Supplementary materials

Supplemental table S1. Comparison of selected compounds that are chemically 'fibrates'

	Pemafibrate	Fenofibrate	Gemfibrozil	Bezafibrate
Structure	Branched fibric acid derivative with 2-aminobenzoxazole ring and phenoxyalkyl chain[1]	Straight chain fibric acid derivative[2]	Straight chain non-halogenated phenoxypentanoic acid[3]	Straight chain monocarboxylic acid amide[4]
Mechanism of action	SPPARMα[5]	PPARα agonist[2]	Unknown[3]	Pan-PPAR agonist[6]
Active moiety	Pemafibrate[7]	Fenofibric acid[2]	Gemfibrozil[3]	Bezafibrate[4]
Selectivity for PPARα/PPARγ	5,375-fold[1]	10-fold[1]	No published data	1.2-fold[1]
Potency: PPARα EC50 (μM)	0.0008[1]	30[1]	No published data	50[1]
Inhibition of enzymes	None Reported[7]	CYP2C8, CYP2C19, CYP2A6, CYP2C9[2]	CYP2C8, CYP2C9, CYP2C19, CYP1A2, UGTA1, UGTA3 and OATP1B1[3]	None Reported[4]
Contraindicated concomitant medications	None[5]	None[2]	repaglinide, dasabuvir, selexipag, simvastatin[3]	MAOi, Statins in patients at risk of myopathy[4]
Major route of elimination	Liver	Kidney	Kidney	Kidney
Urinary excretion	14.5%[1]	64%[1]	70%[1]	69%[1]
Renal Impairment	No dose adjustment[7]	[2]Severe/Dialysis: Contraindicated Moderate: Dose adjustment	[3]Severe: Contraindicated Moderate: Dose adjustment Mild: Dose adjustment	[4]Severe/Dialysis: Contraindicated Moderate: Dose adjustment
Cardiovascular Outcome Trials	Ongoing PROMINENT[8] trial in primary and secondary prevention	FIELD[9]: Missed primary endpoint ACCORD[10]: Missed primary endpoint	HHS[11]: 34% reduction in myocardial infarction and cardiovascular death in primary prevention VA-HIT[12]: 24% reduction in myocardial infarction, stroke and cardiovascular death in secondary prevention	BIP[13]: Missed primary endpoint

1. Yamashita, S., Masuda, D., & Matsuzawa, Y. (2019). Clinical Applications of a Novel Selective PPARα Modulator, Pemafibrate, in Dyslipidemia and Metabolic Diseases. Journal of Atherosclerosis and Thrombosis, 26(5), 389–402. https://doi.org/10.5551/jat.48918
2. Fenofibrate US Prescribing Information
3. Gemfibrozil EU Summary of Product Characteristics
4. Bezafibrate XL EU Summary of Product Characteristics

5. Fruchart, J.-C., Santos, R. D., Aguilar-Salinas, C. A., Aikawa, M., Al Rasadi, K., Amarenco, P., Barter, P. J., Ceska, R., Corsini, A., Després, J., Duriez, P., Eckel, R. H., Ezhov, M. V., Farnier, M., Ginsberg, H. N., Hermans, M. P., Ishibashi, S., Karpe, F., Kodama, T., … Libby, P. (2019). The selective peroxisome proliferator-activated receptor alpha modulator (SPPARMα) paradigm: conceptual framework and therapeutic potential. *Cardiovascular Diabetology*, *18*(1), 71. https://doi.org/10.1186/s12933-019-0864-7
6. Tenenbaum, A., & Fisman, E. Z. (2012). Balanced Pan-PPAR Activator Bezafibrate in Combination With Statin. Cardiovascular Diabetology, 11, 140–149.
7. Investigational Brochure: K-877 (Pemafibrate) for the reduction of triglycerides and prevention of cardiovascular outcomes. Edition 7
8. Pradhan, A. D., Paynter, N. P., Everett, B. M., Glynn, R. J., Amarenco, P., Elam, M., Ginsberg, H. N., Hiatt, W. R., Ishibashi, S., Koenig, W., Nordestgaard, B. G., Fruchart, J.-C., Libby, P., & Ridker, P. M. (2018). Rationale and design of the Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) study. *American Heart Journal*, *206*, 80–93. https://doi.org/10.1016/j.ahj.2018.09.011
9. The FIELD Investigators. (2005). Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *The Lancet*, *366*(9500), 1849–1861. https://doi.org/10.1016/S0140-6736(05)67667-2
10. ACCORD Study Group, & Ginsberg, H. N. (2010). Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus. *New England Journal of Medicine*, *362*(17), 1563–1574. https://doi.org/10.1056/NEJMoa1001282
11. Frick, M. H. (1987). Helsinki Heart Study Primary-Prevention trial with Gemfibrozil in Middle-aged men with dyslipidaemia. *New England Journal of Medicine*, *317*(20), 1237–1247.
12. Rubins, H. B., Robins, S. J., Collins, D., Fye, C. L., Anderson, J. W., Elam, M. B., Faas, F. H., Linares, E., Schaefer, E. J., Schectman, G., Wilt, T. J., & Wittes, J. (1999). Gemfibrozil for the Secondary Prevention of Coronary Heart Disease in Men with Low Levels of High-Density Lipoprotein Cholesterol. *New England Journal of Medicine*, *341*(6), 410–418. https://doi.org/10.1056/NEJM199908053410604
13. Behar, S., Brunner, D., Kaplinsky, E., Mandelzweig, L., & Benderly, M. (2000). Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease: The bezafibrate infarction prevention (BIP) study. *Circulation*, *102*(1), 21–27. https://doi.org/10.1161/01.CIR.102.1.21

Supplemental table S2. Full inclusion and exclusion criteria

Inclusion Criteria
1. Male/female subjects able to provide written, informed consent 2. Age ≥18 years 3. Subjects with or without established CVD and/or Type 2 diabetes 4. Subjects who, after treatment with stable statin therapy for at least 12 weeks prior to screening, had a screening LDL-C ≤10 mg/dL (0.259 mmol/L) above the NCEP ATP III target: • LDL-C <70 mg/dL (1.81 mmol/L) or <100 mg/dL (2.59 mmol/L) for patients with • CHD or CHD equivalent • LDL-C <130 mg/dL (3.36 mmol/L) for patients with multiple risk factors • LDL-C <160 mg/dL (4.14 mmol/L) for patients with 0-1 risk factors 5. Fasting TG levels between 175 mg/dL (1.97 mmol/L) and 500 mg/dL (5.65 mmol/L) at screening 6. HDL-C ≤50 mg/dL (1.30 mmol/L) for men and ≤55 mg/dL (1.43 mmol/L) for women (designed to exclude patients with high HDL-C concentrations) 7. Female subjects who were not pregnant, not breastfeeding and who did not plan to become pregnant during the study 8. All subjects were required to use an effective form of contraception during the study

Exclusion Criteria:
1. Use of lipid-lowering treatments other than the study drug and statins 2. Body mass index ≥40 kg/m^2 3. Homozygous familial hypercholesterolaemia or familial hypoalphalipoproteinaemia 4. Type 1 diabetes mellitus, poorly controlled T2D (glycated hemoglobin >10%), and/or use of insulin or insulin analogue treatment except for stable basal insulin therapy with a single insulin 5. Moderate or severe renal impairment (estimated glomerular filtration rate <50 mL/min/1.73m^2) 6. Serious liver dysfunction (alanine aminotransferase or aspartate aminotransferase >3 × ULN), creatine kinase >3 × ULN, hepatic insufficiency, gall bladder disease, or pancreatitis

7. History of drug or alcohol abuse
8. Myocardial infarction, artery angioplasty, bypass graft surgery, severe/unstable angina pectoris, or symptomatic cerebrovascular disease within 3 months prior to screening
9. Symptomatic heart failure (New York Heart Association class III or IV)
10. Uncontrolled hypertension (seated systolic blood pressure >160 mmHg and/or diastolic blood pressure >100 mmHg)
11. Hypersensitivity/intolerance to PPARα agonists or statins; contraindications for statins
12. History of chronic active hepatitis B or C, or human immunodeficiency virus 1 or 2 infection
13. Known muscular or neuromuscular disease
14. Active/history of neoplastic disease (excluding basal cell cancer); possible requirement for antineoplastic treatment during the study
15. Uncontrolled hypothyroidism or hyperthyroidism
16. Participation in any other clinical studies within 3 months of screening
17. Loss of >400 mL of blood during the 3 months prior to screening
18. A clinically relevant abnormal history, physical examination findings, 12-lead electrocardiogram, or laboratory values at screening that in the opinion of the Investigator could have interfered with the objectives of the study or the safety of the patient
19. High risk of non-compliance with the study protocol
20. A mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study

CHD, coronary heart disease; CVD, cardiovascular disease; TG, triglyceride; ULN, upper limit of normal

Supplemental table S3. Selected demographics and baseline values of patients with a diagnosis of diabetes

	Placebo	Pemafibrate BID			Pemafibrate QD			Total
		0.05 mg	0.1 mg	0.2mg	0.1mg	0.2mg	0.4mg	
N	**23**	**26**	**22**	**20**	**23**	**24**	**16**	**154**
Mean (SD) age (years)	59 (9.0)	62 (6.2)	64 (9.4)	63 (6.2)	57 (10.3)	63 (9.1)	61 (10.5)	61 (8.9)
Female, n (%)	5 (21.7)	9 (34.6)	8 (36.4)	8 (40.0)	9 (39.1)	9 (37.5)	6 (37.5)	54 (35.1)
BMI (SD)	32.2 (3.66)	32.3 (4.20)	29.8 (3.71)	31.4 (3.94)	32.6 (3.86)	33.1 (4.24)	32.5 (3.06)	32.0 (3.93)
HbA1c,% (mmol/mol)	6.94 (52)	6.68 (49)	6.98 (53)	6.79 (51)	6.73 (50)	7.00 (53)	6.84 (51)	6.84 (51)
Baseline Triglycerides (SD) mg/dL	271.28 (78.23)	282.77 (156.69)	271.16 (109.72)	250.43 (78.02)	270.43 (105.95)	242.73 (76.74)	316.28 (107.55)	270.59 (106.54)
Baseline Non-HDL-C (SD) mg/dL	127.52 (36.03)	127.79 (33.27)	124.98 (36.28)	115.08 (20.70)	125.57 (43.20)	126.58 (35.91)	128.34 (42.42)	125.23 (35.45)

BID, twice daily; QD, once daily; TG, SD, Standard Deviation; BMI, Body Mass Index.

Supplemental table S4. Primary efficacy analysis in patients with a diagnosis of diabetes

	Change from baseline to Week 12	Placebo (N=23)	Pemafibrate BID			Pemafibrate QD		
			0.05 mg (N=26)	0.1 mg (N=22)	0.2 mg (N=20)	0.1 mg (N=23)	0.2 mg (N=24)	0.4 mg (N=16)
TG	Percent	+28.2% (8.03); 95% CI 12.3, 44.1						
	Placebo-adjusted		**-46.4 (10.82); p<0.001*†**	**-65.3 (11.23); p<0.001*†**	**-59.9 (11.62); p<0.001*†**	**-42.0 (11.34); p<0.001*†**	**-47.4 (11.08); p<0.001*†**	**-46.39 (12.50); p<0.001*†**
Non HDL-C	Percent	+8.9% (5.04); 95% CI -1.03, +18.9						
	Placebo-adjusted		-12.8 (6.43); P=0.048* p=0.200†	-17.2 (6.68); P=0.011* p=0.052†	-9.83 (7.04); P=0.165* p=0.552†	-4.83 (6.70); p=0.472* p=0.955†	-14.4 (6.65); p=0.032* p=0.139†	-10.0 (7.37); p=0.176* p=0.579†

Values are presented as 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 versus placebo (*unadjusted; †adjusted for multiplicity [Dunnett's test]). Significant adjusted treatment differences ($p<0.05$) are highlighted in bold. *BID, twice daily; MITT, modified intent-to-treat; MMRM, mixed model repeated measures; QD, once daily; TG, triglyceride*

Supplemental table S5. Percent treatment difference (pemafibrate vs placebo) in lipoprotein particles by ion mobility analysis from baseline to Week 12

nmol/L	Particle size (min-max), Angstroms	Pemafibrate BID			Pemafibrate QD		
		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)
n		53	51	51	51	55	54
HDL 3 and 2a	76.5-105.0	-2.14 (2.66); p=0.421	+0.10 (2.69); p=0.969	+0.80 (2.69); p=0.765	+0.28 (2.68); p=0.918	+1.41 (2.63); p=0.594	+1.55 (2.64); p=0.558
HDL 2b	105.0-145.0	**-7.29 (3.32); p=0.029**	**-9.72 (3.35); p=0.004**	**-8.21 (3.35); p=0.015**	-3.25 (3.36); p=0.334	-5.92 (3.29); p=0.073	**-8.91 (3.31); p=0.007**
Midzone between HDL and LDL	145.0-180.0	-6.16 (4.08); p=0.132	-7.85 (4.12); p=0.057	-1.95 (4.12); p=0.637	-2.84 (4.11); p=0.491	-6.00 (4.04); p=0.138	-6.41 (4.06); p=0.115
LDL IVc	180.0-190.0	**-13.8 (5.52); p=0.013**	**-21.0 (5.56); p<0.001**	-9.50 (5.57); p=0.089	**-13.5 (5.56); p=0.015**	**-15.1 (5.46); p=0.006**	**-20.2 (5.48); p<0.001**
LDL IVb	190.0-199.0	**-25.9 (5.29); p<0.001**	**-35.2 (5.32); p<0.001**	**-31.8 (5.35); p<0.001**	**-23.9 (5.32); p<0.001**	**-30.5 (5.22); p<0.001**	**-35.9 (5.25); p<0.001**
LDL IVa	199.0-204.9	**-28.7 (7.62); p<0.001**	**-39.8 (7.63); p<0.001**	**-48.2 (7.69); p<0.001**	**-32.4 (7.66); p<0.001**	**-38.0 (7.50); p<0.001**	**-45.6 (7.53); p<0.001**
LDL IIIb	204.9-208.2	**-16.8 (7.42); p=0.024**	**-31.8 (7.44); p<0.001**	**-41.6 (7.47); p<0.001**	**-23.5 (7.44); p=0.002**	**-26.9 (7.30); p<0.001**	**-35.1 (7.33); p<0.001**
LDL IIIa	208.2-214.1	-2.15 (6.99); p=0.758	-6.74 (7.03); p=0.338	**-15.6 (7.05); p=0.027**	-4.22 (7.03); p=0.548	-6.36 (6.89); p=0.357	-5.39 (6.94); p=0.438
LDL IIb	214.1-220.0	+8.63 (7.88); p=0.275	**+26.66 (7.96); p<0.001**	**+23.53 (7.97); p=0.003**	+14.46 (7.96); p=0.070	**+17.90 (7.81); p=0.022**	**+25.30 (7.86); p=0.001**
LDL IIa	220.0-224.6	+16.79 (9.62); p=0.082	**+49.66 (9.72); p<0.001**	**+53.57 (9.72); p<0.001**	**+23.86 (9.71); p=0.014**	**+36.64 (9.53); p<0.001**	**+43.51 (9.60); p<0.001**
LDL I	224.6-233.3	**+20.10 (9.39); p=0.033**	**+47.83 (9.48); p<0.001**	**+57.95 (9.48); p<0.001**	**+26.42 (9.47); p=0.006**	**+38.91 (9.29); p<0.001**	**+43.51 (9.35); p<0.001**
IDL 2	233.3-250.0	+10.25 (6.54); p=0.118	**+20.61 (6.60); p=0.002**	**+31.28 (6.61); p<0.001**	**+16.72 (6.60); p=0.012**	**+17.73 (6.47); p=0.006**	**+17.81 (6.51); p=0.006**
IDL 1	250.0-296.0	-5.20 (5.24); p=0.322	-4.42 (5.28); p=0.402	+1.53 (5.28); p=0.772	-0.70 (5.27); p=0.895	-4.55 (5.17); p=0.380	-3.07 (5.19); p=0.554
Small VLDL	296.0-335.0	-7.29 (5.20); p=0.162	**-12.1 (5.23); p=0.022**	**-11.3 (5.24); p=0.032**	-6.00 (5.24); p=0.252	**-12.9 (5.13); p=0.012**	**-11.3 (5.16); p=0.029**

Inter-mediate VLDL	335.0-424.0	**-21.1 (6.72); p=0.002**	**-34.4 (6.76); p<0.001**	**-41.6 (6.77); p<0.001**	**-18.8 (6.76); p=0.006**	**-34.3 (6.64); p<0.001**	**-32.6 (6.66); p<0.001**
Large VLDL	424.0-527.0	**-35.4 (9.48); p<0.001**	**-54.3 (9.56); p<0.001**	**-65.0 (9.57); p<0.001**	**-34.3 (9.55); p<0.001**	**-53.5 (9.39); p<0.001**	**-49.7 (9.43); p<0.001**
Diameter of the major LDL particle (Angstrom)	NA	**+1.47 (0.41); p<0.001**	**+2.65 (0.42); p<0.001**	**+3.39 (0.42); p<0.001**	**+1.80 (0.42); p<0.001**	**+2.32 (0.41); p<0.001**	**+2.75 (0.41); p<0.001**

Values are least-squares differences (pemafibrate versus placebo) using the ANCOVA model with fixed effects of treatment, country, and baseline. Significant treatment differences ($p<0.05$) are highlighted in bold. *BID, twice daily; IDL, intermediate density; LOCF, last observation carried forward; QD, once daily*

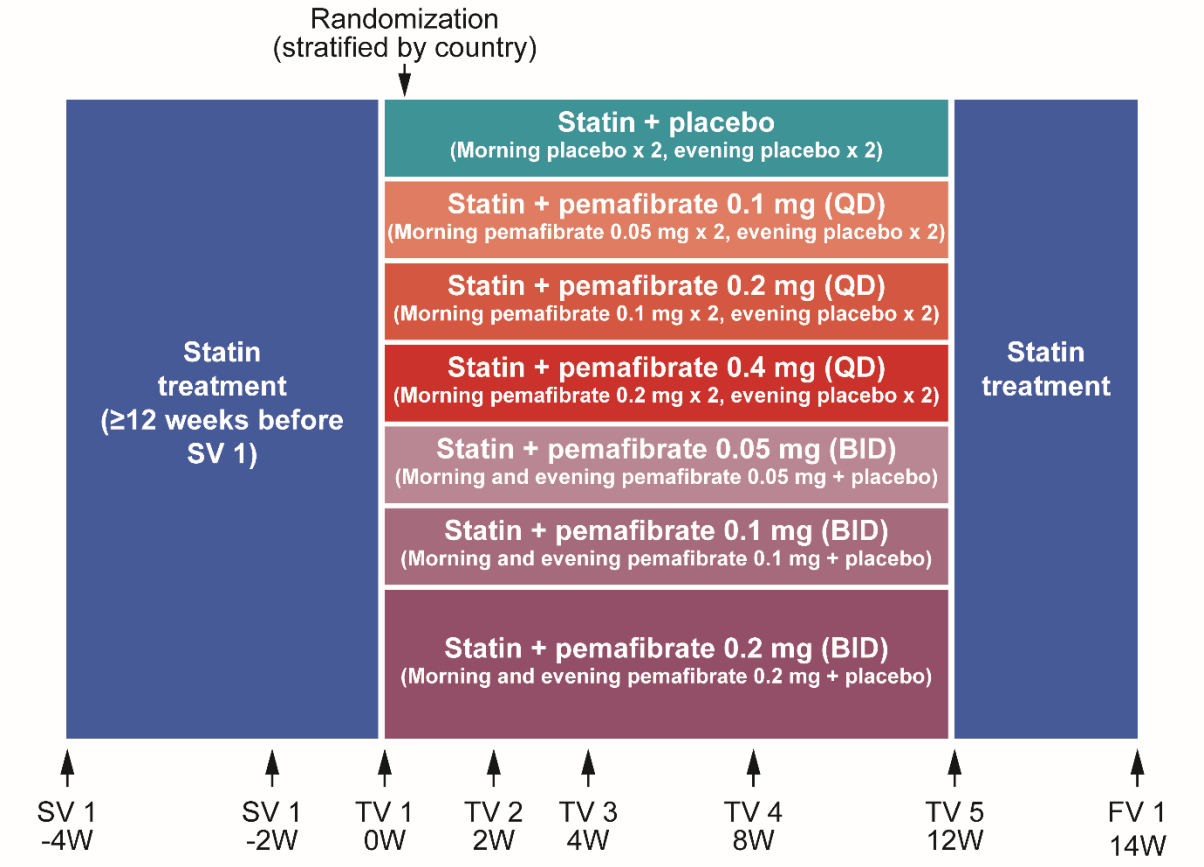
Supplemental table S6. Summary of adverse events

	Placebo	**Pemafibrate BID**			**Pemafibrate QD**			**Total**
		0.05 mg	**0.1 mg**	**0.2mg**	**0.1mg**	**0.2mg**	**0.4mg**	
N (%)	**60**	**57**	**58**	**57**	**58**	**58**	**59**	**407**
TEAE	34 (56.7)	29 (50.9)	21 (36.2)	30 (52.6)	22 (37.9)	29 (50.0)	30 (50.8)	195 (47.9)
TEAE severity:								
Mild	19 (31.7)	22 (38.6)	13 (22.4)	21 (36.8)	17 (29.3)	21 (36.2)	17 (28.8)	130 (31.9)
Moderate	15 (25.0)	6 (10.5)	8 (13.8)	9 (15.8)	3 (5.2)	8 (13.8)	11 (18.6)	60 (14.7)
Severe	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	2 (3.4)	0 (0.0)	2 (3.4)	5 (1.2)
Treatment-emergent SAEs	0 (0.0)	0 (0.0)	1 (1.7)	1 (1.8)	3 (5.2)	2 (3.4)	2 (3.4)	9 (2.2)
TEAE leading to study withdrawal	1 (1.7)	0 (0.0)	2 (3.4)	2 (3.5)*	3 (5.2)	0 (0.0)	1 (1.7)	9 (2.2)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Liver and muscle function								
ALT >3 x ULN	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.6)	1 (1.8)	0 (0.0)	1 (1.7)	4 (1.0)
ALT >5 x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	1 (1.7)	2 (0.5)
AST >3 x ULN	1 (1.7)	0 (0.0)	0 (0.0)	1 (1.8)	1 (1.8)	1 (1.7)	0 (0.0)	4 (1.0)
AST >5 x ULN	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	2 (0.5)
CK >5 x ULN	2 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	3 (0.8)
CK >10 x ULN	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	2 (0.5)
ALP >1.5 x ULN	1 (1.7)	1 (1.8)	0 (0.0)	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	4 (1.0)
Bilirubin >2 × ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

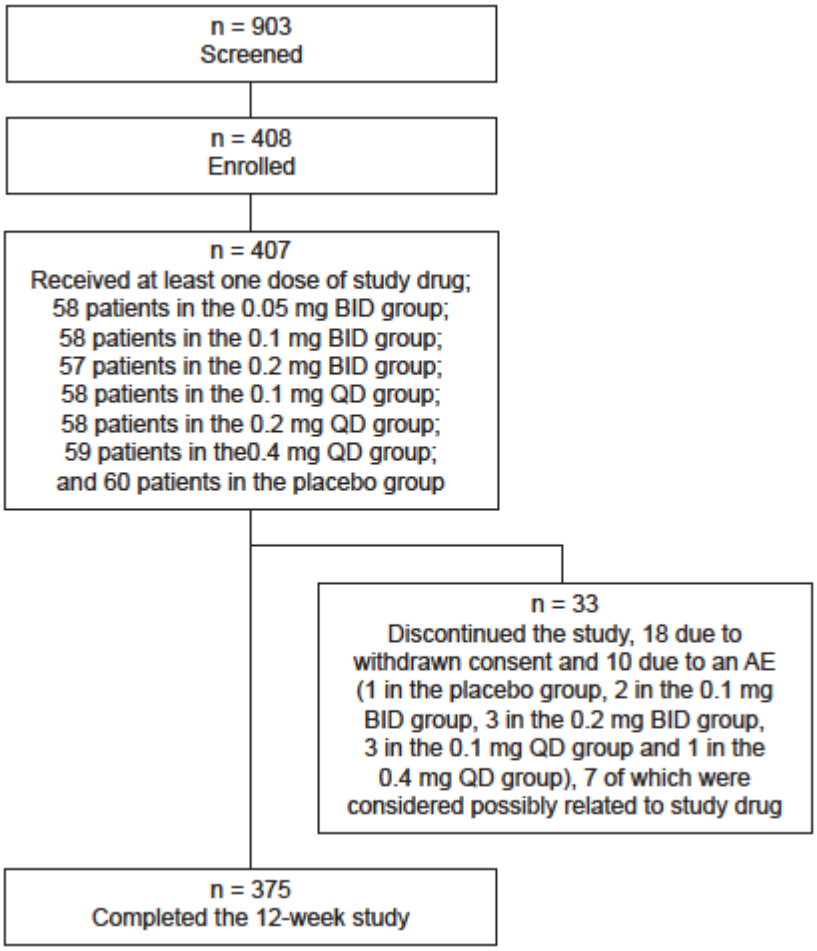
TEAEs were defined as adverse events with a start date on or after the first dose of study drug, or occurring prior to the first dose and worsening in severity during the treatment period. All values are expressed as patient number (percent). *1 patient in the 0.2mg BID had an increase in CK > 5 x ULN after randomization but before receiving treatment and was withdrawn due to an adverse event. *ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; CK, creatine kinase;*

SAE, serious adverse event; TEAE, treatment-emergent adverse event; ULN, upper limit of normal; QD, once daily

Supplemental Figure S1. Study design



Supplemental Figure S2. Flow chart of included and excluded patients



BID, twice daily; TEAE, treatment-emergent adverse event; QD, once daily

A1. Contributions to the study and the manuscript

Conception: Kowa, as Sponsor of the trial

Study Design: Henry Ginsberg and John Kastelein, in discussion with Neil Hounslow and Yusuke Senko. Prof. Kastelein was invited to author the paper but declined.

Execution: Medpace Europe: Faisal Zaman (Project Manager), Alastair Sword (Statistician), and Ursula Schlichtiger (Medical Monitor) whose contribution is gratefully acknowledged.

Principal Investigator: John Kastelein whose contribution is gratefully acknowledged.

Data Acquisition: Kees Hovingh, Pawel Bogdanski, Richard Ceska, Akos Kalina, Roman A. Libis, Tatiana V. Supryadkina, and other investigators listed in section A2.

Data analysis: Alastair Sword of Medpace Europe under the oversight of Hideki Suganami

Data interpretation: Henry Ginsberg, Kees Hovingh, Hideki Suganami

Drafting of manuscript: Jackie Read of GK Pharmacomm Ltd whose contribution is gratefully acknowledged.

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A3. Clinical laboratory and lipoprotein analysis

Routine laboratory tests were performed using standardized methods at central laboratories. Blood and urine tests were performed by Medpace Reference Laboratories (MRL Cincinnati, Ohio, USA or Leuven, Belgium). LDL-C and HDL-C were determined by enzymatic methods from serum samples using the method of beta-quantification with calibration directly traceable to CDC reference procedures. Remnant cholesterol (VLDL-C attached to both apoB100 and apoB48) was calculated by measuring cholesterol in the >1.006 fraction obtained from preparative ultracentrifugation and subtracting this value from total cholesterol values. Serum levels of TGs, total cholesterol, serum creatinine, homocysteine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin, and creatine kinase were measured by photometry. Non-HDL-C levels were calculated by subtracting HDL-C from total cholesterol. ApoAI, apoAII, apoB48, apoB100 (total apoB was sum of apoB48 and apoB100), apoCII, and apoCIII were measured by turbidometry and nephelometry. Ion mobility analysis was carried out at UCSF Benioff Children's Hospital, Oakland, California, USA. Lipoprotein particle concentrations and LDL peak diameter were measured in duplicate by gas-phase electrophoresis (ion mobility) as previously described (1), with a modified procedure for initially separating the lipoproteins from other plasma proteins (2). Lipoprotein subfraction intervals were defined as previously described (3).

A4. Statistical analyses

The primary objective was to evaluate the percent reduction in TG and non-HDL-C (co-primary endpoints) from baseline to Week 12 with pemafibrate versus placebo. The primary analysis population, used for all analyses presented, was the modified intent-to-treat population (patients receiving at least one dose of the study drug, who had a baseline value

and at least one efficacy measure). Analysis of the co-primary endpoint was performed at Weeks 2, 4, 8, and 12 using a restricted maximum likelihood mixed model for repeated measures with fixed categorical effects of treatment, week, treatment-by-week interaction, and country, and a continuous fixed covariate for baseline non-HDL-C or TG levels. Pairwise comparisons between each pemafibrate dose and placebo were performed and the superiority of each pemafibrate treatment group versus placebo was controlled by Dunnett's test as a multiple comparison method.

An alternative ANCOVA repeated measures analysis was performed on the co-primary endpoints using values from Weeks 4, 8, and 12, and was repeated on values from Weeks 8 and 12. This analysis included fixed categorical effects of treatment, week, treatment by-week interaction, and country, as well as a continuous fixed covariate for baseline TG or non-HDL-C level. Within-patient errors were estimated using a compound symmetry structure.

A sensitivity analysis was performed using fixed effects ANCOVA on the percent change from baseline to Week 12 using the last observation carried forward (LOCF) method for missing values, without Dunnett's test. This method was also used for the analysis of secondary lipid endpoints, and the analysis of serum creatinine and log-transformed homocysteine concentrations.

Reference List

1. Caulfield MP, Li S, Lee G, Blanche PJ, Salameh WA, Benner WH, et al. Direct determination of lipoprotein particle sizes and concentrations by ion mobility analysis. Clin Chem 2008;54:1307-1316
2. Mora S, Caulfield MP, Wohlgemuth J, Chen Z, Superko HR, Rowland CM, et al. Atherogenic lipoprotein subfractions determined by ion mobility and first cardiovascular events after random allocation to high-intensity statin or placebo: the Justification for the Use of Statins in Prevention (JUPITER) Trial. Circulation 2015;132:2220-2229
3. Musunuru K, Orho-Melander M, Caulfield MP, Li S, Salameh WA, Reitz RE, et al. Ion mobility analysis of lipoprotein subfractions identifies three independent axes of cardiovascular risk. Arterioscler Thromb Vasc Biol 2009;29:1975-1980