.5)	37	127.5 (11.1)	36	127.9 (13.4)	36	126.7 (12.4)	36	125.4 (11.6)
	% Change		–1.0 (8.0)[##]		2.5 (9.9)		4.6 (9.9)[**†]		6.0 (9.7)[***††]		8.6 (13.9)[***†††]		5.6 (8.0)[***††]
apoAII, mg/dL	Week 0	35	29.75 (3.18)	34	29.24 (3.01)	37	29.65 (3.41)	36	30.07 (3.43)	36	29.94 (3.05)	36	28.79 (3.15)
	% Change		–1.5 (6.5)[###]		9.9 (10.5)[***††##]		14.4 (11.5)[***†††]		21.0 (16.2)[***†††]		30.0 (22.1)[***†††##]		20.1 (13.0)[***†††]
apoB, mg/dL	Week 0	35	114.7 (19.8)	34	114.8 (21.1)	37	110.0 (20.9)	36	115.9 (22.5)	36	123.8 (20.0)	36	118.9 (22.5)
	% Change		–2.0 (9.9)		–1.4 (13.6)		–8.9 (13.6)[***†]		–7.8 (15.0)[**]		–8.1 (11.6)[***]		–5.7 (14.4)[*]
apoB48, μg/mL	Week 0	35	11.54 (7.77)	34	11.31 (7.18)	37	10.67 (5.85)	36	11.73 (6.83)	36	10.40 (7.80)	36	12.26 (7.61)
	% Change		54.6 (171.1)[###]		–28.4 (43.1)[***†††]		–43.1 (47.1)[***†††]		–55.9 (25.6)[***†††]		–51.2 (29.3)[***†††]		–37.9 (42.9)[***†††]
apoCIII, mg/dL	Week 0	35	14.93 (4.59)	34	14.88 (3.46)	37	15.18 (4.72)	36	15.22 (5.63)	36	14.32 (4.37)	36	15.94 (4.86)
	% Change		7.9 (27.4)[###]		–22.2 (14.4)[***†††]		–29.0 (18.9)[***†††]		–34.6 (17.7)[***†††]		–33.4 (19.2)[***†††]		–27.2 (18.9)[***†††]
Glucose, mmol/L	Week 0	35	6.20 (1.15)	34	6.12 (1.06)	37	5.88 (0.87)	36	6.29 (1.19)	36	6.07 (1.27)	36	6.16 (1.48)
	Change		0.20 (0.78)[##]		0.19 (0.45)[*##]		–0.04 (0.49)		–0.28 (0.64)[*††]		–0.06 (0.60)		–0.32 (1.08)[††]
Insulin, pmol/L	Week 0	34	78.46 (45.99)	31	77.94 (41.79)	37	73.07 (35.35)	36	122.87 (151.86)	35	78.26 (72.31)	34	80.01 (45.97)
	Change		5.45 (24.77)		4.57 (35.51)		–8.58 (25.18)[*]		–55.50 (145.21) [*†††##]		–14.52 (47.75)		–3.45 (59.49)
HOMA-R	Week 0	34	3.22 (2.29)	31	3.05 (2.07)	37	2.76 (1.42)	36	5.25 (7.58)	35	3.00 (2.85)	34	3.24 (2.31)
	Change		0.46 (1.49)		0.24 (1.72)		–0.33 (0.93)[*]		–2.65 (7.35)[*†††##]		–0.50 (2.02)		–0.38 (2.76)
Log FGF21, Log(pg/mL)	Week 0	35	5.74 (0.57)	34	6.01 (0.76)	37	5.74 (0.50)	36	5.93 (0.42)	36	5.94 (0.73)	36	5.96 (0.56)
	Change		0.13 (0.36)[*]		0.15 (0.59)		0.66 (0.62)[***†††###]		0.42 (0.46)[***†#]		0.78 (0.54)[***†††###]		0.16 (0.45)[*]

[*]$p < 0.05$, [**]$p < 0.01$, [***]$p < 0.001$ vs Week 0 (one sample *t*-test).
[†]$p < 0.05$, [††]$p < 0.01$, [†††]$p < 0.001$ vs Placebo (two sample *t*-test).
#$p < 0.05$, ##$p < 0.01$, ###$p < 0.001$ vs Fenofibrate 100 mg/day (two sample *t*-test).
[a] Ultracentrifugation.

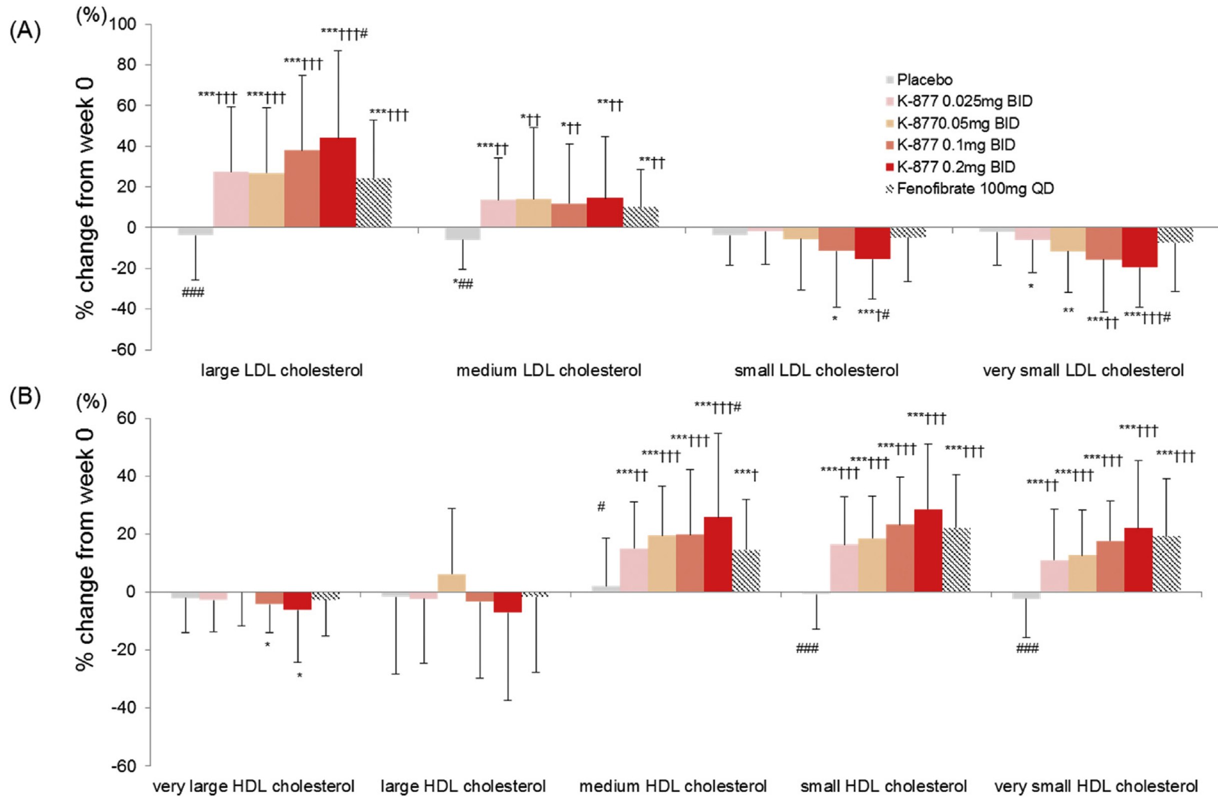

Fig. 2. Subclass analysis of lipoproteins by HPLC (A) LDL, (B) HDL. Mean. Error bars represent standard deviation (SD). *p < 0.05, **p < 0.01, ***p < 0.001 vs Week 0 (one sample *t*-test). †p < 0.05, ††p < 0.01, †††p < 0.001 vs Placebo (two sample *t*-test). #p < 0.05, ##p < 0.01, ###p < 0.001 vs Fenofibrate 100 mg/day (two sample *t*-test).

Table 3
Summary of adverse events (Safety-analysis-set).

	Placebo	K-877				Fenofibrate
		0.025 mg BID	0.05 mg BID	0.1 mg BID	0.2 mg BID	100 mg QD
	n = 36	n = 37	n = 37	n = 38	n = 39	n = 37
AEs	17 (47.2)	21 (56.8)	12 (32.4)	18 (47.4)	16 (41.0)	21 (56.8)
Discontinuations because of AEs	0	0	0	0	0	1 (2.7)
Seasonal allergy	2 (5.6)	2 (5.4)	4 (10.8)	3 (7.9)	3 (7.7)	2 (5.4)
Nasopharyngitis	0	2 (5.4)	3 (8.1)	4 (10.5)	2 (5.1)	5 (13.5)
Upper respiratory tract inflammation	3 (8.3)	2 (5.4)	1 (2.7)	2 (5.3)	2 (5.1)	2 (5.4)
AEs leading to withdrawal	0	0	0	0	0	1 (2.7)
Serious AEs	0	1 (2.7)	0	0	1 (2.6)	0
ADRs	3 (8.3)	2 (5.4)	1 (2.7)	2 (5.3)	2 (5.1)	4 (10.8)
AST > upper limit of normal	3 (8.3)	0	2 (5.4)	3 (7.9)	0	9 (24.3)
ALT > upper limit of normal	5 (13.9)	2 (5.4)	0	4 (10.5)	1 (2.6)	5 (13.5)
CK > upper limit of normal × 2	1 (2.8)	0	0	0	0	0
sCr > 1.5 mg/dL	0	0	0	0	1 (2.6)	0
Fibrinogen < lower limit of normal	0	0	0	0	1 (2.6)	0

The number (percentage) of patients.
AE: adverse event, ADR: adverse drug reaction, sCr: serum creatinine.

fibrates on LDL-C.

With regard to the effects on HDL-C, the K-877- and/or fenofibrate-induced increases in HDL-C were accounted for by the changes in the three smaller subpopulations of HDL (medium, small, and very small). Generally, the smaller subpopulation of particles such as HDL_3 is more closely associated with protection against CHD [18]. Therefore, the current findings, that K-877 specifically increased the smaller subpopulations of HDL, support the possibility that these K-877-induced alterations in HDL are protective against atherosclerosis.

The effects of K-877 on FGF21 are also noteworthy. FGF21 is a member of FGF family, which has insulin-sensitizing activity and is produced mainly by the liver in response to starvation and/or ketogenic diets [19]. Fibrates increase plasma FGF21 by activating PPARα [20,21]. Thus, it is conceivable that effects of K-877 on the metabolism of glucose and lipids are mediated at least in part by the effect of FGF21. Based on our results, K-877 increases FGF21 more preferentially than fenofibrate. However, we did not find a significant difference in body weight and other parameters for glucose tolerance. Therefore, the magnitude of the preferential increase of FGF21 by K-877 may not be sufficient to cause favourable metabolic alterations in terms of glucose tolerance.

In general, both K-877 and fenofibrate were well tolerated without obvious safety concerns. Fibrates are known to increase plasma levels of homocysteine and creatinine, both of which potentially mitigate the other anti-atherogenic effects of fibrates [22,23].

Based on the present results, K-877 did not increase plasma creatinine, and only increased plasma homocysteine modestly at the 0.2 mg BID concentration (Table S3). Therefore, K-877 may be more favourable than fenofibrate in terms of anti-atherogenecity. These effects of K-877 support the SPPARMα concept that separates the benefit of the PPARα agonists from their unfavorable effects. Furthermore, K-877 significantly decreased plasma concentrations of liver enzymes (ALT and γ-GT), while fenofibrate did not (Table S3). Recently, the alleviation of hepatic steatosis by GFT505, a PPARα/δ dual agonist, has been reported in mice [24]. Conceivably, K-877 may have comparable efficacy and can be used to treat NAFLD and/or NASH to inhibit the development of hepatocellular carcinoma.

This study has several potential limitations. First, we excluded patients who were currently receiving treatments for dyslipidaemia, including statins. Moreover, there were several strict exclusion criteria for liver impairment, renal impairment, and diabetes mellitus, all of which are frequently observed in patients with dyslipidaemia in clinical practice. Second, the duration of the treatment period was 12 weeks, which is a relatively short for the evaluation of chronic diseases. A longer study period will be needed to investigate the risk to benefit balance. Third, our study population consisted of only Japanese people; thus, the study results may not be applicable to patients of other ethnicities. Finally, fenofibrate 100 mg, which was used as an active comparator in this study, was half the maximal dose that is allowed for use. Thus, higher doses of fenofibrate will be needed as a point of comparison to demonstrate the superiority of K-877 over fenofibrate.

In conclusion, K-877 improved TG, HDL-C, and other lipid parameters in Japanese patients with dyslipidaemia with high TG and low HDL-C levels. Unlike other PPARα agonists, K-877 reduced the plasma levels of liver enzymes (i.e. ALT and γ-GT) and did not adversely affect serum creatinine or homocysteine. Taken together, these results strongly support that K-877 can be developed as a SPPARMα with an excellent efficacy and safety profile.

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Conflict of interest

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2016.02.029.

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