2.0 SYNOPSIS

Name of Sponsor/Company: Kowa Research Institute, Inc.

Name of Investigational Product: K-877 (pemafibrate) 0.2 mg tablet and matching placebo tablet

Name of Active Ingredient: K-877 (pemafibrate)

Title of Study:

Pemafibrate to Reduce cardiovascular OutcoMes by reducing triglycerides IN patiENts with diabeTes (PROMINENT)

Investigators:

There were 865 investigators at study centers that enrolled and randomized at least 1 subject.

Study Centers:

This study was conducted at 865 study centers in 24 countries (Argentina, Brazil, Bulgaria, Canada, Colombia, Czech Republic, Denmark, France, Germany, Hungary, India, Israel, Japan, Mexico, Netherlands, Poland, Romania, Russian Federation, Slovakia, South Africa, Spain, Ukraine, United Kingdom, and United States [US]) that enrolled and randomized at least 1 subject.

Publications (References):

Pradhan AD, Glynn RJ, Fruchart JC, et al. Triglyceride lowering with pemafibrate to reduce cardiovascular risk. NEJM. Nov 2022;1-12. doi: 10.1056/NEJMoa2210645.

Pradhan AD, Paynter NP, Everett BM, et al. Rationale and design of the Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) study. Am Heart J. 2018;206:80-93.

Study Period:	**Phase of Development:**
23 March 2017 (first subject enrolled) – 27 July 2022 (last subject completed) This study was terminated early due to inefficacy (futility) on 08 April 2022 following the recommendation of the Data Safety Monitoring Board (DSMB).	3

Background and Rationale for the Study:

Hypertriglyceridemia (HTG) is associated with increased cardiovascular (CV) risk, appears to play a causal role in atherothrombosis, and can be effectively reduced with the novel selective peroxisome proliferator activated receptor modulator alpha (SPPARM-α) pemafibrate. Progressive insulin resistance, the core metabolic defect in type 2 diabetes (T2D), is strongly associated with disordered lipid metabolism, which manifests as HTG and low levels of high-density lipoprotein cholesterol (HDL-C). More than 70% of high-risk patients with underlying diabetes have triglyceride (TG) levels above values considered “optimal” by international prevention guidelines. However, no definitive study data have established that lowering TGs by treatment with any available agent can reduce CV event rates. Given the demonstrated favorable safety profile, and the absence of any other agent that has demonstrated a reduction in CV events with TG lowering in targeted population, the potential benefit of the successful clinical development of pemafibrate was considered justified.

The primary scientific aim of the PROMINENT study was to assess the ability of pemafibrate to prevent myocardial infarction (MI), ischemic stroke, coronary revascularization, and CV death in subjects with T2D who had elevated TGs and low HDL-C levels and were at high risk for future CV events.

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Objectives:

The primary objective of the study was to determine whether pemafibrate administered at a dose of 0.2 mg twice daily (BID) would delay the time to first occurrence of any component of the clinical composite endpoint of nonfatal MI, nonfatal ischemic stroke, coronary revascularization, or CV death.

The secondary objectives of this study was to investigate 1) the efficacy (time to first occurrence) of a number of secondary CV and diabetes-related vascular and nonvascular endpoints in the study population, and 2) the efficacy (as measured by the percent change from baseline) for a number of lipid measures.

The tertiary objective of the study was to investigate the effect of pemafibrate on various lipid factors, inflammatory biomarkers, and other circulating biomarkers.

Study Design:

The PROMINENT study was a Phase 3, randomized, double-blind, placebo-controlled, multinational study that was conducted to evaluate the ability of pemafibrate to prevent CV events in high-risk subjects with T2D, moderate HTG and low levels of HDL-C treated with statins. The PROMINENT study was conducted in 24 countries to ensure generalizability and allow for the enrollment and follow-up periods to be completed in 5 years.

Number of Subjects (Planned and Analyzed):

A total of 10,497 subjects were analyzed for efficacy in the intent-to-treat (ITT) population, 7985 subjects were analyzed in the per protocol (PP) population, and 10,538 subjects were analyzed in the safety population.

A total of 10,544 subjects were randomized. Of these, 10,538 subjects received double-blind study treatment. Of the 10,538 treated subjects, 5264 subjects received pemafibrate and 5274 subjects received placebo.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Adult men and women with T2D, -moderate HTG (fasting 200 to 499 mg/dL) and low HDL-C levels (<40 mg/dL), who were taking background moderate-to high-intensity statin therapy (atorvastatin ≥40 mg/day, rosuvastatin ≥20 mg/day, simvastatin ≥40 mg/day, or pitavastatin 4 mg/day) unless meeting low-density lipoprotein cholesterol (LDL-C) criteria with or without statin intolerance. Two-thirds of the enrolled study population had prior evidence of systemic atherosclerosis (secondary prevention cohort, age ≥18 years) while one-third did not and represented the primary prevention cohort (age ≥50 years if male, or ≥55 years if female).

Test Product, Dose, and Mode of Administration, Batch Number:

Test Product: K-877 (pemafibrate) 0.2 mg, 1 tablet BID, administered orally.

Batch number(s): Available upon request.

Reference Therapy, Dose, and Mode of Administration, Batch Number:

Matching placebo tablet, 1 tablet BID, administered orally.

Batch number(s): Available upon request.

Duration of Treatment:

The total expected treatment duration was up to 5 years with a 4-year follow-up period.

Endpoints:

Primary Efficacy Endpoint:

The primary efficacy endpoint was the time from randomization to the first occurrence of any component of the clinical composite endpoint of: nonfatal MI, nonfatal ischemic stroke, coronary revascularization, and CV death.

Secondary Clinical Efficacy Endpoints:

The Group A (clinical) endpoints were time to first occurrence of:

- The 4-component composite endpoint of nonfatal MI, nonfatal ischemic stroke, hospitalization for unstable angina requiring unplanned coronary revascularization or CV death;
- The 3-component composite endpoint of nonfatal MI, nonfatal ischemic stroke, or CV death;
- Any component of the primary endpoint or hospitalization for heart failure (HF);
- Any component of the primary endpoint or all-cause mortality;
- Any new or worsening peripheral artery disease (PAD), defined as incidence of lower extremity revascularization, 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);
- Time to first occurrence of individual endpoints and an analysis of total events (evaluating time to occurrence of the first and all recurrent nonfatal MI, nonfatal ischemic stroke, coronary revascularization, or CV death);
- Additionally, as a prespecified secondary analysis, evidence of any genetic effect modification that may relate to pemafibrate and incident CV events was evaluated. In particular, whether the effect of pemafibrate as compared with placebo on CV events differs according to known genetic polymorphisms in the peroxisome proliferator activated receptor alpha (PPAR-α) gene (such as, but not limited to rs6008845), was assessed.

The Group B (lipid) endpoints were:

- Change from Screening/Enrollment Visit (Visit 1) to Month 4 Visit (Visit 5) for the following lipid biomarkers: total cholesterol (TC), TG, HDL-C, non-HDL-C (calculated), very low-density lipoprotein cholesterol (VLDL-C)* (calculated), apolipoprotein (Apo) A1, ApoC3, and ApoE;
- Change from Randomization Visit (Visit 2) to Month 6 Visit (Visit 6) for nonfasting remnant cholesterol.

*VLDL-C was calculated as TC minus HDL-C minus LDL-C, where LDL-C was measured by a direct homogenous method.

Tertiary Efficacy Endpoints:

Tertiary endpoints included microvascular endpoints as well as exploratory mechanistic studies evaluating differences in average achieved levels and change from baseline between pemafibrate and placebo treatment groups in core lipid parameters (total cohort); advanced lipid parameters (total cohort); inflammatory and glycemic parameters (total cohort); expanded exploratory lipid and nonlipid parameters (US/Canada subcohort). Microvascular endpoints included diabetic retinopathy and diabetic nephropathy.

Safety:

Safety was evaluated through a comprehensive assessment of the extent of exposure to study treatment, the occurrence of adverse events (AEs), clinical laboratory tests (chemistry, hematology, and urinalysis), and vital signs (blood pressure, heart rate, height, body weight, waist circumference, and body mass index).

Statistical Methods:

Primary Analyses:

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The primary analysis of the study used a likelihood ratio test based on a proportional hazards model stratified by sex, prior history of cardiovascular disease (CVD) (primary vs secondary prevention cohorts), and statin use at baseline (defined as those who were taking no statin at baseline or are statin intolerant compared to all others) to test the null hypothesis of no association between assignment to active pemafibrate and the rate of the primary endpoint. The ITT population served as the primary analysis population and included all randomized subjects who received at least 1 dose of study treatment. Estimates of the probability of the primary endpoint by time after randomization within treatment groups were based on the method of Kaplan and Meier. The analyses were repeated on the PP population.

Secondary Analyses:

Secondary clinical endpoint analyses followed the same outline as the primary analysis for time to event data. Secondary lipid efficacy endpoints used the analysis of covariance with adjustment for baseline measurements and imputation of missing values.

Safety Analyses:

The safety population included all subjects who received at least 1 dose of study treatment. Subjects were analyzed according to their randomized treatment group, unless otherwise stated. Safety analyses included comparisons of postrandomization laboratory values by treatment group and rates of serious adverse events and AEs by treatment group, both overall and within system organ class.

Interim Analyses:

Preplanned efficacy analyses occurred only upon accrual of approximately 30%, 50%, and 75% of the planned study primary endpoints. This study was terminated early due to inefficacy (futility) and on the recommendation of the DSMB following review of interim analyses. This decision was made on 08 April 2022 at the accrual of approximately 75% of planned study endpoints.

Sample Size Justification:

Sample size and power were estimated using an event-driven approach where all subjects were followed until a sufficient number of events had accrued. All estimates were based on a 2-sided log-rank test comparing the time to occurrence between the 2 treatment groups at the 0.05 significance level, incorporating interim analyses. In order to achieve 90% power to detect the anticipated 16.6% reduction in the rate of the primary endpoint in the pemafibrate treatment group compared to placebo, at least 1304 subjects meeting a component of the primary endpoint were required, with a minimum of 200 events accrued in women. Given the study sample size of 10,000 subjects, an expected enrollment period of 30 months, and an anticipated annual event rate of 3.5 to 4.5 per 100 person-years in the placebo group, the expected study duration was 5 years (with a 3.75-year average follow-up with approximately uniform enrollment).

Summary – Conclusions:

Disposition and Demography: The PROMINENT study included 10,497 subjects (mean age 63.42 years; 72.5% men and 27.5% women) with T2D, moderate HTG (fasting 200 to 499 mg/dL), and low HDL-C levels (<40 mg/dL). The subjects represented major geographical regions and races and per the inclusion criteria, had a high risk of CV events or recurrence of CV events. The primary prevention cohort included men and women 50 and 55 years and older, respectively, while the secondary prevention group included all adults 18 years and older with atherosclerotic cardiovascular disease. Demographics and baseline characteristics were similar between the treatment groups. The majority of subjects were White (86.1%) and most (85.3%) were ≥55 years of age. Cardiovascular diseases and risk factors at baseline were similar between the treatment groups. Mean duration of diabetes was 7.08 years. Mean baseline estimated glomerular filtration rate (eGFR) was 76.2 mL/min/1.73 m^2, with 24% of subjects having moderate or severe renal impairment (defined as eGFR ≤60 mL/min/1.73 m^2). The majority of subjects had hypertension (91.5%), with mean systolic and diastolic blood pressure of 131.9 mmHg and 76.9 mmHg, respectively.

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Overall, 7567 (71.8%) subjects completed study treatment and 2956 (28.0%) subjects discontinued study treatment. Overall, 9321 (88.4%) subjects completed the study and 1206 (11.4%) subjects discontinued from the study. The primary reason for discontinuation from the study was death (69.2%), followed by withdrawal by subject (17.7%) and lost to follow-up (6.6%). The reasons for discontinuation from the study were similar between the treatment groups. Mean duration of subjects in the study was 1226.6 days.

Protocol Deviations: Overall, 3071 (29.3%) subjects reported at least 1 major protocol deviation. The most frequently reported major protocol deviations were related to investigational product compliance (15.6%), followed by informed consent (4.0%), and randomization criteria (3.9%). The incidence of major protocol deviations was comparable between treatment groups.

Efficacy Results:

Primary Efficacy Endpoint

- The primary endpoint of the study was the time from randomization to first occurrence of any component of the 4-component composite endpoint and included the events of nonfatal MI, nonfatal ischemic stroke, coronary revascularization, or CV death. The analysis of this endpoint was conducted in the ITT population (pemafibrate 5240 subjects; placebo 5257 subjects).
  - Median duration of follow-up was 3.32 years in both treatment groups.
  - The hazard ratio (HR) based on the Cox regression model for pemafibrate vs placebo was 1.03 (95% confidence interval [CI]: 0.92, 1.16; p=0.570). There was no significant difference between the treatment groups in the time to first occurrence of the 4-component composite primary endpoint.
- Sensitivity analyses of the primary endpoint supported the results of the primary analysis (pemafibrate vs placebo HR 1.04 [95% CI: 0.91, 1.20]; p=0.572).
- No significant differences were observed in any of the prespecified subgroups, except for baseline HDL-C, baseline fasting TG, and baseline nonfasting remnant cholesterol.

Conclusion: There was insufficient evidence that treatment with pemafibrate delayed the time to first occurrence of the 4-component composite primary endpoint compared to placebo. This was the first gate in the hierarchical gatekeeping strategy.

Secondary Efficacy Endpoints

- No significant differences were observed between pemafibrate and placebo in the time to first occurrence of the following endpoints, with no effect seen in any of the individual endpoints:
  - 4-component composite endpoint of nonfatal MI, nonfatal ischemic stroke, hospitalization for unstable angina requiring unplanned coronary revascularization, or CV death (secondary clinical endpoint 1)
  - 3-component composite endpoint of nonfatal MI, nonfatal ischemic stroke, or CV death (secondary clinical endpoint 2)
  - 4-component composite primary endpoint or hospitalization for HF (secondary clinical endpoint 3)
  - 4-component composite primary endpoint or all-cause mortality (secondary clinical endpoint 4).
  - Any new or worsening PAD (secondary clinical endpoint 5)
  - Individual events of the 4-component composite primary endpoint (nonfatal MI, nonfatal ischemic stroke, coronary revascularization, and CV death) and an analysis of total events (secondary clinical endpoint 6)
  - PPAR-α rs6008845 genotype in the TT, CT, and CC variants (secondary clinical endpoint 7)

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  - Other individual CVD events (time to hospitalization for unstable angina requiring unplanned coronary revascularization, time to hospitalization for HF, time to all-cause mortality, time to first MI [fatal or nonfatal], time to first stroke (fatal or nonfatal), time to first ischemic stroke [fatal or nonfatal], and time to first hemorrhagic stroke [fatal or nonfatal]).

- At 4 months, treatment with pemafibrate lowered fasting TG levels by 24.4% compared to placebo ($p<0.001$). Additionally, VLDL-C was reduced by 17.7%, with similar reductions seen in remnant cholesterol (lipoprotein) (-29.5%), ApoE (-5.5%), and ApoC3 (-26.3%) ($p<0.001$ each) compared to placebo. In contrast, HDL-C levels increased by 4.7% ($p<0.001$).
- At 4 months, pemafibrate was associated with an increase in TC levels compared to placebo; however, this was not significant (least squares [LS] mean difference 0.8% [95% CI: -0.3, 1.9]; p=0.135).
- At 4 months, pemafibrate was associated with an increase in calculated non-HDL-C levels compared to placebo; however, this was not significant (LS mean difference 0% [95% CI: -1.4, 1.4]; p=0.967).
- At 4 months, pemafibrate was associated with an increase in ApoA1 levels compared to placebo; however, this was not significant (LS mean difference 0.6% [95% CI: -0.1, 1.3]; p=0.092).

Conclusion: There was insufficient evidence that treatment with pemafibrate delayed the time to first occurrence of the secondary CV and diabetes-related vascular and nonvascular endpoints in the study population compared to placebo. Pemafibrate was associated with a significant reduction in fasting TG, VLDL-C, ApoC3, ApoE, and remnant lipoprotein, and a significant increase in HDL-C compared to placebo ($p<0.001$). In contrast, non-HDL-C (calculated), TC, and ApoA1 levels were increased, although these were not significant.

Tertiary Endpoints:

The analyses of all tertiary endpoints were considered exploratory as the primary endpoint did not show significance. Pemafibrate was associated with significant differences compared to placebo at some time points for:

- Core and advanced lipid parameters of cholesterol, nonfasting TG, remnant lipoprotein, LDL size. TG/HDL-C, TG/LDL-C, small dense LDL-C, and LDL-TG
- Inflammatory and glycemic parameter of fibroblast growth factor-21 (FGF-21)
- Expanded exploratory lipid and nonlipid parameters of ApoA5, ApoB48, angiopoietin 3, angiopoietin 4, proprotein convertase subtilisin/kexin type 9 (PCSK9), and type IV collagen.

There was insufficient evidence that treatment with pemafibrate delayed the time to first occurrence of microvascular events (diabetic retinopathy and diabetic nephropathy) compared to placebo.

Quality of Life (Patient-Reported Outcomes):

Overall, subjects appeared to have few problems with mobility, self-care, and usual activities. However, as there was no statistical testing to test trend, these are only numerical observations of the data presented in the statistical output.

Safety Results:

Treatment of subjects with T2D and moderate HTG with low HDL-C with pemafibrate was generally safe and well tolerated. This is supported by the fact that there were:

- No clinically meaningful differences (≥2% difference) comparing pemafibrate with placebo in the proportions of subjects with treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), severe TEAEs, treatment related TEAEs, study treatment-related TESAEs, TEAEs leading to study treatment interruption/discontinuation, or TEAEs leading to death;

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- No clinically meaningful differences (≥2% difference) comparing pemafibrate with placebo in the proportion of subjects who reported any TEAE or study treatment-related TEAE at the preferred term level;
- Three study treatment-related TEAEs leading to death were reported, including 2 subjects in the pemafibrate treatment group (unknown cause and hepatic cirrhosis) and 1 subject in the placebo group (cardiogenic shock); and
- No changes over time in clinical laboratory parameters or vital signs that were of clinical concern or indicative of a safety signal.

Conclusion:

After a median follow-up of 3.32 years, the SPPARM-α pemafibrate did not show a significant difference in lowering the risk of nonfatal MI, ischemic stroke, coronary revascularization, or death from CV causes when compared against placebo in subjects with T2D, moderate HTG, and low levels of HDL-C treated with statins.

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