Rationale and design of the Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) study☆

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Observational, genetic, and experimental data indicate that triglyceride rich lipoproteins (TRLs) likely participate causally in atherothrombosis. Yet, robust clinical trial evidence that triglyceride (TG) lowering therapy reduces cardiovascular events remains elusive. The selective peroxisome proliferator-activated receptor alpha modulator (SPPARM-α), pemafibrate, will be used to target residual cardiovascular risk remaining after treatment to reduce low-density lipoprotein cholesterol (LDL-C) in individuals with the dyslipidemia of type 2 diabetes mellitus (T2). The PROMINENT study will randomly allocate approximately 10,000 participants with T2D, mild-to-moderate hypertriglyceridemia (TG: 200–499 mg/dl; 2.26–5.64 mmol/l) and low high-density lipoprotein cholesterol levels (HDL-C: ≤40 mg/dl; 1.03 mmol/l) to either pemafibrate (0.2 mg twice daily) or matching placebo with an average expected follow-up period of 3.75 years (total treatment phase 5 years; 24 countries). At study entry, participants must be receiving either moderate-to-high intensity statin therapy or meet specified LDL-C criteria. The study population will be one-third primary and two-thirds secondary prevention (established cardiovascular disease). The primary endpoint is a composite of nonfatal myocardial infarction, nonfatal ischemic stroke, hospitalization for unstable angina requiring urgent coronary revascularization, and cardiovascular death. This event-driven study will complete when 1092 adjudicated primary endpoints have accrued with at least 200 occurring in women. Statistical power is at least 90% to detect an 18% reduction in the primary endpoint. Pre-specified secondary and tertiary endpoints include all-cause mortality, hospitalization for heart failure, new or worsening peripheral artery disease, new or worsening diabetic retinopathy and nephropathy, and change in biomarkers including select lipid and non-lipid biomarkers, inflammatory and glycemic parameters. (Am Heart J 2018;206:80-93.)

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Mild to moderate hypertriglyceridemia is particularly common in patients with insulin resistant conditions such as metabolic syndrome and type 2 diabetes (T2D),[1-3] yet current treatment guidelines do not recommend whether elevated triglycerides should be treated in order to decrease CVD events and to which target levels.[4] This situation results in large part from lack of definitive cardiovascular (CV) outcomes data demonstrating that reducing triglycerides (TGs) lowers cardiovascular events.[5] Nonetheless, a growing body of evidence has emerged to support triglyceride-rich lipoproteins (TRLs) as instigators of atherosclerosis. With escalating rates of diabetes, obesity, and cardiovascular disease especially in the developing world, appropriate management of hypertriglyceridemia is an unresolved issue among strategies for reducing residual cardiovascular risk.[6] Indeed, CVD deaths are projected to exceed 23 million deaths annually by 2030, and low to middle-income

countries will bear much of this burden (~80% of CVD deaths) owing to increasing rates of obesity, diabetes, and dyslipidemia.[7,8] The PROMINENT study will test the hypothesis that TG-lowering with the selective peroxisome proliferator activator modulator-α (SPPARM-α) pemafibrate reduces cardiovascular events in T2D patients with mild-to-moderate hypertriglyceridemia and low levels of HDL cholesterol (HDL-C).

Rationale

Role of TRLs in atherogenesis

Although low-density lipoprotein cholesterol (LDL-C) remains unquestionably the chief priority in lipid management, emerging secondary targets such as subclinical inflammation and hypertriglyceridemia have garnered considerable attention. While recent large-scale clinical trial evidence[9] supports a role for anti-inflammatory therapy, robust data for TG lowering remains elusive and has engendered controversy regarding biologic plausibility.

TGs are the major constituent of TRLs, which include chylomicrons and very-low-density lipoprotein (VLDL), synthesized and secreted from intestinal enterocytes and the liver, respectively, and metabolized in plasma. Dynamic intravascular remodeling results in a spectrum of particles (remnant lipoproteins) that are heterogeneous in size, density, lipid, and protein composition. This process primarily occurs through hydrolysis of core TGs by lipoprotein lipase (LPL),[10] yielding TRLs progressively enriched with cholesterol, depleted of TGs and reduced in size. Some of these particles undergo hepatic clearance, while those in circulation undergo further modification by LPL and hepatic lipase, with ultimate conversion to cholesterol enriched LDL. In the absence of robust commercial assays that capture TRL cholesterol concentration, plasma TG level serves as the integrated pathway biomarker most commonly used in clinical and research settings.

Despite strong and consistent epidemiologic associations between hypertriglyceridemia and incident cardiovascular events,[11] the scientific community has struggled to elucidate mechanisms by which hypertriglyceridemia per se induces atherosclerosis since, in humans, cholesterol accumulation and *not TG accumulation* characterizes atherosclerotic lesions. Thus, most conventional explanations for increased atherosclerosis susceptibility do not clarify the observed relationship between hypertriglyceridemia and increased vascular risk. However, partially hydrolyzed remnant TRLs share with LDL the potential to infiltrate the arterial intima and cause atherosclerosis by delivery of their cholesterol content.

Lipoproteins normally flux into and out of the arterial wall through transcytosis via specialized transport vesicles having diameters of 70–100 nm, thus imposing a size restriction to lipoprotein trafficking. Nascent chylomicrons and VLDL particles are too large to penetrate the endothelial barrier, but smaller remnant lipoprotein particles having undergone TG hydrolysis (ie, chylomicron remnants, smaller VLDL, and IDL) can enter the sub-intimal space. In animal studies utilizing in situ perfusion systems to quantify arterial transit and retention of different lipoprotein classes, remnant lipoprotein particles exhibit a 10-fold lower rate of *influx* compared to LDL particles but *efflux* less readily (~20-fold) in a size-dependent manner (Figure 1).[12] Thus, TRLs have prolonged residence time within the vascular space. Additionally, TRLs carry much more cholesterol per particle than LDL and can therefore promote massive cholesterol loading, foam cell formation, and the cascade of events leading to atheromatous disease.[13] These concepts and experimental findings are consistent with the seminal Zilversmit hypothesis[14,15] which proposed that TRLs act additively to LDL-C via remnant infiltration at the arterial wall.

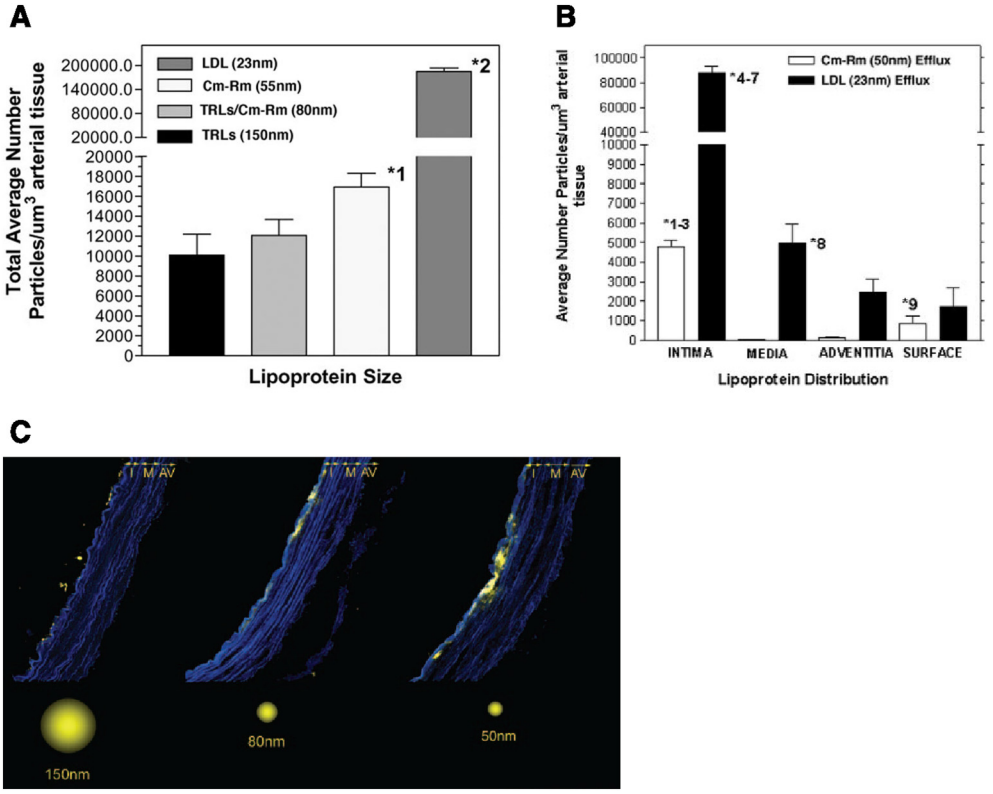
Genetic evidence for a causal role of triglycerides in atherosclerosis

Because they vary inversely, disentangling the vascular risk attributable to elevated TGs from that attributable to low HDL-C has presented an enduring challenge.[16] In prospective studies, adjustment for HDL-C and for other potential lipid intermediates, largely attenuates the association between TG concentration and cardiovascular disease.[17] While this statistical adjustment is controversial, these findings served to fuel intensive focus on potential cardiovascular benefits of therapeutic manipulation of HDL-C. However, HDL-C raising trials[18-23] have proven disappointing and accumulating evidence from human genetic studies[24-26] has now shifted the focus to a causal role for TRLs in atherothrombosis.

The evidence accrues primarily from studies of genetic variants that affect LPL activity.[27] This enzyme associates with the luminal surface of vascular endothelial cells and promotes TG hydrolysis from circulating TRLs, thus reducing plasma TRL concentration. LPL requires the cofactor apolipoprotein (apo) C-II for full activation and apo A-V for stabilization and efficient TG lipolysis.[28,29] LPL is further highly regulated by various proteins, including apo C-III as well as angiopoietin-like proteins 3 and 4, which all inhibit LPL function. Multiple lines of evidence from mutational analyses,[30-37] genome-wide association studies,[38-41] and Mendelian randomization studies[25,42-45] have shown that higher LPL pathway activity associates with reduced TGs and is linked causally to lower CVD risk.[46] The ultimate destination of LPL modified TRLs, whether cleared more efficiently, converted to less atherogenic intermediates or both, remains unclear.

Almost all genetic variation in TG metabolism identified in human genetic studies also influences at least one other lipid trait, usually HDL-C.[47] Two notable exceptions are the studies from Varbo et al[43] and Do et al[41] Varbo[43] et al used genetic variants associated either selectively with elevated TRL cholesterol, selectively with both elevated TRL cholesterol and reduced HDL-C, or selectively with

Figure 1



Comparative analysis of arterial permeability and efflux of isolated lipoprotein fractions.

reduced HDL-C alone. This study demonstrated that elevated TRLs were independently linked with increased CHD risk while low HDL cholesterol was not. Do et al[41] used multivariable Mendelian randomization to separate TG-associated effects on CHD risk from other lipid determinants. This analysis reaffirmed an isolated LDL-C genetic effect and demonstrated an isolated TG genetic effect, which was similar in magnitude to LDL-C without altering HDL-C substantially. Exactly which constituent risk factor or factors is embodied in plasma TG concentration remains to be fully elucidated, although as noted above, current best evidence implicates substrates of LPL pathway modulation. In this framework, clinical trial evidence is urgently needed to establish whether potent TG-lowering therapy confers a clinical benefit commensurate with the promise of epidemiologic and genetic work in this area.

Selective PPAR-α modulation to reduce residual cardiovascular risk

Peroxisome proliferator-activated receptors (PPARs) are nuclear hormone receptors, which bind to DNA as a heterodimer with the retinoid × receptor (RXR). When bound together these heterodimeric partners recognize specific DNA sequences in the vicinity of target genes. The three types of PPARs include α, β, and γ.[48] When activated by the binding of either an endogenous ligand or synthetic PPAR agonist (such as a fibrate for PPAR-α), heterodimerization with a ligand-activated RXR results in a conformational change, leading to the transrepression or transactivation of target genes. While a large number of genes carry response elements for PPARs, PPAR-α plays a key role in metabolic homeostasis as a regulator of lipid metabolism. Genes regulated by PPAR-α include those involved in HDL synthesis and metabolism and in VLDL turnover, among them apo A-I, A-II, A-V and C-III, LPL, scavenger receptor B1 (SR-B1), the ATP binding cassette transporters ABCA1 and ABCG1, and acyl CoA synthetase.[49-51] PPAR-α additionally regulates the transcription of LPL itself, and may act through post-translation mechanisms that affect cellular LPL trafficking.[10,52] Pharmacological PPAR-α activation may also participate in regulation of glucose homeostasis (although the underlying mechanism in humans is unknown), as well as reduction in inflammation and thrombogenesis, and improvement of vascular function.[49-51,53]

Fibrates currently in clinical use have relatively weak PPAR-α agonistic potency yet can lower TG concentrations and modestly raise HDL-C levels. Five large randomized clinical trials have evaluated the effects of

Table I. Effects of fibrates on cardiovascular events in large randomized controlled trials

Trial	Drug	Patient Characteristics	CV Outcome*	Trial Duration (years)	RR Reduction Entire Cohort	Atherogenic Dyslipidemia Subgroup	RR Reduction Subgroup‡
HHS[82,83]	Gemfibrozil	Non-HDL-C >5.2 mmol/l No CHD Men	Non-fatal MI and CHD Death	5.0	–34% ($P < .02$)	TG >204 mg/dL LDL-C/HDL-C ratio> 5.0	–71% ($P = .005$)
V A - HIT[56,84,85]	Gemfibrozil	HDL-C <1.0 mmol/l CHD Men	Nonfatal MI and CHD Death	5.1	–22% ($P = .006$)	TG >180 mg/dL <40 mg/dl	–30% ($P < .05$)
BIP[86]	Bezafibrate	Previous MI or angina Men and women	Fatal/Nonfatal MI and Sudden Death	6.2	–7% ($P = .26$)	TG ≥200 mg/dL	–40% ($P = .02$)
FIELD[54,87]	Fenofibrate	Type 2 diabetes Some patients receiving statins Men and women	MI, stroke, CVD death, coronary or carotid revascularization	5.0	–11 ($P = .035$)	TG ≥204 mg/dL HDL-C < 40 mg/dL (men) or <50 mg/dL (women)	–27% (P = .005)
ACCORD[55,56]	Fenofibrate	Type 2 diabetes CVD or >2 CVD risk factors Patients receiving simvastatin Men and women	Nonfatal MI, Nonfatal stroke, and CVD death	4.7	–8% ($P = .32$)	TG ≥204 mg/dL HDL-C ≤34 mg/dL	–29% (P < .05)

HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglycerides; T2D: Type 2 Diabetes.
To convert TG from mg/dl to mmol/l, multiply by 0.0113; to convert HDL-C from mg/dl to mmol/L, multiply by 0.0259.
* The CV outcome presented is the pre-specified primary endpoint in all trials except FIELD. In this trial, the primary endpoint (CHD) was not reported in. subgroups and the data are shown for the secondary endpoint of total CVD.
‡ Risk reductions and *P* values for subgroups when not presented in publications by trial investigators were taken from the meta-analysis of Bruckert et al, *J Cardiovas Pharmacol* 2011;57:267–272.[56]

fibrates on cardiovascular risk (Table I). Although early trials suggested benefit of fibrate monotherapy, the more recent FIELD[54] and ACCORD[55] studies showed no benefit of fenofibrate on cardiovascular outcomes in the setting of background statin therapy (unplanned drop-in of about 20% in FIELD and by design in ACCORD). Importantly, none of these trials enrolled participants on the basis of hypertriglyeridemia and in each trial, post-hoc subgroup analyses have suggested marked clinical benefit in this patient population (Table I). For example, in meta-analyses evaluating subgroup effects,[56,57] consistently greater benefit was found in patients with high TG levels or mixed dyslipidemia (elevated TG and low HDL-C). In these subgroups, fibrates appear to reduce cardiovascular risk by 28% [95% confidence interval (CI), 15% to 39%; $P < .001$] or 30% (95% CI, 19% to 40%, $P < .0001$), respectively, but only by 6% (95% CI, −2% to 13%, $P = .13$) in subjects without these lipid abnormalities.

Advances in approaches to drug discovery and appreciation of PPAR-α structure and binding properties has fostered the development of a novel generation of potent synthetic agonists. PPARs possess a large lipid-binding pocket that can encompass a range of endogenous ligands.[58] On binding, ligands of different structures can trigger distinct conformational changes in the nuclear receptor, leading to differential patterns of co-activator or co-repressor recruitment, which in turn can yield tissue- and gene-selective effects. Modulating the receptor–cofactor binding profile of the PPAR by ligands of various structure offers the opportunity to improve desirable biological effects (via transactivation of desirable target genes), and limit known adverse effects (via transrepression of undesirable genes) of PPAR activation. This concept provides the rationale for the development of SPPARMs which induce a differential receptor cofactor binding profile that aims to confer improved efficacy while minimizing unwanted side effects.[59]

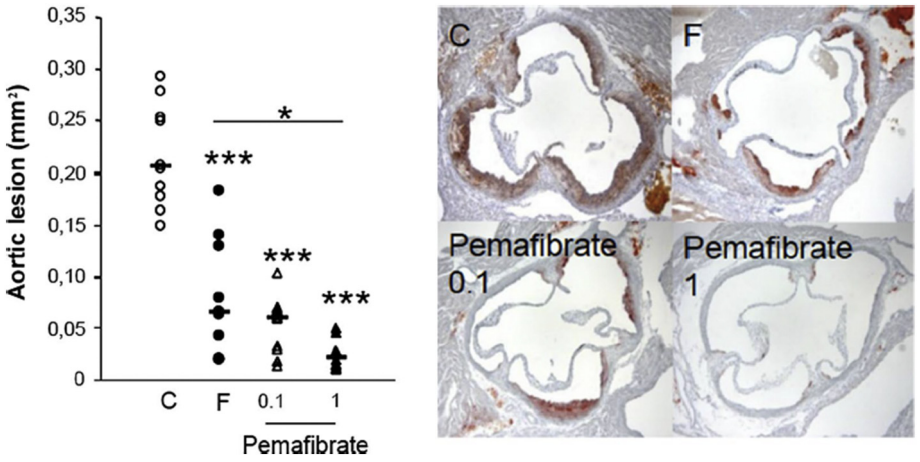
Pemafibrate drug development

Pemafibrate (K-877, Parmodia) differs fundamentally in structure from other currently available PPAR-α agonists and was designed to optimize potency and diminish unwanted actions.[60] Structurally, pemafibrate (K-877) has an acidic region as in other PPAR-α agonists, but the addition of benzoxazole and phenoxyalkyl side-chains, greatly increases PPAR-α activity and selectivity through comparatively enhanced interactions with the PPAR-α ligand-binding pocket.[61] In cell-based transactivation assays, pemafibrate exhibits >2500-fold more potency than fenofibric acid (the active metabolite of fenofibrate) for human PPAR-α with >5000-fold greater activity for PPAR-α than either PPAR-γ or -δ, thus requiring much lower doses for lipid effects and thus limiting unwanted effects.[59]

Pre-clinical data and clinical data

In C57BL/6 J mice consuming a Western diet, pemafibrate attenuated fasting and postprandial hypertriglyceridemia, as well as accumulation of remnant lipoproteins, by enhancing LPL activity and reducing

Figure 2



Anti-atherogenic effects of pemafibrate in apolipoprotein E transgenic mice.

weight gain.[62] Additionally, in mice with dyslipidemia due to expression of human apoE2 under control of the endogenous apoE promoter (apoE2KI mice) and consuming a Western diet, administration of pemafibrate at 1/2500th the dose compared to fenofibrate reduced atherosclerotic lesion area to a greater degree (Figure 2).[63] Pemafibrate also reduced the expression of inflammatory mediators including monocyte chemoattractant protein 1 and interleukin-6 mRNA and protein expression in both cultured THP-1 macrophages and Western-diet fed apoE2KI mice to a greater extent than fenofibrate.

A worldwide clinical trial program is investigating pemafibrate as both monotherapy and as add-on to statin therapy. This program has studied over 2000 patients, the majority with dyslipidemia and over one-quarter with concomitant T2D. Table II summarizes the key published data. A recent study in statin-treated patients[64] showed that pemafibrate (0.4 mg daily) reduced TG ~50%, lowered Apo C-III by 35–38%, and increased HDL-C by 13–16%.[64] LDL-C increased by up to 13%, an effect also produced by currently available fibrates[65,66] and potentially linked to VLDL conversion to LDL particles.[67-69] Indeed, pemafibrate significantly decreased apoB by 8% and non-HDL-C by 8–13%, and lipoprotein analysis indicated that only large and medium LDL fractions increased during treatment (Figure 3).[64] As such, pemafibrate improved both the total to HDL cholesterol ratio and the apo B to apo A1 ratio.

Safety and tolerability

Evidence from the phase II and III studies has shown that pemafibrate, whether or not co-administered with statins, is well tolerated with adverse event rates similar to or lower than those reported for placebo or fenofibrate.[64,70-72] In a phase III study,[71] pemafibrate (0.4 mg/d, n = 74) compared with fenofibrate (106.6 mg/day n = 76) had a lower rate of total adverse drug reactions (ADRs) (6.8% versus 23.7%, respectively; $P = .006$) with no drop outs due to ADRs. In addition, in this study, estimated glomerular filtration rate (eGFR) did not change with pemafibrate, whereas fenofibrate was associated with a significant decline in eGFR over 24 weeks ($P < .001$), consistent with previous findings from both the FIELD[73] and ACCORD[74] studies, although reversibility of the effects of fenofibrate on eGFR was demonstrated after treatment ended in both those trials. Additional safety data are shown in Table II. Despite promising phase 2 safety and efficacy data that support potential clinical benefits of pemafibrate, two prior short-term clinical trials[75] of the potent PPAR-α agonist LY518674 have been completed and raised safety concerns. While LY518674 improved atherogenic dyslipidemia parameters at 12 weeks of therapy, increased levels of creatinine and LDL-C were observed. The PROMINENT study will assess whether the favorable safety profile of pemafibrate persists when administered to a larger population followed for a substantially longer period of time.

Methods

PROMINENT: will targeting triglycerides in high-risk patients with type 2 diabetes ameliorate cardiovascular risk?

The PROMINENT randomized, double-blind, placebo-controlled trial will test whether treatment of mild to moderate hypertriglyceridemia with the SPPARM-α, pemafibrate, reduces cardiovascular events in high risk patients with diabetes who have elevated TG levels, low HDL-C levels, and largely already receive aggressive statin therapy (Figure 4). The trial involves approximately 850 clinical sites in 24 countries and will furnish contemporary information to guide therapeutic decisions in diabetic patients at residual triglyceride risk for whom no consistent guideline-based recommendations currently exist. It will also provide high quality data regarding

Table II. Summary efficacy data from published phase II/III clinical trials of pemafibrate

Study Population	No. Participants	Baseline Statin Use	Weeks	Dose (mg/day)	Mean Δ TG (%)	Mean Δ HDL-C (%)	Mean Δ LDL-C (%)	Mean Δ Apo B (%)	Mean Δ Creatinine (mg/dl)	Mean Δ ALT (U/L)
[70] Japanese patients with atherogenic dyslipidemia[a]	224	None	12	Pemafibrate						
				0.05	−30.9 ± 6.9	+12.0 ± 14.3	+8.9 ± 21.3	−1.4 ± 13.6	−0.011 ± 0.055	−5.9 ± 9.0
				0.1	−36.4 ± 6.6	+16.4 ± 16.9	+8.3 ± 29.4	−8.9 ± 13.6	−0.014 ± 0.062	−6.6 ± 10.8
				0.2	−42.6 ± 6.7	+16.1 ± 16.7	+5.0 ± 28.0	−7.8 ± 15.0	+0.013 ± 0.049	−7.6 ± 18.1
				0.4	−42.7 ± 6.7	+20.5 ± 22.5	+7.4 ± 26.5	−8.1 ± 11.6	+0.050 ± 0.239	−8.7 ± 13.0
				Fenofibrate						
				100	−29.7 ± 6.7	+14.6 ± 16.3	+5.3 ± 23.4	−5.7 ± 14.4	+0.086 ± 0.089	−4.2 ± 13.4
				Placebo	+28.5 ± 6.8	−2.0 ± 13.5	−6.3 ± 16.2	−2.0 ± 9.9	−0.022 ± 0.064	−1.9 ± 11.6
[71] Japanese patients with atherogenic dyslipidemia[b]	225	None	24	Pemafibrate						
				0.2	−46.2 ± 2.0	+22.3 ± 15.4	−6.3 ± 19.2	−8.7 ± 15.2	+0.009 ± 0.072	−8.1 ± 13.5
				0.4	−45.9 ± 1.9	+17.4 ± 17.7	−3.5 ± 20.0	−5.6 ± 16.2	+0.015 ± 0.065	−4.7 ± 13.4
				Fenofibrate						
				106.6	−39.7 ± 1.9	+17.6 ± 15.0	−6.3 ± 16.9	−9.9 ± 12.9	+0.091 ± 0.097	+1.9 ± 18.5
[64] Japanese patients with TG ≥200 mg/dl and non-HDL-C ≥150 mg/dl treated with pitavastatin	188	All	12	Pemafibrate						
				0.1	−46.1 ± 3.9	+13.6 ± 15.4	+1.0 ± 21.6	−8.1 ± 15.1	+0.007 ± 0.060	−1.0 ± 18.3
				0.2	−53.4 ± 3.8	+19.7 ± 19.3	+6.6 ± 32.1	−8.6 ± 18.3	+0.014 ± 0.068	−10.1 ± 19.7
				0.4	−52.0 ± 3.9	+12.7 ± 19.3	+ 2.9 ± 25.8	−7.9 ± 18.6	+0.044 ± 0.080	−9.6 ± 14.2
				Placebo	−6.9 ± 4.0	+3.4 ± 12.5	−2.3 ± 18.0	−3.3 ± 11.6	−0.011 ± 0.071	+3.4 ± 18.1
[64] Japanese patients with TG ≥200 mg/dl treated with any statin	423	All	24	Pemafibrate						
				0.2	−46.8 ± 2.6	+17.6 ± 17.2	+8.2 ± 28.3	−7.3 ± 17.6	+0.024 ± 0.079	−12.8 ± 16.8
				0.2→0.4	−50.8 ± 2.5	+16.3 ± 14.6	+12.6 ± 38.4	−7.5 ± 19.2	+0.030 ± 0.099	−8.0 ± 17.5
				Placebo	−0.8 ± 3.0	+4.4 ± 12.7	+3.7 ± 20.0	−3.6 ± 14.9	+0.007 ± 0.071	−0.9 ± 13.8
[72] Japanese T2D patients with TG 150–1000 mg/dl	166	39.2%	24	Pemafibrate						
				0.2	−44.3 ± 3.7	+17.0 ± 17.3	−4.9 ± 23.1	−9.1 ± 15.7	+0.026 ± 0.073	−6.6 ± 13.4
				0.4	−45.1 ± 3.6	+9.7 ± 18.3	+1.7 ± 26.2	−1.8 ± 18.3	+ 0.031 ± 0.085	−13.1 ± 20.5
				Placebo	−10.8 ± 3.6	+4.7 ± 12.5	+2.1 ± 15.5	+1.6 ± 11.5	−0.013 ± 0.091	−0.3 ± 18.0

HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglycerides; T2D: Type 2 Diabetes.
To convert TG from mg/dl to mmol/l, multiply by 0.0113; to convert HDL-C and LDL-C from mg/dl to mmol/L, multiply by 0.0259; to convert Apo B from mg/dl to g/l, multiply by 0.01; to convert creatinine from mg/dl to μmol/l, multiply by 88.4; to convert ALT from U/L to μkat/l, multiply by 0.0167.
a TG 200–499 mg/dl; HDL-C <50 mg/dl in men, HDL-C <55 mg/dl in women.
b TG 150–499 mg/dl; HDL-C <50 mg/dl in men, HDL-C <55 mg/dl in women.
Data are mean ± standard deviation except for TG for which least squares mean ± standard error are presented.
Change in ApoB for reference [79] and serum creatinine for all studies was sourced from the Pharmaceuticals and Medical Devices Agency (PMDA). *PARMODIA Table 0.1. mg: Common Technical Document Summaries.* Available from: http://www.pmda.go.jp/drugs/2017/P20170718001/index.html [Accessed 26th December 2017].

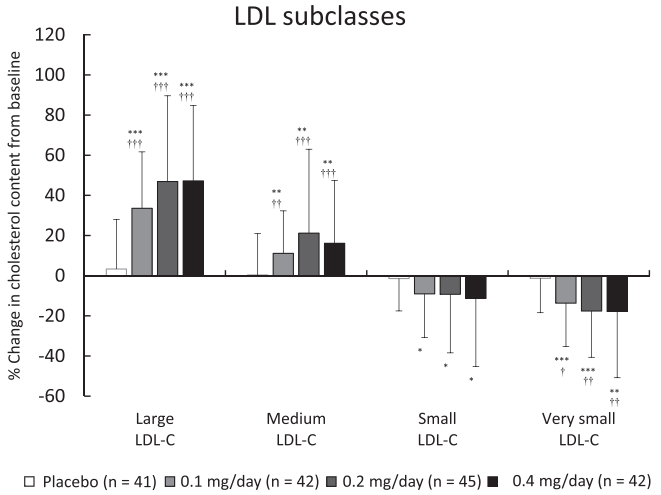
risk reduction for several important secondary endpoints including heart failure, peripheral artery disease, diabetic retinopathy and nephropathy. Recruitment began in April 2017 and as of April 27th, 2018, 3281 subjects have been randomized of whom 27.7% are women. Recruitment is anticipated to complete October 2019.

Study design, objectives, outcomes, eligibility, statistical analysis, and oversight

PROMINENT is a phase III, event-driven, double-blinded, placebo-controlled, multinational, randomized controlled trial. Figure 2 summarizes the design. Participants must have T2D with elevated TG [200–499 mg/dl (2.26–5.64 mmol/l)] and low HDL-C [≤40 mg/dl (1.03 mmol/l] and be on moderate to high intensity statin therapy (either atorvastatin ≥40 mg/day, rosuvastatin ≥20 mg/day, simvastatin ≥40 mg/day, or pitavastatin 4 mg/day) or have LDL-C ≤70 mg/dl (1.81 mmol/l) within 12 months prior to enrollment. Statin intolerant participants are eligible if LDL-C ≤100 mg/dl (2.59 mmol/l). Participants must also have either prior history of cardiovascular disease (secondary prevention cohort) or be at high risk defined as age≥ 50 years if male or≥ 55 years if female (primary prevention cohort). Table III details inclusion and exclusion criteria. The trial defines prior CVD as previous MI or ischemic stroke, coronary angiographic evidence of coronary artery disease, carotid stenosis, symptomatic peripheral artery disease, or prior arterial revascularization (Table IV).

The trial is sponsored by Kowa Company, Ltd, Nagoya, Japan. The academic research organization (ARO) is located at the Center for Cardiovascular Disease Prevention (CCVDP), Brigham and Women's Hospital (BWH), Boston, MA, USA. The protocol was designed through a collaboration between CCVDP and the Sponsor (Kowa).

Figure 3



Percent changes from baseline to week 12 in cholesterol content in LDL subclasses measured by high-performance liquid chromatography.

The Sponsor, along with CCVDP and the trial Executive and Steering Committees, monitors ongoing conduct of the trial. The study Contract Research Organization (CRO), IQVIA (Durham, NC, USA) will recruit and follow-up participants and collect data. Institutional review boards and health authorities in all participating countries approved the protocol. All participants provide written informed consent.

Primary objectives

PROMINENT's primary scientific aim is to assess whether treatment with the SPPARM-α, pemafibrate 0.2 mg twice daily, compared to placebo reduces time to first occurrence of the composite outcome of myocardial infarction, ischemic stroke, hospitalization for unstable angina requiring unplanned coronary revascularization, and cardiovascular death. Secondary and tertiary outcomes are listed in Supplementary Table V and include individual components of the primary endpoint, all-cause mortality, hospitalization for heart failure, any coronary revascularization, new or worsening peripheral artery disease, change in mechanistic lipid biomarkers as well as nonfasting remnant cholesterol.

Outcomes

The primary efficacy outcome is the composite of nonfatal MI, nonfatal ischemic stroke, hospitalization for unstable angina requiring urgent coronary revascularization, and cardiovascular death. Only confirmed primary endpoints are counted for the primary analysis. PROMINENT uses the Third Universal Definition of Myocardial Infarction[76] and uses the definitions of ischemic stroke and cardiovascular death proposed by Hicks et al[77] and Sacco et al[78] An independent Clinical Endpoints Committee (CEC) blinded to study treatment allocation will adjudicate primary endpoints and a select number of secondary endpoints (any coronary revascularization, hospitalization for heart failure, and new or worsening peripheral artery disease.) A separate CEC Charter fully describes the methods used by the CEC.

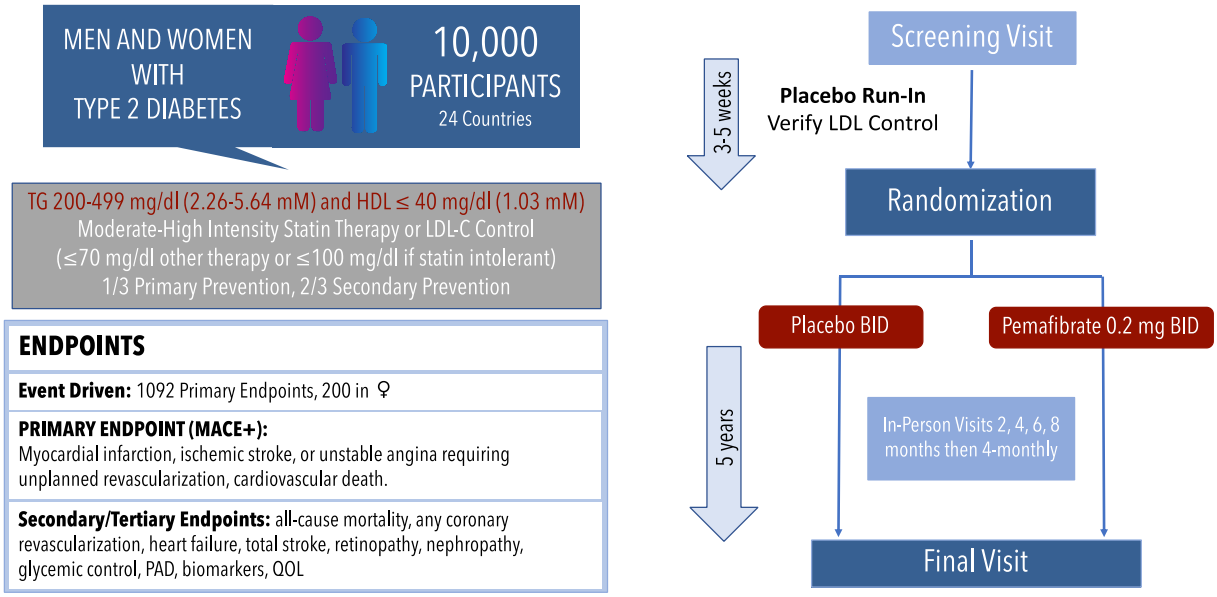
Eligibility assessment

The screening approach begins by documentation of pre-screening evidence of fasting or non-fasting hypertriglyceridemia and low HDL-C through local laboratory evaluation within the previous 12 months (Supplemental Figure 1). Informed consent is obtained at the pre-screening visit with submission of these values as well as medical record documentation of T2D, CVD, statin intolerance (if applicable) and LDL-C (if needed to meet inclusion criteria). Screening (on-protocol) laboratory assessment is then performed and participants are enrolled into the run-in period. A single retesting of enrollment TG and/or HDL-C may occur if subjects are in borderline categories. No subject may be randomized without meeting entry lipid values or submission of qualifying medical records. In addition to eligibility laboratory tests, blood samples are also collected for advanced lipid testing, glycemic measures, inflammatory and additional exploratory biomarkers and urine is tested for microalbuminuria.

Run-in

During the 3 to 5-week placebo run-in period, potentially eligible subjects receive placebo twice daily, are assessed for lipid entry criteria (initial and retest, if needed) and qualifying medical records are collected for verification of prior cardiovascular disease, T2D, and statin intolerance when applicable.

Figure 4



PROMINENT Study Design.

Randomization

Subjects who complete the run-in period successfully with high compliance (≥ 75% by tablet count) and meet lipid eligibility and other clinical criteria are randomized in a 1:1 ratio to receive pemafibrate or placebo. Randomization is stratified by age, prior history of CVD, and statin use at baseline, defined as those who are taking statins at baseline versus those taking no statins or who are statin intolerant. Within each stratum, participants are randomized with equal probability to active pemafibrate or placebo. A non-fasting sample for lipid testing is collected at this visit.

Study drug

To improve compliance, safety, and drug accountability, all study drug is dispensed in blistered calendar packs during both the trial run-in and active treatment phase.

Follow-Up

Telephone visits alternate with in-person visits throughout the treatment period with a greater frequency of visits occurring during year 1. At each study visit, outcomes and adverse events are recorded, concomitant medications documented, and adherence is reinforced. At 2 weeks post randomization, a well-being phone visit is conducted to provide general support and to reinforce dosing instructions. Participants are seen at 2, 4, 6, 8 and 12 months and 4-month intervals thereafter. A common study end date (CSED) visit will be scheduled within a 60-day window after study termination is announced. Participants will continue study medications through the CSED unless the study is stopped for evidence of increased hazard. A post-study safety call will occur approximately 30 days after the CSED visit at which time final adverse events and post-study efficacy events will be collected.

Additional follow-up procedures include collection of serial information on quality of life and serial specimen collection for both efficacy and safety assessment and biobanking. A self-administered quality of life questionnaire (the European Quality of Life 5 Dimensions 5 Level Questionnaire; EQ-5D-5 L) is completed at randomization, annually, at the first in-person visit after a primary endpoint, and at the CSED visit. Fasting blood specimens for safety and efficacy and urine samples for microalbuminuria are collected throughout the study period. Non-fasting specimens are collected at 6 months. At enrollment, randomization, and 4 months post-randomization, willing participants donate blood and DNA specimens for archiving in the central biobank.

Post-randomization lipid-lowering therapy

Phase 2 studies have shown that pemafibrate modestly but statistically significantly increases LDL-C *concentration* without increasing LDL *particles*. A favorable shift in LDL particle size distribution accompanies this elevation in LDL-C level, specifically a rise in large and medium LDL subclasses, a decrease in smaller LDL subclasses, and an overall decrease in non-HDL-C and decrease in ApoB.[64] Despite these favorable effects in LDL particles, off-

Table III. Eligibility Criteria

Inclusion Criteria

- Fasting TG ≥ 200 mg/dL (2.26 mmol/L) and <500 mg/dL (5.65 mmol/L)
- HDL-C ≤40 mg/dL (1.03 mmol/L)
- Type 2 diabetes of longer than 12 weeks duration documented in medical records, for example: local laboratory evidence through medical record review of elevated HbA1c (≥ 6.5% [48 mmol/mol]), elevated plasma glucose (fasting ≥126 mg/dL [7.0 mmol/L]), 2-hour ≥200 mg/dL [11.1 mmol/L] during oral glucose tolerance testing, or random value ≥200 mg/dL with classic symptoms, or currently taking medication for treatment of diabetes; AND either
  a) Age ≥ 50 years if male or ≥ 55 years if female (primary prevention cohort); OR
  b) Age ≥ 18 years and established systemic atherosclerosis (secondary prevention cohort; Table IV)
- Participants must be either:
  a) Receiving treatment with a stable dose (ie, for at least 12 weeks) of a qualifying moderate- to high-intensity statin (atorvastatin ≥40 mg/day, rosuvastatin ≥20 mg/day, simvastatin ≥40 mg/day*, or pitavastatin 4 mg/day); or
  b) Have evidence of LDL-C ≤70 mg/dL (1.81 mmol/L) by local laboratory determination within the previous 12 months#, or
  c) Statin intolerant† and have evidence of LDL-C ≤100 mg/dL (2.59 mmol/L) by local laboratory determination within the previous 12 months
- Ability to understand and comply with study procedures and give written informed consent

Exclusion Criteria

- Current or planned use of fibrates or agents with potent peroxisome proliferator activated receptor (PPAR)-α agonist activity (eg, saroglitazar) within 6 weeks of enrollment.
- Known sensitivity to PPAR-α agonists or tablet excipients
- Initiation of, or change in, current TG-lowering therapy within 12 weeks of enrollment
- Type 1 diabetes mellitus
- Uncontrolled diabetes mellitus as defined by a HbA1c >9.5% [80 mmol/mol]
- Untreated or inadequately treated hypothyroidism [thyroid stimulating hormone (TSH) >2.0 × the upper limit of normal (ULN) or free thyroxine (T4) ≤ the lower limit of normal] or hyperthyroidism; controlled thyroid disease (permitted) requires normal TSH and stable therapy for at least 4 weeks
- Recent CVD event (eg, MI or stroke) within 8 weeks of randomization
- Recent or planned vascular intervention within 8 weeks of randomization
- New York Heart Association Class IV heart failure
- Known homozygous familial hypercholesterolemia (heterozygous is permitted) or familial hypoalphalipoproteinemia
- Documented previous occurrence of myositis/myopathy
- Unexplained creatine kinase (CK) >5× ULN
- Liver disease defined as cirrhosis or Child-Pugh class B and C, or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3× ULN
- Biliary obstruction or hyperbilirubinemia (ie, total bilirubin >2× ULN, except with a documented diagnosis of Gilbert's disease)
- Chronic renal insufficiency, defined by an estimated glomerular filtration rate (eGFR)
- <30 mL/min/1.73 m^2 by the Chronic Kidney Disease Epidemiology Collaboration
- (CKD-EPI) formula or kidney transplant, regardless of renal function
- Unexplained anemia (hematocrit ≤30%)
- Uncontrolled hypertension (seated systolic blood pressure >160 mmHg and/or diastolic blood pressure >100 mmHg) at randomization.
- History of chronic active hepatitis B or hepatitis C, or known infection with human immunodeficiency virus (HIV); participants with documented hepatitis C resolution after treatment are permitted
- Active malignancy, except non-melanoma skin cancer or carcinoma in situ of the cervix, within the last 2 years.
- Prior organ transplant or any condition likely to lead to organ transplantation in the next 5 years
- Current or anticipated chronic use of cyclosporine, rifampicin, or other inhibitors of organic anion transporting polypeptides (OATP)1B1, or OATP1B3
- History of alcoholism or unwillingness to limit alcohol intake to <15 alcoholic beverages (or units) per week or <5 alcoholic beverages (or units) during a single occasion for men and <8 alcoholic beverages (or units) per week or <4 alcoholic beverages (or units) during a single occasion for women during the study period. Note: One alcoholic beverage (unit) is defined as 12 oz. (350 mL) of beer, 5 oz. (150 mL) of wine, or 1.5 oz. (45 mL) of liquor
- History of hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption
- Women who are pregnant, lactating, planning to be pregnant or lactating during the study period, or WOCP who are not using an acceptable method of contraception
- A medical condition, other than vascular disease, with life expectancy <3 years, which might prevent the participant from completing the study
- Any factors likely to limit adherence to the study medications and procedures, such as substance abuse, dementia, plans to move within the next 2 years, and/or history of noncompliance with medication or scheduled appointments, and
- Participation in another clinical study at the time of informed consent, or has received an investigational drug within 90 days before signing the informed consent for this study.

* Participants enrolled on simvastatin >40 mg/day must have been taking and tolerating that dose for at least 12 months.
# If untreated or on stable dosing (ie, for at least 12 weeks) of another lipid-lowering regimen that may include a statin with or without ezetimibe and/or a PCSK9 inhibitor
† Statin intolerance is defined as: the inability to tolerate at least 2 statins: 1 statin at the lowest daily starting dose (defined as rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg or pitavastatin 2 mg), AND another statin at any dose, due to skeletal muscle-related symptoms, other than those due to strain or trauma, such as pain, aches, weakness, or cramping, that begins or increases during statin therapy and stops when statin therapy is discontinued. Participants not receiving a daily regimen of a statin (e.g., 1–3 times weekly) could also be considered "statin intolerant" if they cannot tolerate a cumulative weekly statin dose of 7 times the lowest approved tablet size, and the criteria outlined above are also met.

protocol LDL-C measurement and resultant changes to statin dosing or addition of other LDL-C lowering therapies may lead to an undesirable imbalance in use of these agents between the two treatment arms. Thus, central monitoring of ApoB levels and an algorithm to standardize changes in lipid-lowering therapy is used to

Table IV. PROMINENT secondary prevention cohort eligibility

- Prior MI or ischemic (non-hemorrhagic) stroke
- Coronary angiographic lesion of ≥60% stenosis in a major epicardial vessel or ≥50% left main stenosis
- Asymptomatic carotid disease with ≥70% carotid artery stenosis
- Symptomatic carotid disease with ≥50% carotid artery stenosis
- Symptomatic lower extremity peripheral artery disease (PAD) (ie, intermittent claudication, rest pain, lower extremity ischemic ulceration, or major amputation with either ankle-brachial index ≤0.9 or other diagnostic testing [eg, toe-brachial index, angiogram, or other imaging study])
- Prior arterial revascularization procedure (including coronary, carotid, or peripheral angioplasty/stenting, bypass, or atherectomy/endarterectomy)

maximize study-wide consistency of lipid management. In brief, while investigators remain blinded to post-randomization lipid values, they are notified when elevations in ApoB occur and if persistent, a recommendation is issued for lipid lowering drug titration in the increments provided (Supplemental Figure 2). The electronic reporting system captures any resulting changes to therapy.

Safety evaluations and adverse events

Safety evaluations include an assessment of adherence, monitoring of clinical chemistry variables related to safety, side effects, and any reported adverse events. Adverse events will be categorized as serious or non-serious and will be graded by investigators with respect to the possibility of relatedness to the study drug. In addition, a number of pre-specified adverse events and events of clinical interest are collected at each study visit (Supplementary Table II). Occurrence of any of these events prompts further investigation including collection of information pertaining to diagnostic testing and/or therapeutic interventions. Muscle-related adverse events and the occurrence of liver disease, designated events of special interest, will be monitored rigorously throughout the trial.

Sample size

PROMINENT is an event-driven trial that is designed to continue until at least 1092 participants (with a minimum of 200 women) experience a confirmed primary efficacy outcome. The recruitment goal for women is 20% of the total randomized population. The planned sample size of approximately 10,000 subjects was chosen on the basis of the following assumptions: a 2-arm study with 1:1 randomization, interim efficacy and futility monitoring, overall 2-sided type I error level of 5%, an annual event rate in the placebo control group of 3.5 to 4.5%, 10% non-adherence, 1% annual loss to follow-up, and 90% power to detect an 18% reduction in the relative hazard with pemafibrate. The current trial design provides 80% power to detect a 15% reduction in HR and 60% power to detect a 12% reduction. The expectation for duration of recruitment is 2.5 years. Loss to follow-up is expected to be low as participants are assumed to have a strong affiliation with their treatment centers, will have undergone assessment for adherence to study procedures during the placebo run-in period, provide next-of-kin contact information, and a retention protocol is in place to minimize drop out during the trial. The total expected treatment period is 5 years with an expected average follow-up period of 3.75 years.

Analyses

Analysis of the primary outcome will be based on the intention to treat principle. Thus, participants will be analyzed according to their randomized treatment group, regardless of whether they adhere to their assigned treatment. The primary endpoint of the study is the time from randomization to the first occurrence of any component of the clinical composite endpoint of nonfatal MI, nonfatal ischemic stroke, hospitalization for unstable angina requiring urgent coronary revascularization, and CV death. Comparisons will use a likelihood ratio test based on a proportional hazards model stratified on sex, prior history of CVD, and statin use at baseline to test the null hypothesis of no association between assignment to pemafibrate and the rate of occurrence of the primary endpoint. Estimates of the probability of the primary endpoint by time after randomization within treatment groups will use the method of Kaplan and Meier.[79] If Kaplan–Meier plots of event-free survival by study time, or related plots of log(−log)(survival), indicate violations of the proportional hazards assumption, or a formal test of trend in the scaled Schoenfeld residuals indicates such a violation, then weighted log-rank tests will be used according to strategies described by Pecková and Fleming.[80] However, even in the presence of an apparent violation of the proportional hazards assumption, the primary analysis described above gives a valid test of the main study hypothesis and will remain the primary analytic strategy, with these weighted log-rank tests serving as sensitivity analyses. The statistical analysis plan (Appendix A) provides details of the statistical approach.

Data safety and monitoring board

A fully independent Data and Safety Monitoring Board (DSMB) is monitoring enrollment and adherence, biomarkers for safety and efficacy, serious adverse events, the occurrence of trial endpoints, and participant and site burden. Two formal interim analyses to assess efficacy will occur when approximately 50% and 75% of the

primary efficacy outcomes have accrued. The design of the study, including implications of interim monitoring on study power, considered that stopping boundaries are based on the Haybittle-Peto method. Under this approach, the Z-values for the boundary at the 50% and 75% information times correspond to 2-sided *P* values of 0.001. Additionally, the DSMB will consider the direction of effect for each of the components of the primary endpoint as well as the sensitivity analysis for loss to follow-up, ensuring that the point estimate for each is consistent with the composite result and there is no concern for safety. The DSMB will also consider the direction of the effect in women, again ensuring consistency with the overall result and no concern for safety. Specifically, for the study to be stopped early for efficacy, the point estimate of the HR for the pemafibrate group compared to placebo must be <1 for each component of the primary endpoint *as well as* for the subgroup of women. Further, the HR of 1.36 seen in ACCORD[55] must not be in the 95% CI for the primary endpoint in the subgroup of women.

As a guideline for considering a recommendation to terminate the study early because of convincing evidence of inefficacy (futility), preplanned inefficacy bounds will also be considered at accrual of approximately 30%, 50%, and 75% of primary efficacy outcomes. Based upon the Linear 10% Inefficacy Boundary approach described by Freidlin, Korn, and Gray,[81] the inefficacy boundary will be crossed if the observed relative hazard of the primary outcome associated with pemafibrate assignment is greater than 1.000 at the first interim futility analysis, greater than 0.996 at the second interim futility analysis, or greater than 0.988 at the third interim futility analysis and the 95% CI excludes the expected effect.

No formal boundaries were set for terminating the study for safety reasons as this determination will be made by the DSMB in the presence of clear and consistent evidence of harm that overwhelms the net benefit. The formal DSMB Charter is available from the investigators.

Trial organization and management

The trial is independently managed by CCVDP, a Steering Committee (SC) and an Executive Committee (EC) in collaboration with the Sponsor, Kowa Research Institute, and the study Contract Research Organization (CRO, IQVIA). The trial is registered at www.clinicaltrials.gov (NCT03071692). Current membership of the EC, SC, SAB, Operations Committee (OC), Data Coordinating Center, CEC, Scientific Advisory Committee, and DSMB is provided in Supplementary Appendix B.

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Conclusion

A growing body of evidence supports a causal role for hypertriglyceridemia and TRLs in atherogenesis. Increasing rates of diabetes, obesity, and cardiovascular disease compels investigation of pharmacologic interventions to address this mounting global issue. However, no study has yet tested whether TG lowering therapy in statin-treated patients with mild-to-moderate TG elevation (and thus at residual hypertriglyceridemic risk) confers a cardiovascular benefit. Pemafibrate holds considerable promise as a potent and selective PPAR-α agonist with a desirable safety profile and favorable pre-clinical and clinical data which support an improved risk–benefit ratio beyond fibrates. PROMINENT will provide rigorous evaluation of the efficacy and safety of this agent in a large population with diabetes and dyslipidemia treated with contemporary standard of care concomitant therapies. The trial could offer a new option for management of residual cardiovascular risk in these patients.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2018.09.011.

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