Report on the Deliberation Results

June 13, 2017

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Parmodia Tab. 0.1 mg
Non-proprietary Name	Pemafibrate (JAN*)
Applicant	Kowa Company, Ltd.
Date of Application	October 19, 2015

Results of Deliberation
In its meeting held on June 9, 2017, the First Committee on New Drugs concluded that the product may be approved and that this result should be reported to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product.The re-examination period is 8 years. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Condition of Approval
The applicant is required to develop and appropriately implement a risk management plan.

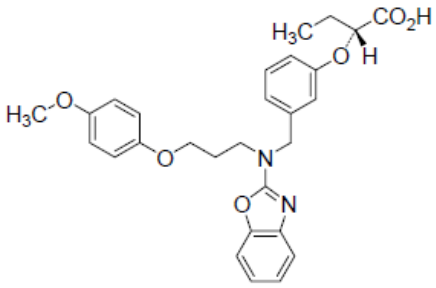
**Japanese Accepted Name (modified INN)*

Review Report

May 17, 2017

Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Parmodia Tab. 0.1 mg
Non-proprietary Name	Pemafibrate
Applicant	Kowa Company, Ltd.
Date of Application	October 19, 2015
Dosage Form/Strength	Film-coated tablet: Each tablet contains 0.10 mg of Pemafibrate.
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Chemical Structure	

Molecular formula: $C_{28}H_{30}N_2O_6$
Molecular weight: 490.55
Chemical name: (2*R*)-2-[3-({1,3-Benzoxazol-2-yl[3-(4-methoxyphenoxy)propyl]amino}methyl) phenoxy] butanoic acid

Items Warranting Special Mention

Prior assessment consultation conducted

Reviewing Office Office of New Drug II

Results of Review

On the basis of the data submitted, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the product has efficacy in the treatment of hyperlipidemia and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. Rhabdomyolysis-related adverse events, safety in patients with renal or hepatic impairment, effects on low-density lipoprotein cholesterol (LDL-C), effects on cardiovascular events, and other issues should undergo further evaluation.

Indication
Hyperlipidemia (including familial hyperlipidemia)

Dosage and Administration
The usual adult dosage is 0.1 mg of pemafibrate orally administered twice daily in the morning and evening. The dose may be adjusted according to the patient's age and symptoms. The maximum dose should be 0.2 mg twice daily.

Condition of Approval
The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

March 13, 2017

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency.

Product Submitted for Approval

Brand Name	Parmodia Tab. 0.1 mg
Non-proprietary Name	Pemafibrate
Applicant	Kowa Company, Ltd.
Date of Application	October 19, 2015
Dosage Form/Strength	Film-coated tablet: Each tablet contains 0.10 mg of Pemafibrate.
Proposed Indication(s)	Hyperlipidemia (including familial hyperlipidemia)
Proposed Dosage and Administration	The usual adult dose is 0.2 mg/day of pemafibrate orally administered in 2 divided doses in the morning and evening. The dose can be increased up to 0.4 mg/day in patients with inadequate response to the initial dose as long as due attention is given to the clinical course.

Table of Contents

List of Abbreviations

A/G ratio	Albumin/globulin ratio
A→B	Apical-to-basolateral direction
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
Apo	Apolipoprotein
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve of the analyte in plasma
$AUC_{0\text{-inf}}$	AUC from time 0 to infinity
$AUC_{0\text{-t}}$	AUC from time 0 to time t
$AUC_{0\text{-}\tau}$	AUC within the interval
B→A	Basolateral-to-apical direction
BA	Bioavailability
BCRP	Breast cancer resistance protein
BE	Bioequivalence
BE Guideline for	Guideline for Bioequivalence Studies for Formulation Changes of

Formulation Changes	Oral Solid Dosage Forms (PMSB/ELD Notification No. 67 dated February 14, 2000; partially revised by PFSB/ELD Notification No. 0229-10 dated February 29, 2012)
BID group	Bis in die group
BMI	Body mass index
BSEP	Bile salt export pump
BUN	Blood urea nitrogen
CCK	Cholecystokinin
CCr	Creatinine clearance
CI	Confidence interval
CK	Creatine phosphokinase
CL	Clearance
C_{max}	Maximum concentration of analyte in plasma
CQA	Critical quality attribute
Cr	Creatinine
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
EAS	European Atherosclerosis Society
EC_{50}	Half maximal effective concentration
eGFR	Estimated glomerular filtration rate
ESC	European Society of Cardiology
FAS	Full analysis set
FF	Fenofibrate
FGF21	Fibroblast growth factor 21
FSH	Follicle stimulating hormone
GC	Gas chromatography
HDL-C	High-density lipoprotein cholesterol
HDPE	High density polyethylene
hERG	Human ether-a-go-go related gene
HPLC	High performance liquid chromatography
IC_{50}	Half maximal inhibitory concentration
ICH Q1E Guideline	Guideline for Evaluation for Stability Data (PFSB/ELD Notification No. 0603004 dated June 3, 2003)
IR	Infrared absorption spectrum
k_a	Absorption rate constant
K_m	Michaelis-Menten constant
LC-MS-MS	Liquid chromatography and tandem mass spectrometry
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LH	Luteinizing hormone
LOCF	Last observation carried forward
LPL	Lipoprotein lipase
LSC	Liquid scintillation counter
MATE	Multidrug and toxin extrusion
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
mRNA	messenger ribonucleic acid
MRP	Multidrug resistance-associated protein
MS	Mass spectrometry
NMR	Nuclear magnetic resonance spectrum
non HDL-C	Non-high-density lipoprotein cholesterol
NTCP	Sodium/taurocholate cotransporting polypeptide

OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
OCTN	Carnitine/organic cation transporter
P_{app}	Apparent permeability coefficient
Parmodia	Parmodia Tab. 0.1 mg
Pemafibrate	Pemafibrate
PEPT	Peptide transporter
P-gp	P-glycoprotein
PMDA	Pharmaceuticals and Medical Devices Agency
PP	Polypropylene
PPAR	Peroxisome proliferator-activated receptor
PPK	Population pharmacokinetic
PPS	Per protocol set
PT	Prothrombin time
PT-INR	Prothrombin time-international normalized ratio
PTP	Press through packaging
QbD	Quality by design
QD group	Quaque die group
RNA	Ribonucleic acid
SD rat	Sprague-Dawley rat
SMQ	Standardised MedDRA query
SOC	System organ class
Statin	Hydroxymethylglutaryl-coenzyme A reductase inhibitor
$t_{1/2}$	Half-life
T_3	Triiodothyronine
T_4	Thyroxine
TC	Total cholesterol
TG	Triglyceride
TGSR	Triglyceride secretion rate
TIBC	Total iron binding capacity
t_{max}	Time to reach the maximum plasma concentration
TSH	Thyroid stimulating hormone
TUNEL	Terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling
UGT	Uridine diphosphate glucuronosyltransferase
UIBC	Unsaturated iron binding capacity
ULN	Upper limits of normal
UVA	Ultraviolet A
UV-VIS	Ultraviolet-visible spectrophotometry
V_{max}	Maximum velocity
V_{ss}	Volume of distribution at steady state
γ-GTP	γ-glutamyltransferase

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Pemafibrate, which was discovered by the applicant, is a peroxisome proliferator-activated receptor (PPAR)α agonist (a drug of the fibrate class). In Japan, fibrates such as fenofibrate (FF), bezafibrate, clinofibrate, and clofibrate are approved with the indication of "hyperlipidemia (including familial hyperlipidemia)" or "hyperlipemia" as drugs lowering trigryceride (TG). As with these fibrates, pemafibrate has also been developed as a TG-lowering drug.

The applicant initiated the development of pemafibrate in 20[redacted]. Based on the results from Japanese clinical studies and other data, a marketing application was filed for approval of pemafibrate in the treatment of "hyperlipidemia (including familial hyperlipidemia)." As of March 2017, pemafibrate has not been approved in any country or region.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance occurs as a white powder, and its description, solubility, hygroscopicity, melting point, dissociation constant, partition coefficient, optical rotation, and crystalline polymorphism have been determined. While the drug substance exists in either of 2 enantiomeric forms (*S* and *R*), the commercial manufacturing process produces only the *R*-form.

The chemical structure of the drug substance has been elucidated by elemental analysis, mass spectrometry (MS), infrared absorption spectrum (IR), ultraviolet-visible spectrophotometry (UV-VIS), nuclear magnetic resonance spectrum (NMR) (^{1}H, ^{13}C), and single crystal X-ray diffractometry.

2.1.2 Manufacturing process

The drug substance is synthesized through [redacted] steps, and [redacted] is used as the starting material. The Quality by Design (QbD) approach was used to investigate the following matters.

- [redacted], [redacted], [redacted] ([redacted]), [redacted] ([redacted], [redacted]) have been identified as the critical quality attributes (CQAs).
- Manufacturing process parameters that may affect the CQAs have been identified based on quality risk assessment.

In addition, [redacted] ([redacted], [redacted], [redacted]), [redacted], and [redacted] were identified as critical steps. The process controls and process control values have been established in [redacted] ([redacted], [redacted], [redacted], [redacted]) and all the critical steps except for [redacted]. No critical intermediates were identified.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description (appearance), identification (UV-VIS, IR), melting point, purity (heavy metals, related substances [high performance liquid chromatography (HPLC)], enantiomer [HPLC], residual solvents [gas chromatography (GC)]), water content, residue on ignition, particle size (laser diffraction method), and assay (HPLC).

2.1.4 Stability of drug substance

Table 1 shows main stability studies of the drug substance. Photostability testing showed that the drug substance is photostable.

Table 1. Stability studies of drug substance

Study	Primary batch	Temperature	Humidity	Storage container	Storage period
Long-term	3 commercial-scale batches	25°C	60%RH	Polyethylene bag	24 months
Accelerated		40°C	75%RH		6 months

Based on the above, a retest period of [redacted] months has been proposed for the drug substance when stored in the polyethylene bag at room temperature. The retest period was determined in accordance with the

Guideline for Evaluation for Stability Data (ICH Q1E Guideline, PFSB/ELD Notification No. 0603004 dated June 3, 2003). Long-term testing will be continued for [redacted] months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a film-coated tablet with a score line, each containing 0.10 mg of pemafibrate. The drug product contains the following excipients: lactose hydrate, croscarmellose sodium, microcrystalline cellulose, hydroxypropylcellulose, magnesium stearate, hypromellose, triethyl citrate, light anhydrous silicic acid, titanium oxide, and carnauba wax.

2.2.2 Manufacturing process

The manufacturing process of the drug product consists of [redacted], [redacted], and [redacted]; [redacted]; [redacted]; [redacted]; [redacted]; film-coating; and filling, packaging, and labeling. [redacted] was identified as a critical step. The process controls and process control values has been established in the critical step as well as [redacted], [redacted], and [redacted].

2.2.3 Control of drug product

The proposed specifications for the drug product include strength, description (appearance), identification (HPLC), purity (related substances [HPLC]), uniformity of dosage units (content uniformity [HPLC]), dissolution (HPLC), and assay (HPLC).

2.2.4 Stability of drug product

Table 2 shows main stability studies of the drug product. Photostability testing showed that the drug product is photostable.

Table 2. Stability studies for drug product

Study	Primary batch	Temperature	Humidity	Storage container	Storage period
Long-term	3 commercial-scale batches	25°C	60%RH	PTP[a] + aluminum pillow bag[b] Bottle[c]	24 months
Accelerated		40°C	75%RH		6 months

[a] Polyvinyl chloride film and aluminum foil
[b] Aluminum-foil-laminated film
[c] HDPE bottle + PP cap

Based on the above, a shelf life of 36 months has been proposed for the drug product when packed in press through packaging (PTP) sheet plus an aluminum pillow bag or in a high density polyethylene (HDPE) bottle stoppered with a polypropylene (PP) cap and stored at room temperature. The shelf life was determined in accordance with the ICH Q1E Guideline. Long-term testing will be continued for [redacted] months.

2.R Outline of the review conducted by PMDA

On the basis of its review of the submitted data and the applicant's responses to inquiries, PMDA concluded that the quality of the drug substance and drug product is controlled adequately.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

3.1 Primary pharmacodynamics

3.1.1 PPARα activation (CTD 4.2.1.1-1)

Transactivation assay was performed in COS-7 cells expressing a chimeric protein containing the Gal4-deoxyribonucleic acid (DNA)-binding domain fused to the ligand-binding domain of human PPARα, PPARγ, or PPARδ. The results showed that the half maximal effective concentration (EC_{50}) of pemafibrate and fenofibric acid for human PPARα activation was 0.00080 and 2.1 μmol/L, respectively. In addition, the EC_{50} of pemafibrate for human PPARγ and PPARδ activation was 4.3 and 9.0 μmol/L, respectively.

3.1.2 Activation of PPARα by metabolites and enantiomer (CTD 4.2.1.1-1, 4.2.1.1-2)

The activation of human PPARα by the metabolites of pemafibrate was evaluated by transactivation assay. The metabolites evaluated include K-15823 (hydroxylated 4-methoxyphenyl group of pemafibrate [position 3]), K-15825 (hydroxylated 4-methoxyphenyl group of pemafibrate [position 2]), K-15834 (hydroxylated benzoxazole group of pemafibrate [position 6]), K-15824 (desmethylated and

methylated K-15823), K-15828 (desmethylated 4-methoxyphenyl group of pemafibrate), K-15830 (desmethylated 4-methoxyphenyl group of K-15834), K-15827 (methoxyphenyl-removed form of pemafibrate), K-23467 (N-dealkylated pemafibrate), K-23469 (dicarboxylated pemafibrate), and K-23605 (oxidized benzyl position of pemafibrate). The results showed that the EC_{50} of K-15825 for human PPARα activation was 0.027 μmol/L, and the EC_{50} values of other metabolites were higher than 0.027 μmol/L.

The activation of human PPARα by the *S*-enantiomer of pemafibrate was evaluated in the same manner. The results showed that the EC_{50} of the *S*-form was 0.64 μmol/L.

3.1.3 Up-regulation of expression of PPARα target gene *CPT1A* by pemafibrate in human primary hepatocytes (CTD 4.2.1.1-3)

The activation of PPARα by pemafibrate in human primary hepatocytes was evaluated based on the expression of *CPT1A* gene, a PPARα target gene. Pemafibrate (0.0001, 0.001, 0.01, 0.1, or 1 μmol/L), fenofibric acid (1, 10, or 100 μmol/L), or vehicle (dimethyl sulfoxide) was added to medium. After 12 hours of incubation, ribonucleic acid (RNA) was collected to measure the level of expression of *CPT1A* gene. Pemafibrate at ≥0.01 μmol/L and fenofibric acid at ≥10 μmol/L significantly up-regulated expression of *CPT1A* gene compared with vehicle.

3.1.4 Effect on plasma TG concentrations in normal rats (CTD 4.2.1.1-4)

Pemafibrate (0.003, 0.01, 0.03, 0.1, 0.3, or 1 mg/kg), fenofibrate (FF) (1, 3, 10, 30, or 100 mg/kg), or vehicle (0.5% methylcellulose solution) was orally administered once daily for 7 days to male Sprague-Dawley (SD) rats (6 weeks of age) (n = 12/group). On Day 7, both pemafibrate and FF decreased plasma TG concentrations in a dose-dependent manner. Significant differences were observed between the vehicle group and any of the groups treated at doses of ≥0.1 mg/kg of pemafibrate or ≥30 mg/kg of FF. The doses of pemafibrate and FF which resulted in decreases in plasma TG concentrations by 20% compared with vehicle (ED_{20}) were 0.052 and 6.5 mg/kg, respectively.

3.1.5 Plasma TG-lowering effect in fructose-loaded hypertriglyceridemia rats (CTD 4.2.1.1-5)

Male SD rats (6 weeks of age) were fed with fructose solution (250 mg/mL) ad libitum to induce hypertriglyceridemia. After 14 days of fructose-loading, pemafibrate (0.1, 0.3, 1, or 3 mg/kg), FF (10, 30, or 100 mg/kg), or vehicle was orally administered once daily for 14 days to these rats (n = 8/group). On Day 14 of administration, both pemafibrate and FF decreased plasma TG concentrations in a dose-dependent manner. Significant differences were observed between any of the dose groups and the vehicle group. The doses of pemafibrate and FF which resulted in decreases in plasma TG concentrations by 50% compared with vehicle (ED_{50}) were 0.14 and 21 mg/kg, respectively.

3.1.6 Plasma TG-lowering effect in Zucker fatty rats (CTD 4.2.1.1-6)

Pemafibrate (0.1, 0.3, 1, or 3 mg/kg), FF (100 mg/kg), or vehicle was orally administered once daily for 14 days to male Zucker fatty rats (10 weeks of age) (n = 8/group). On Day 14, pemafibrate decreased plasma TG concentrations in a dose-dependent manner. Significant differences were observed between the groups treated with pemafibrate at ≥0.3 mg/kg and the vehicle group. FF also decreased plasma TG concentrations significantly compared with vehicle, and the resultant plasma TG concentrations were comparable to those in the pemafibrate 0.3 mg/kg group.

3.1.7 Plasma TG-lowering effect in normal dogs (CTD 4.2.1.1-7)

Pemafibrate (0.01, 0.03, or 0.1 mg/kg), FF (10 or 30 mg/kg), or vehicle was orally administered once daily for 14 days to male beagle dogs (36 months of age) (n = 6/group). According to the analysis of changes from baseline in plasma TG concentrations, pemafibrate and FF showed a significant plasma TG-lowering effect at ≥0.03 and ≥10 mg/kg, respectively, compared with vehicle. In the pemafibrate 0.1 mg/kg and FF 30 mg/kg groups, plasma TG reached its lowest level on Day 7. In both groups, plasma TG concentrations decreased by 66% from baseline.

3.1.8 Activity of pemafibrate in human ApoAI transgenic mice (CTD 4.2.1.1-8)

Pemafibrate (0.1, 0.3, or 1 mg/kg), FF (10, 30, or 100 mg/kg), or vehicle was orally administered once daily for 14 days to human apolipoprotein A-I (ApoAI) transgenic mice (male, 7-8 weeks of age) (n = 6/group). On Day 14, high-density lipoprotein cholesterol (HDL-C) and human ApoAI concentrations

in plasma were significantly higher in the groups treated with pemafibrate at ≥0.3 mg/kg or FF at ≥30 mg/kg than in the vehicle group.

3.1.9 Inhibition of TG synthesis in rat liver (CTD 4.2.1.1-9)

Pemafibrate (1 mg/kg), FF (100 mg/kg), or vehicle was orally administered once daily for 14 days to male Zucker fatty rats (10 weeks of age), and the liver was isolated from the animals (n = 6/group). ^{14}C-acetic acid was added to the prepared liver sections, and then the radioactivity incorporated into TG was measured to investigate the effect of treatment on TG synthesis in the liver. The results showed that both pemafibrate and FF significantly inhibited TG synthesis compared with vehicle.

3.1.10 Effect on TG secretion into blood in rats (CTD 4.2.1.1-10)

Pemafibrate (0.3 mg/kg), FF (30 mg/kg), or vehicle was orally administered once daily for 7 days to male SD rats (6 weeks of age) (n = 10/group). On Day 7, blood was collected immediately before and 2 hours after intravenous administration of tyloxapol (600 mg/kg), an inhibitor of lipoprotein lipase (LPL) activity. Trigryceride secretion rate (TGSR) was then calculated from the increase in plasma TG concentrations. TGSR in the pemafibrate group was significantly lower than that in the vehicle group. There was a trend toward a decrease in TGSR in the FF group, but no significant difference was observed between the FF and vehicle groups.

3.1.11 LPL activation in rats (CTD 4.2.1.1-11)

Pemafibrate (1 mg/kg), FF (30 mg/kg), or vehicle was orally administered once daily for 7 days to male SD rats (7 weeks of age) (n = 8/group). LPL activities in both pemafibrate and FF groups increased to approximately twice that in the vehicle group.

3.1.12 Enhancing effect on plasma TG clearance in rats (CTD 4.2.1.1-12)

Pemafibrate (1 mg/kg), FF (30 mg/kg), or vehicle was orally administered once daily for 7 days to male SD rats (6 weeks of age) (n = 6-8/group). On Day 7, lipid emulsion was intravenously administered followed by measurement of plasma TG concentrations over time. Half-life ($t_{1/2}$) of plasma TG concentrations in the pemafibrate and FF groups was 10.7 and 12.0 minutes, respectively, and these values were significantly shorter than that in the vehicle group (18.6 minutes).

3.1.13 Effects on rat plasma proteins (ApoCIII and Angiopoietin-like Protein 3) and gene expression (*Apoc3*, *Angptl3*, *Aco*, and *Cpt1a*) in the liver (CTD 4.2.1.1-13)

Because ApoCIII and Angiopoietin-like Protein 3 inhibit LPL activity (*J Clin Invest.* 1986;78:1287-95, *J Biol Chem.* 2010;285:27561-70), experiments were performed to investigate the effects of pemafibrate on these plasma protein concentrations and gene expression (*Apoc3* and *Angptl3*). In addition, free fatty acid, a degradation product resulting from TG hydrolysis mediated by LPL, inhibits LPL activity (*Eur Heart J.* 2005;26:1579-81). Thus, experiments were performed to investigate the effects of pemafibrate on expression of genes coding acyl-coenzyme A oxidase 1 (*Aco*) and carnitine palmitoyltransferase type-1a (*Cpt1a*), which are involved in β oxidation of this fatty acid.

Pemafibrate (1 mg/kg), FF (30 mg/kg), or vehicle was orally administered once daily for 7 days to male SD rats (6 weeks of age) (n = 8/group). The plasma concentrations of ApoCIII and Angiopoietin-Like Protein 3 in both pemafibrate and FF groups were significantly lower than those in the vehicle group. The expression of *Apoc3* and *Angptl3* in the liver was significantly inhibited in both groups compared with the vehicle group, but that of *Aco* and *Cpt1a* was significantly enhanced.

3.1.14 Effect on plasma FGF21 concentrations in Zucker fatty rats (CTD 4.2.1.1-6)

Pemafibrate (0.1, 0.3, 1, or 3 mg/kg), FF (100 mg/kg), or vehicle was orally administered once daily for 14 days to male Zucker fatty rats (10 weeks of age) (n = 8/group). Pemafibrate at ≥1 mg/kg significantly increased plasma fibroblast growth factor 21 (FGF21) concentrations compared with vehicle. FF also tended to increase plasma FGF21 concentrations, but no significant difference was observed between the FF and vehicle groups.

3.1.15 Antiarteriosclerotic effect in LDL-receptor knockout mice (CTD 4.2.1.1-14)

Pemafibrate (0.01 or 0.03 mg/kg), FF (100 mg/kg), or vehicle was orally administered once daily for 12 weeks to male low density lipoprotein (LDL)-receptor knockout mice (6 weeks of age) (n = 15/group).

The animals had been fed with a Western diet (containing 21% fat and 0.2% cholesterol) for 1 week before the start of treatment. After the end of treatment, lipid deposits in the aortic sinus (from the aortic root to the cardiac valve wall) were stained with Oil Red O, and the area of stained lipid deposits was evaluated as an arteriosclerotic indicator. The area of lipid deposits in the aortic sinus in the pemafibrate 0.03 mg/kg group was significantly smaller than that in the vehicle group, but no clear effect was observed in the FF group.

3.2 Secondary pharmacodynamics

3.2.1 Duration of TG-lowering effect in normal rats (CTD 4.2.1.2-1)

Pemafibrate (1 mg/kg), FF (30 mg/kg), or vehicle was orally administered once daily for 7 days to male SD rats (6 weeks of age) (n = 8/group). Plasma TG concentrations in both pemafibrate and FF groups remained at a decreased level for 2 days post-dose and then returned to a level comparable to that in the vehicle group.

3.2.2 Effect on bile secretion in rats (CTD 4.2.1.2-2)

Pemafibrate (1 or 3 mg/kg), FF (100 mg/kg), or vehicle was orally administered once daily for 7 days to male SD rats (6 weeks of age) (n = 10/group). The lithogenic index (*Gastroenterology.* 1973;65:698-700) was calculated from lipid and total bile acid concentrations in bile as a cholesterol saturation index. The lithogenic index values and the amount of secreted bile were analyzed. The results showed that the amount of secreted bile was not affected by pemafibrate or FF. The lithogenic index values in the pemafibrate or FF groups were significantly lower than that in the vehicle group.

3.2.3 *In vitro* effects on various enzymes, receptors, and transporters (CTD 4.2.1.2-3 [reference data])

Inhibitory effects or binding affinity of pemafibrate were investigated using 72 types of enzymes, receptors, and transporters. Pemafibrate inhibited cytochrome P450 (CYP) 3A4 and uridine diphosphate glucuronosyltransferase (UGT) 1A1 with half maximal inhibitory concentration (IC_{50}) being 4.04 and 2.21 μmol/L, respectively, but it had no clear inhibitory effect or binding affinity for any of other enzymes, receptors, or transporters at the concentration up to 10 μmol/L.

3.3 Safety pharmacology

Results from safety pharmacology studies are shown in Table 3.

Table 3. Summary of safety pharmacology studies

Object	Test system	Endpoints and evaluation methods, etc.	Dose	Route of administration	Findings	CTD
Clinical signs and effects on central nervous system	SD rat (6 males)	Clinical observation by Irwin method	A single dose of 0, 1, 10, or 100 mg/kg	Oral	No effects	4.2.1.3-1
Effects on cardiovascular systems	Beagle dog (4 males)	Blood pressure, heart rate, electrocardiogram	A single dose of 0, 1, 10, or 100 mg/kg	Oral	Systolic blood pressure decreased at 10 mg/kg	4.2.1.3-3
	Guinea-pig isolated papillary muscle	Action potential	0, 0.1, 1, or 10 μmol/L	*in vitro*	No effects	4.2.1.3-4
	HEK293 cell expressing hERG channel	hERG current	0, 0.1, 1, or 10 μmol/L	*in vitro*	No effects	4.2.1.3-5
Effects on respiratory system	SD rat (8 males)	Respiratory rate, tidal volume, minute ventilation	A single dose of 0, 1, 10, or 100 mg/kg	Oral	Minute ventilation increased at 10 mg/kg	4.2.1.3-2

3.R Outline of the review conducted by PMDA

3.R.1 TG-lowering effect

PMDA's view on the primary pharmacodynamics studies submitted:

Both *in vitro* and *in vivo* studies have demonstrated that pemafibrate activates PPARα by binding to this receptor, and that it decreases TG concentrations in a dose-dependent manner in multiple animal species. These findings suggest that pemafibrate decreases TG concentrations also in humans as in the case of the existing fibrates that are PPARα agonists. However, the efficacy and safety of pemafibrate should

be evaluated based on data from head-to-head clinical studies comparing pemafibrate with the existing fibrates [see Sections "7.R.2 Efficacy," "7.R.3 Effect on lipid parameters other than TG," and "7.R.6 Safety"].

3.R.2 Selectivity to PPARα

The applicant's explanation about the selectivity of pemafibrate to PPARα:
Apart from pemafibrate, all the existing fibrates (especially, bezafibrate) have low selectivity to PPARα and thus are likely to activate not only PPARα but also PPARγ and PPARδ at the clinical dose (*J Med Chem.* 2000;43:527-50). PPARγ activation may lead to increased insulin sensitivity and decreased hepatic gluconeogenesis, resulting in hypoglycemia. Furthermore, PPARα and PPARδ may be partly responsible for elevated creatine phosphokinase (CK), a common adverse reaction to fibrates; activation of these receptors stimulates peroxisomal and mitochondrial β-oxidation, causing oxidative stress injury in tissue (*Toxicol Sci.* 2008;105:384-94).

Given that pemafibrate is a selective and potent PPARα agonist and in view of currently expected blood pemafibrate concentrations at the clinical dose, the above-mentioned effects mediated by activation of PPARγ and PPARδ are unlikely to occur in patients receiving pemafibrate at the clinical dose. In addition, a risk of elevated CK resulting from PPARα activation induced by pemafibrate is unlikely to be high compared with such effect caused by FF, for the following reasons: (i) The degree of PPARα activation by pemafibrate at the clinical dose (ratio of EC_{50} for PPARα activation to plasma concentrations) does not exceed that by FF, though pemafibrate has high selectivity to PPARα; and (ii) neither pemafibrate nor FF presented any trend toward an increased risk of elevated CK in clinical studies.

PMDA's view:
Although *in vitro* studies have demonstrated that pemafibrate activates PPARα by binding to this receptor selectively, how the binding selectivity of pemafibrate affects the efficacy and safety of pemafibrate in humans should be assessed based on clinical data, including those from clinical studies comparing pemafibrate with the existing fibrates [see Sections "7.R.2 Efficacy," "7.R.3 Effect on lipid parameters other than TG," and "7.R.6 Safety"].

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Plasma pemafibrate concentrations were measured by liquid chromatography and tandem mass spectrometry (LC-MS-MS). The lower limits of quantitation (LLOQs) of mouse, rat, dog, and monkey plasma were 0.3, 0.05 to 1, 0.2 to 0.3, and 0.3 ng/mL, respectively. Following administration of ^{14}C-pemafibrate, the radioactivity was measured using liquid scintillation counter (LSC).

Unless otherwise specified, the pharmacokinetic parameters are expressed as the mean or mean ± standard deviation (SD).

4.1 Absorption

4.1.1 Single-dose administration (CTD 4.2.2.2-1 to 4.2.2.2-4)

Table 4 shows the pharmacokinetic parameters of pemafibrate following oral (p.o.) or intravenous (i.v.) administration of a single dose of pemafibrate or ^{14}C-pemafibrate to rats, dogs, and monkeys under fasted or fed conditions.

Table 4. Pharmacokinetic parameters following oral or intravenous administration of a single dose of pemafibrate or ^{14}C-pemafibrate

Route of administration	Dose (mg/kg)	Sex	Dose timing	C_{max} (ng/mL or ng eq/mL)	t_{max}[a] (h)	AUC[b] (ng·h/mL or ng eq·h/mL)	$t_{1/2}$ (h)	CL (mL/min/kg)	V_{ss} (L/kg)	BA or absorption rate (%)
Rat										
i.v.	0.3[c]	Male	Fasted	-	-	348 ± 26	-[e]	-[e]	-[e]	-
		Female	Fasted	-	-	417 ± 50	4.46, 6.04[f]	10.5, 10.4[f]	0.887, 1.80[f]	-
p.o.	0.1[c]	Male	Fasted	4.53 ± 2.26	0.25	17.1 ± 3.9	-[e]	-	-	14.7 ± 3.4
		Female	Fasted	3.27 ± 0.94	0.25	17.0 ± 4.9	-[e]	-	-	12.3 ± 3.5
	0.3[c]	Male	Fasted	8.81 ± 3.45	4	53.2 ± 21.1	-[e]	-	-	15.3 ± 6.1
		Female	Fasted	9.87 ± 3.08	0.5	39.4 ± 16.5	-[e]	-	-	9.45 ± 3.96
	1[c]	Male	Fasted	33.8 ± 16.6	1	168 ± 33	-[e]	-	-	14.5 ± 2.9
		Female	Fasted	34.0 ± 15.1	0.5	273 ± 98	-[e]	-	-	19.6 ± 7.0
		Male	Fed	9.45 ± 0.20	2	97.2 ± 31.8	-	-	-	-
		Female	Fed	18.9 ± 0.4	0.5	148 ± 42	-	-	-	-
i.v.	0.3[d]	Male	Fasted	-	-	419 ± 51	-[e]	-	-	-
		Female	Fasted	-	-	368 ± 28	-[e]	-	-	-
p.o.	1[d]	Male	Fasted	48.4 ± 25.0	2	365 ± 237	-[e]	-	-	27.3 ± 19.7
		Female	Fasted	76.8 ± 31.8	0.5	499 ± 219	-[e]	-	-	40.1 ± 14.7
Dog										
i.v.	0.3[e]	Male	Fasted	-	-	457 ± 117	-[e]	-	-	-
p.o.	0.1[c]	Male	Fasted	7.35 ± 2.37	0.5	22.2 ± 6.0	-[e]	-	-	14.5 ± 4.0
	0.3[c]	Male	Fasted	29.2 ± 5.6	0.5	85.8 ± 23.9	-[e]	-	-	18.7 ± 5.2
	1[c]	Male	Fasted	99.7 ± 73.1	0.25	237 ± 22	-[e]	-	-	15.6 ± 1.5
		Female	Fasted	100 ± 67	0.25	277 ± 55	-[e]	-	-	18.2 ± 3.6
		Male	Fed	35.9 ± 16.9	1.5	219 ± 49	-	-	-	-
Monkey										
i.v.	1[c]	Male	Fasted	-	-	1510 ± 300	2.45 ± 1.02	8.89 ± 1.60	0.268 ± 0.165	-
p.o.	1[c]	Male	Fasted	694 ± 500	2	1560 ± 860	2.45 ± 1.48	-	-	87.4 ± 47.9

-, Not calculated; n = 3/group
[a] Median
[b] $AUC_{0\text{-}t}$ for rats and dogs, $AUC_{0\text{-}inf}$ for monkeys
[c] Pemafibrate (unlabeled)
[d] Pemafibrate (^{14}C-labeled)
[e] Not calculated because plasma concentrations re-elevated in the elimination phase.
[f] n = 2

4.1.2 Repeated-dose studies (CTD 4.2.3.4.1-1 to 4.2.3.4.1-2, 4.2.3.2-3 to 4.2.3.2-4, 4.2.3.2-6, 4.2.3.2-11)

The applicant submitted toxicokinetic data from repeated oral dose toxicity studies as pharmacokinetic data following repeated oral administration of pemafibrate.

Table 5 shows the pharmacokinetic parameters of pemafibrate in male and female mice following 13-week repeated oral administration of pemafibrate.

Table 5. Pharmacokinetic parameters of pemafibrate in mice following 13-week repeated oral administration

Dose (mg/kg/day)	Sampling time point	Male			Female		
		C_{max} (ng/mL)	t_{max}[a] (h)	AUC_{0-24} (ng·h/mL)	C_{max} (ng/mL)	t_{max}[a] (h)	AUC_{0-24} (ng·h/mL)
0.1	Day 1	5.7	1	16.6	8.9	0.5	27.9
	Week 4	3.0	0.5	14.5	10.1	0.5	37.3
	Week 13	2.6	1	17.1	14.3	1	74.0
0.2	Day 1	9.0	0.5	26.4	11.5	1	61.2
	Week 4	6.3	0.5	39.5	16.5	1	106.1
	Week 13	11.4	2	51.1	18.2	1	127.9
0.4	Day 1	12.1	0.5	35.1	30.7	0.5	87.2
	Week 4	15.1	0.5	94.4	104.2	0.5	247.2
	Week 13	19.5	1	115.7	49.3	0.5	333.6
0.5	Day 1	23.4	0.5	67.5	56.0	0.5	156.1
	Week 13	115.1	1	540.9	75.2	1	714.3
0.75	Day 1	31.8	0.5	98.2	95.2	0.5	233.4
	Week 13	220.9	4	1967.9			
1	Day 1	38.3	0.5	127.9	89.8	0.5	324.7
	Week 13	245.6	2	2567.7			

n = 2 to 3/time point
[a] Median

Table 6 shows the pharmacokinetic parameters of pemafibrate in male and female rats following 26-week repeated oral administration of pemafibrate.

Table 6. Pharmacokinetic parameters of pemafibrate in rats following 26-week repeated oral administration

Dose (mg/kg/day)	Sampling time point	Male[a]			Female[b]		
		C_{max} (ng/mL)	t_{max}[c] (h)	AUC_{0-24} (ng·h/mL)	C_{max} (ng/mL)	t_{max}[c] (h)	AUC_{0-24} (ng·h/mL)
0.03	Day 1	0.85	1	5.56	0.67	0.75	6.27
	Week 13	0.88	0.75	5.12	1.23	0.5	5.51
	Week 26	1.15	0.25	5.92	1.21	0.75	7.52
0.1	Day 1	2.97	4	20.68	2.30	0.75	20.27
	Week 13	2.19	0.25	13.29	2.66	1	18.16
	Week 26	3.91	0.25	13.31	2.99	0.75	18.67
0.3	Day 1	9.0 ± 2.4	0.5	-			
	Week 13	4.3 ± 1.4	2	-			
	Week 26	6.1 ± 4.1	0.5	-			
1	Day 1	39.3 ± 7.7	1.25	-	33.2	2	256.5
	Week 13	14.4 ± 2.8	0.5	-	23.2	0.5	158.3
	Week 26	25.2 ± 13.5	0.5	-	31.2	0.5	174.2
3	Day 1	169.1 ± 43.8	0.5	-			
	Week 13	98.2 ± 24.1	0.5	-			
	Week 26	110.3 ± 26.1	0.5	-			
5	Day 1				225.4	0.5	1568.1
	Week 13				130.2	0.5	523.9
	Week 26				147.8	0.5	706.3
25	Day 1				6142.7	0.5	16,340.9
	Week 13				1387.8	0.5	3367.0
	Week 26				129.7	0.5	594.1

-, Not calculated
[a] n = 4 (0.3, 1, or 3 mg/kg/day), n = 3 to 4/time point (0.03 or 0.1 mg/kg/day)
[b] n = 4/time point
[c] Median

Table 7 shows the pharmacokinetic parameters of pemafibrate in male and female dogs following 13-week repeated oral administration of pemafibrate.

Table 7. Pharmacokinetic parameters of pemafibrate in dogs following 13-week repeated oral administration

Dose (mg/kg/day)	Sampling time point	Male			Female		
		C_{max} (ng/mL)	t_{max}[a] (h)	AUC_{0-24} (ng·h/mL)	C_{max} (ng/mL)	t_{max}[a] (h)	AUC_{0-24} (ng·h/mL)
0.1	Day 1	9.5 ± 5.0	0.5	29.6 ± 14.2	5.3 ± 2.1	1.0	21.0 ± 3.0
	Week 13	6.3 ± 2.3	0.5	30.0 ± 6.5	10.8 ± 4.6	0.5	43.1 ± 7.7
0.3	Day 1	19.4 ± 3.5	0.5	57.5 ± 4.4	17.3 ± 11.5	0.5	49.1 ± 28.2
	Week 13	40.0 ± 16.0	0.5	103.6 ± 26.0	30.4 ± 4.5	1.0	173.6 ± 18.9
1	Day 1	279.8 ± 109.5	0.5	429.5 ± 149.3	168.3 ± 33.5	0.5	317.2 ± 120.2
	Week 13	194.0 ± 75.3	0.5	1201.9 ± 577.4	212.9 ± 143.3	0.5	1144.8 ± 560.8
3	Day 1	748.1 ± 73.7	0.5	1193.1 ± 193.0	241.6 ± 25.1	0.5	631.6 ± 219.6
	Week 13	625.3, 570.1[b]	0.5, 0.5[b]	2334.7, 3718.8[b]	791.7 ± 309.0	0.5	4505.7 ± 2766.4

n = 2 to 3/group
[a] Median
[b] n = 2

Table 8 shows the pharmacokinetic parameters of pemafibrate in male and female monkeys following 52-week repeated oral administration of pemafibrate.

Table 8. Pharmacokinetic parameters of pemafibrate in monkeys following 52-week repeated oral administration

Dose (mg/kg/day)	Sampling time point	Male			Female		
		C_{max} (ng/mL)	t_{max}[a] (h)	AUC_{0-24} (ng·h/mL)	C_{max} (ng/mL)	t_{max}[a] (h)	AUC_{0-24} (ng·h/mL)
0.1[b]	Day 1				17.6 ± 10.6	0.5	29.9 ± 10.5
	Day 182				9.3 ± 4.2	0.5	-
	Day 364				9.1 ± 1.1	0.5	25.0 ± 8.8
0.3[b]	Day 1	32.7 ± 10.3	1.25	89.9 ± 20.0	41.7 ± 17.6	0.5	99.9 ± 57.2
	Day 182	32.0 ± 9.3	0.5	-	29.1 ± 16.3	0.5	-
	Day 364	37.8 ± 13.9	0.5	72.4 ± 11.8	46.4 ± 7.8	0.5	89.4 ± 16.8
1[b]	Day 1	145.2 ± 64.0	0.5	343.0 ± 121.5	103.8 ± 66.2	0.5	245.3 ± 17.9
	Day 182	193.2 ± 45.0	1.25	-	113.0 ± 30.5	0.5	-
	Day 364	160.6 ± 81.1	1.25	334.7 ± 119.7	141.0 ± 80.6	0.5	356.7 ± 154.0
3[b]	Day 1	621.8 ± 475.7	0.75	860.3 ± 295.3	561.1 ± 192.8	0.5	718.3 ± 249.6
	Day 182	561.3 ± 183.9	0.5	-	661.1 ± 299.6	0.5	-
	Day 364	527.6 ± 105.8	1	1098.9 ± 120.2	558.9 ± 129.5	0.5	991.3 ± 335.3
10[c]	Day 1	8448.6 ± 4566.6	1	9528.9 ± 2983.8			
	Day 182	3621.7 ± 2068.5	0.5	-			
	Day 364	3882.2 ± 1328.2	1	8368.7 ± 3832.6			

-, Not calculated
[a] Median
[b] n = 4 (n = 1 [female] at 3 mg/kg/day, n = 6 on Day 182, n = 5 on Day 364)
[c] n = 6

4.1.3 Absorption sites (CTD 4.2.2.2-5)

Following a single injection of pemafibrate at 1 mg/kg into the stomach, duodenum, jejunum, ileum, and colon loop in male rats under fasted conditions, the AUC_{0-t} of pemafibrate was 57.9 ± 23.5, 1040 ± 840, 165 ± 19, 138 ± 38, and 152 ± 23 ng·h/mL, respectively. The highest amount of pemafibrate was absorbed in the duodenum, followed in descending order by the jejunum, colon, ileum, and stomach.

4.2 Distribution

4.2.1 Tissue distribution (CTD 4.2.2.3-1 to 4.2.2.3-3, 4.2.2.2-6)

A single oral dose of ^{14}C-pemafibrate (1 mg/kg) was administered to male and female albino rats to evaluate the distribution of radioactivity by wholebody autoradiography (n = 1/sex/time point). The radioactivity in tissues such as the stomach, intestine, liver, and portal vein remained higher than that in blood from 0.5 to 6 hours post-dose, and then the radioactivity was eliminated from all the tissues by 168 hours post-dose.

A single intravenous dose of ^{14}C-pemafibrate (1 mg/kg) was administered to male and female albino rats to evaluate the distribution of radioactivity by wholebody autoradiography (n = 1/sex/time point).

The radioactivity in tissues such as the liver, portal vein, and intestine remained higher than that in blood from 0.5 to 6 hours post-dose, and then the radioactivity was eliminated from all the tissues by 168 hours post-dose.

A single oral dose of ^{14}C-pemafibrate (1 mg/kg) was administered to male albino rats to evaluate the distribution of radioactivity by quantitative wholebody autoradiography (n = 3/time point). The peak radioactivity level was reached at 0.5 hours post-dose in most of the tissues, and the radioactivity in the liver, renal cortex, bladder wall, urine in the bladder, and gastrointestinal tissues remained higher than that in plasma from 0.5 to 6 hours post-dose. The radioactivity was detected in the liver and large intestine wall at 72 hours post-dose, but was below the LLOQ (0.003 μg eq/g) in all the tissues at 168 hours post-dose.

A single oral dose of ^{14}C-pemafibrate (1 mg/kg) was administered to male pigmented rats to evaluate the distribution of radioactivity by quantitative wholebody autoradiography (n = 1/time point). The radioactivity levels in the whole blood, kidney, non-pigmented skin, and liver in these pigmented rats were comparable to those in the albino rats. The radioactivity was detected in the eyeball, uvea and retina, and pigmented skin at 6 hours post-dose, but was below the LLOQ (0.003 μg eq/g) in all the tissues at 24 hours post-dose.

A single oral dose of ^{14}C-pemafibrate (1 mg/kg) was administered to pregnant rats on gestation day 12 or 18 to evaluate the distribution of radioactivity by quantitative wholebody autoradiography (n = 1/time point). On gestation day 12, the radioactivity level in the placenta was lower than that in plasma and was below the LLOQ (3.20 ng eq/g) at 24 hours post-dose. The radioactivity levels in the fetuses were below the LLOQ at any time point. On gestation day 18, the radioactivity levels in the placenta and fetuses were lower than that in plasma and were below the LLOQ at 24 hours post-dose.

A single oral dose of ^{14}C-pemafibrate (1 mg/kg) was administered to male monkeys to evaluate the distribution of radioactivity by quantitative wholebody autoradiography (n = 1/time point). The peak radioactivity level was reached at 1 hour post-dose in most of the tissues. The radioactivity levels higher than that in plasma were detected in the kidney, liver, and gallbladder (bile) at 1 hour post-dose, liver and gallbladder (bile) at 6 hours post-dose, and gallbladder (bile) at 24 hours post-dose. The radioactivity levels fell below the LLOQ (0.003 μg eq/g) in most of the tissues by 504 hours post-dose, at which the level in any quantitative tissue was lower than that in plasma (0.015 μg eq/g).

4.2.2 Plasma protein binding and distribution in blood cells (CTD 4.2.2.3-4)

^{14}C-pemafibrate was added to mouse, hamster, rat, dog, and monkey plasma at a final concentration of 0.5 to 10 μg/mL. The fractions of unbound pemafibrate in mouse, hamster, rat, dog, and monkey plasma represented 0.46% to 0.48%, 0.25% to 0.29%, 0.27% to 0.29%, 0.17% to 0.18%, and 0.17% to 0.22%, respectively. There was no concentration dependency.

When ^{14}C-pemafibrate was added to mouse, hamster, rat, dog, and monkey blood at a final concentration of 0.5 to 10 μg/mL, the distribution of pemafibrate in blood cells represented 9.6% to 12.2%, 5.1% to 13.7%, 18.2% to 41.4%, 1.4% to 7.8%, and 17.2% to 27.2%, respectively. The values tended to decrease with increasing concentrations of pemafibrate.

4.3 Metabolism

4.3.1 *In vitro* metabolism

4.3.1.1 Metabolism of pemafibrate (CTD 4.2.2.4-7 to 4.2.2.4-10)

Pemafibrate was incubated with liver microsomes from the mouse, rats, dog, and monkey at a concentration of 10 μmol/L at 37°C. K-15823 (hydroxylated 4-methoxyphenyl group of pemafibrate [position 3]), K-15824 (desmethylated and methylated K-15823), K-15825 (hydroxylated 4-methoxyphenyl group of pemafibrate [position 2]), K-15827 (4-methoxyphenyl-removed form of pemafibrate), K-15828 (desmethylated 4-methoxyphenyl group of pemafibrate), K-15830 (desmethylated 4-methoxyphenyl group of K-15834), and K-15834 (hydroxylated benzoxazole group of pemafibrate [position 6]) were detected in the samples from all the animal species tested.

^{14}C-pemafibrate was incubated with liver microsomes from the mouse, hamster, rat, dog, and monkey at a concentration of 0.5 μmol/L at 37°C. The metabolic clearance in the phase I reaction was high in hamster liver microsomes and low in mouse and rat liver microsomes. The metabolic clearance in the phase II reaction was high in dog liver microsomes.

^{14}C-pemafibrate was incubated with hepatic cytosols, hepatic S9 fraction, or hepatocytes from the mouse, rat, dog, and monkey at a concentration of 5 μmol/L at 37°C. The reaction hardly occurred in the hepatic cytosols. The reaction pattern in the hepatic S9 fraction was similar to that in the liver microsomes, and K-15827, K-15828, and K-15834 were mainly detected. Glucuronide conjugates of pemafibrate were detected in the hepatocytes from all the animal species tested, and they were more frequently found in dog and rat hepatocytes.

4.3.2 *In vivo* metabolism

4.3.2.1 Plasma metabolites (CTD 4.2.2.2-1 to 4.2.2.2-3, 4.2.2.2-6, 4.2.2.4-1, 4.2.2.4-12 to 4.2.2.4-13)

Following oral administration of a single dose of pemafibrate (1 mg/kg) to male and female rats, unchanged pemafibrate was the predominant compound in terms of C_{max} and $AUC_{0\text{-}t}$. The metabolites detected were K-15828, K-15834, and K-15827 (only in males) in descending order, but the amount of any of these metabolites was <10% of unchanged pemafibrate.

A single oral dose of pemafibrate, K-23467 (*N*-dealkylated pemafibrate), or K-23469 (dicarboxylated pemafibrate) was administered to male rats at a dose of 3 mg/kg to predict the pathway of metabolism of pemafibrate to K-23605 (oxidized benzyl position of pemafibrate), a major metabolite found in human plasma. K-23605 was detected after administration of pemafibrate and K-23467 (with $AUC_{0\text{-}t}$ being 35.8 and 8.74 ng·h/mL, respectively), but it was not detected after administration of K-23469. These results suggested that K-23605 was formed via K-23467.

Following oral administration of a single dose of ^{14}C-pemafibrate (1 mg/kg) to male rats, unchanged pemafibrate was the predominant compound in plasma. The metabolites detected were K-23467, K-23605, and K-15827/K-23469 (calculated as the total amount because K-15827 and K-23469 could not be separately quantified), and their amounts were 15.5%, 9.7%, and 1.8% of unchanged pemafibrate, respectively.

Following oral administration of a single dose of pemafibrate (0.1 to 1 mg/kg) or a single intravenous dose of pemafibrate (0.3 mg/kg) to male and female dogs, unchanged pemafibrate was the predominant compound in plasma. The metabolites detected were K-15827, K-15828, and K-15834 in descending order, but the amount of any of these metabolites was <10% of unchanged pemafibrate.

Following oral or intravenous administration of a single dose of pemafibrate (1 mg/kg) to male monkeys, K-23467 and K-23469 were detected in plasma in addition to unchanged pemafibrate, and the amount of either metabolite was ≥10% of unchanged pemafibrate.

Following oral administration of a single dose of ^{14}C-pemafibrate (1 mg/kg) to male monkeys, K-23467, K-15827/K-23469, and K-23605 were mainly detected in plasma in addition to unchanged pemafibrate, and their amounts were 1050%, 977%, and 560% of unchanged pemafibrate, respectively.

4.3.2.2 Metabolites in urine and feces (CTD 4.2.2.2-6, 4.2.2.4-3 to 4.2.2.4-5)

Following oral administration of a single dose of pemafibrate (0.1 to 1 mg/kg), or following intravenous administration of a single dose of pemafibrate (0.3 mg/kg), to male and female rats, unchanged pemafibrate (24.3% to 54.4%, percentage of the dose), K-15828 (9.0% to 24.9%), and K-15834 (1.2% to 6.3%) were mainly found in feces. Unchanged pemafibrate or metabolites were scarcely excreted in urine.

Following oral administration of a single dose of ^{14}C-pemafibrate (1 mg/kg) to male and female rats, unchanged pemafibrate (40%), K-15828 (29%), K-15834 (7%), and K-15827 (5%) were mainly found in feces. Unchanged pemafibrate or metabolites were scarcely excreted in urine.

Following oral administration of a single dose of pemafibrate (0.1 to 1 mg/kg) or a single intravenous dose of pemafibrate (0.3 mg/kg) to male and female dogs, unchanged pemafibrate (31.3% to 41.1%), K-15828 (3.4% to 6.5%), K-15834 (2.0% to 3.6%), and K-15827 (1.5% to 2.6%) were mainly found in feces. Unchanged pemafibrate or metabolites were scarcely excreted in urine.

Following oral administration of a single dose of ^{14}C-pemafibrate (1 mg/kg) to male monkeys, K-23467 (2%) and K-23605 (4%) were mainly found in urine. K-15827/K-23469 (14%), K-15828 (10%), K-15834 (4%), K-23605 (3%), K-23467 (2%), and K-23599 (2%) were found in feces.

4.3.2.3 Metabolites in bile (CTD 4.2.2.4-6)

Following oral administration of a single dose of ^{14}C-pemafibrate (1 mg/kg) to male rats, its metabolite deemed as a conjugate of pemafibrate (50%), unchanged pemafibrate (10%), and its metabolite deemed as a conjugate of K-15828 (5%) were mainly found in bile.

4.3.2.4 *In vivo* chiral inversion (CTD 4.2.2.4-2)

Following oral administration of a single dose of pemafibrate or *S*-form of pemafibrate (3 mg/kg) or a single intravenous dose of pemafibrate or *S*-form of pemafibrate (0.3 mg/kg) to male and female rats, the percentage of chiral inversion was ≤1%.

4.4 Excretion

4.4.1 Excretion in urine, feces, and expired air (CTD 4.2.2.2-6, 4.2.2.3-1)

Following oral administration of a single dose of ^{14}C-pemafibrate (1 mg/kg) to male and female rats, 1.1% and 0.6% of the administered radioactivity, respectively, were excreted in urine up to 168 hours post-dose, while 98.7% and 97.3% of the administered radioactivity, respectively, were excreted in feces.

Following intravenous administration of a single dose of ^{14}C-pemafibrate (1 mg/kg) to male and female rats, 2.0% and 0.5% of the administered radioactivity, respectively, were excreted in urine up to 168 hours post-dose, while 98.1% and 98.4% of the administered radioactivity, respectively, were excreted in feces. No radioactivity was detected in expired air.

Following oral or intravenous administration of a single dose of ^{14}C-pemafibrate (1 mg/kg) to male monkeys, 11.0% and 12.2% of the administered radioactivity, respectively, were excreted in urine up to 168 hours post-dose, while 50.8% and 42.0% of the administered radioactivity, respectively, were excreted in feces.

4.4.2 Biliary excretion and enterohepatic circulation (CTD 4.2.2.4-6)

Following oral administration of a single dose of ^{14}C-pemafibrate (1 mg/kg) to male rats, 69.5% of the administered radioactivity was excreted in bile up to 48 hours post-dose. When the bile sample collected up to 8 hours post-dose was injected into the duodenum in other male rats, 60.0% of the administered radioactivity was excreted in bile up to 48 hours post-dose.

4.4.3 Excretion in milk (CTD 4.2.2.5-1)

Following oral administration of a single dose of ^{14}C-pemafibrate (1 mg/kg) to lactating rats on postpartum day 12, the peak radioactivity level (29.4 ng eq/mL) was reached in milk at 6 hours post-dose and then radioactivity levels in milk decreased with decreasing plasma radioactivity levels.

4.5 Pharmacokinetic drug-drug interactions

4.5.1 Metabolic enzyme induction (CTD 4.2.2.6-1)

When pemafibrate (0.1, 0.3, or 1 mg/kg) was orally administered once daily for 7 days to male rats, testosterone 16β-hydroxylase activity (CYP2B activity) increased at ≥0.3 mg/kg.

4.5.2 Effect of anion exchange resin (CTD 4.2.2.6-10)

Various anion exchange resins were added to fasted or fed state-simulated intestinal juice to investigate adsorption of pemafibrate (0.8 μmol/L). The rates of adsorption of pemafibrate to cholestyramine and colestimide after 120 minutes of incubation ranged from 97.0% to 100% and from 90.7% to 98.3%, respectively.

4.5.3 Dialysis property (CTD 4.2.2.7-1)

Dialysis properties of pemafibrate, K-23467, K-23469, and K-23605 (5 or 50 ng/mL) were investigated using a polysulfone hemodialysis membrane. The residual rates of pemafibrate, K-23467, K-23469, and K-23605 after 120 minutes of dialysis were 80.9% to 83.4%, 86.8% to 90.4%, 89.6% to 98.1%, and 81.0% to 92.1%, respectively. All the results were comparable to the residual rate of albumin.

4.R Outline of the review conducted by PMDA

4.R.1 Enzyme induction

Data obtained after repeated administration of pemafibrate to rats showed that exposure to pemafibrate after repeated dose was lower than that after the first dose. The metabolic enzyme induction study showed a significant increase in testosterone 16β-hydroxylase activity (CYP2B activity). PMDA therefore asked the applicant to explain whether enzyme induction may occur as a consequence of multiple doses of pemafibrate in humans, and whether such enzyme induction may pose clinically relevant problems.

The applicant's explanation:

The testosterone 16β-hydroxylase activity in rats receiving repeated doses of pemafibrate at 0.3 or 1 mg/kg/day was increased by approximately 1.5-fold that in the control group. However, the C_{max} of pemafibrate in rats which received repeated doses of pemafibrate at 0.3 and 1 mg/kg/day for 4 weeks (CTD 4.2.3.7.5-6) was 3.82 to 4.91 and 27.5 ng/mL, respectively, which were approximately 1.0- to 1.3-fold and 7.3-fold that in humans at the maximum clinical dose (0.2 mg twice daily). In addition, an *in vitro* study using human hepatocytes showed that none of pemafibrate and its metabolites (K-23467, K-23469, and K-23605) induced CYP2B6 [see Section "6.2.1.2.4 Induction of CYP isoforms"], although the maximum concentration (20 μmol/L) in this study was ≥2591-fold the C_{max} values of pemafibrate, K-23467, K-23469, and K-23605 in humans (3.787, 0.655, 0.369, and 0.517 ng/mL, respectively) at the maximum clinical dose.[1)] Based on the above, pemafibrate is unlikely to cause clinically relevant metabolic enzyme induction, because (i) plasma pemafibrate concentrations at which enzyme induction was observed in rats were higher than those in humans at the clinical dose, and (ii) none of pemafibrate and its metabolites showed enzyme induction in a study using human hepatocytes.

PMDA's view:

Although the metabolic enzyme induction in rats was explained by the applicant, the exposure causing enzyme induction in rats is not significantly higher than that in humans at the maximum clinical dose. However, it is unlikely that metabolic enzymes are induced in humans following multiple doses of pemafibrate, leading to a clinically relevant decrease in blood pemafibrate concentrations, for the following reasons: (1) Results from an *in vitro* study using human hepatocytes (based on the expression of the corresponding messenger ribonucleic acid [mRNA]) have demonstrated that none of pemafibrate and its metabolites induce metabolic enzymes; and (2) blood pemafibrate concentrations were not decreased in human subjects treated with multiple doses of pemafibrate at the clinical dose in clinical pharmacology studies [see Section "6.2.3.1 Multiple-dose study"].

4.R.2 Safety in tissues in which pemafibrate is distributed at high concentrations

PMDA asked the applicant to identify tissues in which the radioactivity was distributed at high levels after administration of ^{14}C-pemafibrate in tissue distribution studies and tissues in which elimination of the radioactivity was slow in the same studies, and then to explain the safety in these tissues.

The applicant's explanation:

According to the wholebody autoradiography in rats treated with pemafibrate, the radioactivity level ≥2 fold that in plasma (or whole blood from pigmented rats) was found in the liver, renal cortex, mesenteric lymph node, cisterna chyli, amniotic membrane, bladder wall, and gastrointestinal tract; and radioactivity was eliminated more slowly from the liver, amniotic membrane, and large intestine wall than from plasma. Toxicological findings in these tissues in repeated-dose toxicity studies in rats [see Section "5.2 Repeated-dose toxicity"] included necrosis, periportal hypertrophy, eosinophilic change, fibrillization/regenerative hyperplasia in the liver, and chronic nephropathy in the kidney. Findings in repeated-dose toxicity studies in monkeys [see Section "5.2 Repeated-dose toxicity"] were increased

1) Data from subjects receiving pemafibrate alone in a pharmacokinetic interaction study of pemafibrate with pravastatin, simvastatin, or fluvastatin (Study K-877-18)

liver weight, eosinophilic change in hepatocytes, vacuolation, pigmentation of hepatocytes/Kupffer cells, but no structural toxicity was observed. There were no noteworthy findings in other tissues.

Pooled analysis was performed for adverse events coded to "Drug related hepatic disorders - comprehensive search (Standardised Medical dictionary for regulatory activities [MedDRA] query [SMQ])," "Acute renal failure (SMQ)," "Gastrointestinal disorders" in system organ class (SOC), and adverse events involving the bladder (including "bladder" in MedDRA preferred terms) in clinical studies. According to the pooled analysis of 12-week data,[2)] the incidences of these adverse events in the pemafibrate group were comparable to those in the placebo group and the incidences of the adverse events did not tend to increase with increasing dose of pemafibrate. In addition, the pooled analysis of data[3)] from subjects who received pemafibrate 0.2 or 0.4 mg for 52 weeks showed no trend toward an increase in the incidences of the above adverse events with increasing treatment duration. There were no events possibly related to the mesenteric lymph node, cisterna chyli, or amniotic membrane.

As shown above, there have been no clinically relevant problems in the tissues in which pemafibrate is distributed at high concentrations post-dose and tissues in which its elimination is slow, and thus the tissue distribution profile of pemafibrate is unlikely to affect the safety.

PMDA's view:
The tissue distribution studies showed that pemafibrate was present in the liver, kidney, mesenteric lymph node, cisterna chyli, amniotic membrane, bladder, and gastrointestinal tract at high concentrations, and that radioactivity was eliminated more slowly from the liver, amniotic membrane, and large intestine wall than from plasma. Taking the applicant's explanation into account, however, accumulation of pemafibrate in these tissues associated with its distribution and delayed elimination is unlikely to be relevant to humans.

4.R.3 Adsorption to anion exchange resin

The applicant's explanation about adsorption of pemafibrate to anion exchange resin:
The results of an *in vitro* study for adsorption of pemafibrate to anion exchange resin indicate that pemafibrate is readily adsorbed by an anion exchange resin. In clinical studies, on the other hand, plasma pemafibrate concentrations after oral dosing declined in a monophasic manner after t_{max} (1-2 hours post-dose), and the elimination half-life (approximately 2.3 hours) was comparable to that after intravenous dosing (2.5 hours). In addition, the absorption rate of pemafibrate after oral dosing was as high as 92.6% (calculated from $AUC_{0\text{-}inf}$ obtained in Study K-877-07). Pemafibrate was therefore inferred to be immediately absorbed in the upper gastrointestinal tract and then almost eliminated from the gastrointestinal tract after t_{max}; its persistent absorption would not occur. Accordingly, anion exchange resin administered 2 hours after treatment with pemafibrate is unlikely to have a significant impact on the absorption of pemafibrate. Moreover, The package inserts of cholestyramine and colestimide allow co-administration of cholestyramine (or colestimide) with drugs that may adsorb to cholestyramine (or colestimide) by advising that "concomitant drugs should be used carefully, for example, by administering the concomitant drugs at least 4 to 6 hours after administration of cholestyramine (or colestimide) or at the longest possible interval." Accordingly, the absorption of pemafibrate is unlikely to be affected by an anion exchange resin agent (cholestyramine and colestimide) if pemafibrate is administered at least 4 to 6 hours after administration of the anion exchange resin agent.

On the above grounds, the applicant considers it appropriate to provide advice about the co-administration of pemafibrate and anion exchange resin preparations, and to include advice in the package insert stating that it is desirable to administer pemafibrate at an adequate interval, or 2 hours before or at least 4 to 6 hours after administration of an anion exchange resin agent.

PMDA's view:
Based on the results from the *in vitro* study for adsorption of pemafibrate to anion exchange resin, an adequate interval between administrations of pemafibrate and a concomitant anion exchange resin agent is possibly needed, because the concomitant drug may decrease the absorption of pemafibrate. There are no clinical data on appropriate timing for administration of pemafibrate and a concomitant anion exchange resin agent, and thus whether the administration method proposed by the applicant is

2) Data from Studies K-877-04, K-877-09, K-877-13, K-877-15, K-877-16 (only Period 1), K-877-17, and K-877-19
3) Data from Studies K-877-14 and K-877-16 (only patients who received pemafibrate in Periods 1 and 2)

appropriate remains unknown. Accordingly, the package insert should include advice stating that it is desirable to use pemafibrate, taking an adequate interval after administration of any anion exchange resin agent, because co-administration of pemafibrate and an anion exchange resin agent may decrease the absorption of pemafibrate.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant conducted toxicity studies of pemafibrate, including those on single-dose toxicity, repeated-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, and other toxicity studies (study for mechanism of toxicity development, phototoxicity study, metabolite toxicity studies, pemafibrate/atorvastatin co-administration toxicity study).

5.1 Single-dose toxicity (CTD 4.2.3.1-1, 4.2.3.1-2)

Single-dose oral toxicity studies were conducted in rats and dogs. The approximate lethal doses in rats and dogs were determined to be >2000 mg/kg and 2000 mg/kg, respectively. Post-dose findings in rats included a decrease in locomotor activity, loose stool or diarrhea, decreased food consumption, and reduced body weight gain. Findings in dogs included vomiting, diarrhea, reduced body weight gain, and increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

5.2 Repeated-dose toxicity

Repeated-dose oral toxicity studies were conducted in rats (4, 13, 26 weeks), dogs (4, 13 weeks), and monkeys (13, 26, 52 weeks). Major toxicological target organs of pemafibrate included liver (rats, dogs, and monkeys), heart (rats and dogs), bone marrow (dogs), kidney (rats), and adrenal gland (rats). Changes in erythrocyte parameters (red blood cell count, hemoglobin level, and hematocrit level) were observed in all the animal species tested. Hepatocellular hypertrophy in the liver and hypertrophy of follicular epithelial cells in the thyroid were observed, but these were considered by the applicant to be adaptive changes. In addition, eosinophilic change (eosinophil granules) and vacuolation in hepatocytes were considered by the applicant to be attributable to the pharmacological effect of pemafibrate but not toxicological findings. The no observed adverse effect level (NOAEL) was determined to be 0.03 and 0.3 mg/kg/day in a 26-week repeated-dose study in rats and 52-week repeated-dose study in monkeys, respectively. Exposure to pemafibrate in rats and monkeys which repeatedly received pemafibrate at the corresponding NOAEL was 0.20- to 0.25-fold and 2.4- to 3.0-fold, respectively, AUC in humans at the maximum clinical dose (0.2 mg twice daily) (data from a pharmacokinetic interaction study of pemafibrate with pravastatin, simvastatin, or fluvastatin [Study K-877-18]).

5.2.1 Four-week repeated-dose oral toxicity study in rats (CTD 4.2.3.2-1)

Pemafibrate (0 [vehicle, 0.5% methylcellulose solution], 0.1, 0.5, 5, or 50 mg/kg/day) was administered to male and female SD rats for 4 weeks (n = 12/sex/group). Findings included decreased glucose, elevated albumin and albumin/globulin ratio (A/G ratio), reduced fibrinogen, and increased liver weight in males and females at ≥0.5 mg/kg; prolonged activated partial thromboplastin time (APTT) in males at ≥0.5 mg/kg; decreased red blood cell count, reduced hemoglobin and hematocrit levels, increases in ALT, AST, lactate dehydrogenase (LDH), alkaline phosphatase (ALP), and total protein, increased kidney and heart weights, and hepatic necrosis in males and females at ≥5 mg/kg; reduced TG and urine bilirubin positive in males at ≥5 mg/kg; increased white blood cell count, and myocardial degeneration and necrosis accompanied by inflammatory cell infiltration in males at 50 mg/kg; and increased food consumption in females at 50 mg/kg. All changes were reversible after a 4-week recovery period. The NOAEL was determined to be 0.5 mg/kg/day, because the applicant interpreted the findings in males and females at ≥0.5 mg/kg as follows: Elevated albumin and A/G ratio were considered adaptive changes in response to enhanced hepatic function, and reduced fibrinogen and prolonged APTT were not accompanied by other changes suggestive of bleeding tendency.

5.2.2 Thirteen-week repeated-dose oral toxicity study in rats (CTD 4.2.3.2-2)

Pemafibrate (0, 1, 3, or 10 mg/kg/day [males] or 0, 3, 10, or 30 mg/kg/day [females]) was administered to male and female SD rats for 13 weeks (n = 10/sex/group). Findings included elevated blood urea nitrogen (BUN) and total protein in males at ≥1 mg/kg; reduced hemoglobin and hematocrit levels, anisocytosis, increased white blood cell and platelet counts, elevated ALP, elevated albumin, increased weights of the liver, heart, kidney, and thyroid/parathyroid gland, periportal hepatocellular hypertrophy, hepatocellular eosinophilic change, and hypertrophy of thyroid follicular epithelial cells in males at ≥1

mg/kg and in females at ≥3 mg/kg; hemorrhagic necrosis of hepatic parenchymal cells in males at ≥1 mg/kg and in females at ≥10 mg/kg; shortened prothrombin time (PT), elevated TG, increased spleen weight, focal vacuolation in the anterior pituitary gland in males at ≥3 mg/kg; reduced AST, elevated glucose in females at ≥3 mg/kg; decreases in mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and mean corpuscular volume (MCV) in males at ≥3 mg/kg and females at ≥10 mg/kg; elevated γ-glutamyltransferase (γ-GTP), increased lung weight, centrilobular hepatocellular hypertrophy, hepatocellular fibrillization/regenerative hyperplasia in males at 10 mg/kg; zona glomerulosa hypertrophy in the adrenal gland in males and females and decreased adrenal gland weight in females at ≥10 mg/kg; decreased body weight in males at 10 mg/kg and females at 30 mg/kg; and reduced total cholesterol (TC) and creatinine in females at 30 mg/kg. None of the following changes were interpreted by the applicant as toxicity: (1) Reduced erythrocyte laboratory values in males and females at ≤3 mg/kg were only <10% lower than those in the control group; (2) increased platelet count in females at ≥3 mg/kg was not accompanied by a change in the bone marrow; and (3) for elevated ALP in females at ≥3 mg/kg, aggravated liver disorder did not occur. In addition, none of the following changes at ≥3 mg/kg were interpreted by the applicant as toxicity: (i) The focal vacuolation in the anterior pituitary gland in males was a secondary reaction to enhanced thyroxine (T_4) clearance due to T_4 UGT induction in the liver; (ii) periportal hepatocellular hypertrophy in females is an adaptive change associated with PPARα activation; and (iii) increased TG is a non-specific change commonly observed in toxicity studies of drugs in the same class. Given the finding of hemorrhagic necrosis of hepatic parenchymal cells, the NOAEL was determined to be <1 mg/kg/day in males and 3 mg/kg/day in females.

5.2.3 Twenty-six-week repeated-dose oral toxicity study in rats (a) (CTD 4.2.3.2-3)

Pemafibrate (0, 0.3, 1, or 3 mg/kg/day [male] or 0, 1, 5, or 25 mg/kg/day [female]) was administered to male and female SD rats for 26 weeks (n = 12/sex/group). One male in the 3.0 mg/kg group died at Week 16, and 1 male in the control group, 1 female in the 1 mg/kg group, and 1 female in the 25 mg/kg group were sacrificed in extremis due to aggravated clinical signs at Weeks 14, 19, and 6, respectively. The applicant considered that all of the above events except for euthanization due to chronic progressive nephropathy in 1 female at 1 mg/kg were accidental changes. Findings included increases in ALT, AST, and TC, reduced urinary pH, increased heart and spleen weights, vacuolation of cells in the anterior pituitary gland in males at ≥0.3 mg/kg; decreases in hemoglobin, hematocrit, serum iron, and transferrin saturation levels, increases in ALP, albumin, and A/G ratio, increased liver and kidney weights, aggregation of alveolar macrophages, centrilobular and periportal hepatocellular hypertrophy and eosinophilic change in the liver, hemorrhagic necrosis, hepatocellular apoptosis, multinucleated hepatocytes, increased mitosis, pigmentation of Kupffer cells and macrophages, hyperplasia and inflammation in the bile duct, chronic progressive nephropathy, hypertrophy of follicular epithelial cells and follicular colloid concentration in the thyroid, zona glomerulosa hypertrophy in the adrenal gland in males at ≥0.3 mg/kg and in females at ≥1 mg/kg; reduced MCHC in males and females, decreased red blood cell count, and elevated BUN and TG in males, and corpus luteum cyst in females at ≥1 mg/kg; reduced body weight gain, increased food consumption, increased (male) or decreased (female) adrenal gland weight in males at ≥1 mg/kg and in females at ≥5 mg/kg; reduced MCH and increased thyroid and parathyroid gland weights in males at 3 mg/kg and females at ≥1 mg/kg groups; reduced MCV and increased white blood cell count in males at 3 mg/kg and in females at ≥5 mg/kg; reduced unsaturated iron binding capacity (UIBC) in males at 3 mg/kg and in females at 25 mg/kg; and increased frequency of estrous cycle prolongation in females at 25 mg/kg. All changes except for chronic progressive nephropathy, hyperplasia in the bile duct, and pigmentation of macrophages and Kupffer cells were reversible after a 5-week recovery period. Based on the above, the NOAEL was determined to be <0.3 mg/kg/day in males and <1 mg/kg/day in females.

5.2.4 Twenty-six-week repeated-dose oral toxicity study in rats (b) (CTD 4.2.3.2-4)

Pemafibrate (0, 0.03, or 0.1 mg/kg/day) was administered to male and female SD rats for 26 weeks (n = 12/sex/group). Findings included reduced serum iron in males and females, increased albumin and A/G ratio in males, and reduced UIBC and total iron binding capacity (TIBC) in females at ≥0.03 mg/kg; and a trend toward increased water consumption, increased neutrophil count, increases in ALT, AST, and ALP, hemorrhagic focal necrosis and fibrillization in the liver, pigmentation of macrophages in the portal vein, hyperplasia and inflammation in the bile duct in males, and chronic progressive nephropathy in females at 0.1 mg/kg. The NOAEL was determined to be 0.03 mg/kg/day, because decreases in serum

iron, UIBC, and TIBC in males and females at ≥0.03 mg/kg were not accompanied by changes in hematological parameters.

5.2.5 Four-week repeated-dose oral toxicity study in dogs (CTD 4.2.3.2-5)

Pemafibrate (0, 0.3, 3, 30, or 100 mg/kg/day) was administered to male and female beagle dogs for 4 weeks (n = 3/sex/group). In the 100 mg/kg group, 1 female died on Day 26, and 1 male and 1 female were sacrificed in extremis due to aggravated clinical signs on Days 20 and 26. Findings included fecal abnormalities (diarrhea, loose stool, decreased fecal amount), and decreases in TG, TC, and phospholipid in males and females at ≥0.3 mg/kg; decreases in body weight, food consumption, and water consumption, decreases in red blood cell count and reticulocyte count, reduced hemoglobin land hematocrit levels, elevated fibrinogen, elevated ALT and AST, decreased erythroid cell count in the bone marrow, vacuolation of myocardial cells in males and females at ≥3 mg/kg; prolonged APTT, decreased hematopoietic cell count in the bone marrow, and hepatocellular eosinophilic change in males and females at ≥30 mg/kg; and myocardial degeneration and microgranuloma in males at 100 mg/kg. All changes were reversible after an 8-week recovery period. The NOAEL was determined to be 0.3 mg/kg/day, because the applicant interpreted the findings in males and females at ≥0.3 mg/kg as follows: Fecal abnormalities were not changes suggestive of aggravated clinical signs such as decreases in body weight, and reduced TG, TC, and phospholipid were considered attributable to the pharmacological effect of pemafibrate.

5.2.6 Thirteen-week repeated-dose oral toxicity study in dogs (CTD 4.2.3.2-6)

Pemafibrate (0, 0.1, 0.3, 1, or 3 mg/kg/day) was administered to male and female beagle dogs for 13 weeks (n = 3/sex/group). In the 3 mg/kg group, 1 male was sacrificed in extremis due to aggravated clinical signs on Day 44. Findings included decreased red blood cell count, reduced hemoglobin and hematocrit levels, decreases in TG, TC, and phospholipid, elevated ALT, increased pancreas weight in males and females at ≥0.1 mg/kg; loose stool, diarrhea, decreased heart rate, increased platelet count, decreases in total protein and albumin, brown pigment in the sinusoidal cells of the liver, and increases in AST and ALP in males and females at ≥0.3 mg/kg; decreases in body weight and food consumption, decreased body temperature, decreased pulse rate, elevated BUN, decreases in UIBC, TIBC, calcium, and inorganic phosphorus, reduced urine electrolytes, hepatocellular eosinophilic change, degeneration and necrosis, and brown pigment in the red pulp of the spleen in males and females at ≥1 mg/kg; decreased respiratory rate, abnormal T wave, increases in LDH and total bilirubin, urine bilirubin, oval cell hyperplasia in the liver, decreased hematopoietic cell count in the bone marrow in males and females; urine urobilinogen, cellular atrophy in the islets of Langerhans in the pancreas, acinar cell degeneration and necrosis, infiltration of interstitial inflammatory cells, and interstitial edema in males, and a trend toward prolonged PR interval as an electrocardiographic finding in females at 3 mg/kg. Based on the above, the NOAEL was determined to be <0.1 mg/kg/day.

5.2.7 Thirteen-week repeated-dose oral toxicity study in monkeys (CTD 4.2.3.2-9)

Pemafibrate (0, 0.1, 0.3, 1, or 10 mg/kg/day) was administered to male and female cynomolgus monkeys for 13 weeks (n = 3/sex/group). Findings included hepatocellular eosinophil granules in males and females at ≥0.3 mg/kg; hepatocellular granular pigment in males, and decreased body weight, decreased red blood cell count, and reduced hemoglobin and hematocrit levels in females at ≥1 mg/kg; increases in AST and ALT in males and females, and decreased food consumption, and decreased in total protein and A/G ratio in females at 10 mg/kg. Based on the above, the NOAEL was determined to be 1 mg/kg/day in males and 0.3 mg/kg/day in females.

5.2.8 Twenty-six-week repeated-dose oral toxicity study in monkeys (CTD 4.2.3.2-10)

Pemafibrate (0, 0.3, or 1 mg/kg/day [male] or 0, 0.1, or 0.3 mg/kg/day [female]) was administered to male and female cynomolgus monkeys for 26 weeks (n = 3/sex/group). Findings included hepatocellular eosinophil granules in the liver in males at ≥0.3 mg/kg and in females at ≥0.1 mg/kg; hepatocellular vacuolation in males at ≥0.1 mg/kg; prolonged PT, and elevated UIBC and TIBC in males at 1 mg/kg. The NOAEL was determined to be 0.3 mg/kg/day, because the applicant interpreted the above findings as changes attributable to the pharmacological effect, but not toxic changes including bleeding.

5.2.9 Fifty-two-week repeated-dose oral toxicity study in monkeys (CTD 4.2.3.2-11)

Pemafibrate (0, 0.3, 1, 3, or 10 mg/kg/day [male] or 0, 0.1, 0.3, 1, or 3 mg/kg/day [female]) was administered to male and female cynomolgus monkeys for 52 weeks (n = 4/sex/group). In the 3 mg/kg group, 1 female was sacrificed in extremis due to changes in clinical signs potentially attributable to bacterial hemorrhagic cystitis on Day 241. Findings included hepatocellular eosinophil granules and vacuolation in the liver in males at ≥0.3 mg/kg and females at ≥0.1 mg/kg; elevated TIBC in males and females at ≥0.3 mg/kg; increased liver weight in males at ≥0.3 mg/kg and in females at 1 mg/kg; prolonged PT, hepatocellular granular pigmentation, and Kupffer cell pigmentation in males at ≥1 mg/kg and in females at ≥0.3 mg/kg; decreased body weight in males and females and reduced albumin and A/G ratio in males at ≥1 mg/kg; decreased fibrinogen in males at ≥1 mg/kg and in females at 3 mg/kg; elevated ALT and AST in males at ≥3 mg/kg and in females at ≥1 mg/kg; elevated TC in males at 10 mg/kg; and elevated UIBC in males at 10 mg/kg and in females at 0.3 and 1 mg/kg. All changes were reversible after a 4-week recovery period. The NOAEL was determined to be 0.3 mg/kg/day, because the applicant interpreted the findings in males and females at ≥0.3 mg/kg as follows: Elevated TIBC was not accompanied by anemia; prolonged PT was not accompanied by hemorrhagic changes; and granular pigmentation and Kupffer cell pigmentation were changes related to the pharmacological effect of pemafibrate, and not accompanied by toxic changes such as necrosis or inflammatory changes, which were not considered toxicological findings.

5.3 Genotoxicity (CTD 4.2.3.3.1-1, 4.2.3.3.1-2, 4.2.3.3.2-1)

The applicant conducted genotoxicity studies including bacterial reverse mutation assay, chromosomal aberration assay in mammalian cell (CHL/IU cells), and rat bone marrow micronucleus assay. All the assays produced negative results.

5.4 Carcinogenicity

The applicant conducted 104-week carcinogenicity studies in mice and rats. In mice, the incidences of hepatocellular carcinoma and hepatocellular adenoma were increased. In rats, the incidences of hepatocellular carcinoma, hepatocellular adenoma, pancreatic acinar cell carcinoma, pancreatic acinar cell adenoma, testicular interstitial cell adenoma, and thyroid follicular epithelial cell adenoma were increased.

5.4.1 104-week carcinogenicity study in mice (CTD 4.2.3.4.1-3)

Pemafibrate (0, 0.075, 0.15, or 0.3 mg/kg/day) was orally administered to male and female ICR mice for 104 weeks (n = 60/sex/group). The incidence of hepatocellular adenoma was increased in males and females at ≥0.075 mg/kg, and that of hepatocellular carcinoma was increased in males and females at ≥0.15 mg/kg. Non-neoplastic lesions observed included hepatocellular hypertrophy, regenerative hyperplasia and eosinophilic change, and Kupffer cell pigmentation in males at ≥0.075 mg/kg; and thyroid follicular cell pigmentation in males and females at 0.3 mg/kg.

5.4.2 104-week carcinogenicity study in rats (CTD 4.2.3.4.1-4)

Pemafibrate (0, 0.3, 1, or 3 mg/kg/day [male] or 0, 1, 3, or 10 mg/kg/day [female]) was orally administered to male and female SD rats for 104 weeks (n = 70/sex/group). The incidences of the following changes were increased: pancreatic acinar cell carcinoma in males at ≥0.3 mg/kg; pancreatic acinar cell adenoma and thyroid follicular epithelial cell adenoma in males at ≥0.3 mg/kg and in females at ≥1 mg/kg; and hepatocellular carcinoma and hepatocellular adenoma in males and females, and testicular interstitial cell adenoma in males at ≥1 mg/kg. Non-neoplastic lesions observed included hepatocellular focal changes, hypertrophy, eosinophilic change and hemorrhagic necrosis, macronuclear/multinuclear hepatocytes, acinar cell hyperplasia in the pancreas, follicular cell hypertrophy and pigmentation in the thyroid, aggregation of alveolar macrophages accompanied by cholesterol granuloma, and zona glomerulosa hypertrophy in the adrenal gland in males at ≥0.3 mg/kg and in females at ≥1 mg/kg; chronic progressive nephritis and renal cortex and tubular pigmentation in males and females at ≥1 mg/kg; and regenerative hyperplasia in the liver and testicular interstitial cell hyperplasia in males at ≥1 mg/kg; and pituitary terminal cell vacuolation in males at 3 mg/kg.

5.5 Reproductive and developmental toxicity

The applicant conducted reproductive and developmental toxicity studies, including studies of fertility and early embryonic development to implantation in rats, studies of embryo-fetal development in rats

and rabbits, and a rat study on pre- and postnatal development, including maternal function. Changes related to pemafibrate included decreases in corpora lutea count and number of live conceptuses (rats), suppressed growth in the offspring (rats), and premature birth and abortion (rabbits). The NOAEL in embryos and fetuses was determined to be 100 mg/kg/day for both rats and rabbits in the embryo-fetal development studies. The exposure to pemafibrate ($AUC_{0\text{-}24h}$) at the NOAEL in rats and rabbits was approximately 623- and 2020-fold, respectively, AUC in humans at the maximum clinical dose. In addition, the NOAEL for maternal general and reproductive toxicity and developmental toxicity was determined to be 0.3 mg/kg/day in the rat study on pre- and postnatal development, including maternal function. The exposure to pemafibrate ($AUC_{0\text{-}24h}$) at the NOAEL was approximately 1.8-fold AUC in humans at the clinical maximum dose. Furthermore, the placental transfer and lacteal excretion of pemafibrate were observed in rats.

5.5.1 Fertility and early embryonic development to implantation in rats (CTD 4.2.3.5.1-1)

Pemafibrate (0, 5, 15, or 50 mg/kg/day) is orally administered to male SD rats for a total of 49 to 52 days from 2 weeks prior to mating and to female SD rats from 2 weeks prior to mating to gestation day 7 (n = 20/sex/group). Findings included reduced body weight gain, decreased red blood cell count, reduced hemoglobin and hematocrit levels in males and females, and increased platelet count and enlarged liver in males at ≥5 mg/kg; and increased white blood cell count in males, and decreases in corpora lutea count and number of live conceptuses in females at 50 mg/kg. There were no treatment-related changes in fertility. Based on the above, the NOAEL for male reproductive toxicity was determined to be 50 mg/kg/day, and that for female reproductive and developmental toxicity was 15 mg/kg/day.

5.5.2 Embryo-fetal development in rats (CTD 4.2.3.5.2-2)

Pemafibrate (0, 10, 30, or 100 mg/kg/day) was orally administered to pregnant SD rats from gestation day 7 to gestation day 17 (n = 19-20/group). Findings in dams included reduced body weight gain and decreased food consumption at ≥10 mg/kg, and decreased body weight at 100 mg/kg. There were no treatment-related changes in fetuses. Based on the above, the NOAEL for maternal general toxicity was determined to be <10 mg/kg/day; and that for both reproductive and developmental toxicities was 100 mg/kg/day.

5.5.3 Embryo-fetal development in rabbits (CTD 4.2.3.5.2-4)

Pemafibrate (0, 1, 10, or 100 mg/kg/day) was orally administered to pregnant Japanese White rabbits from gestation day 6 to gestation day 18 (n = 18-20/group). Death occurred in 1 rabbit in the 10 mg/kg group, but no abnormalities were observed after administration on gestation day 7. At 100 mg/kg, decreased food consumption and reduced body weight gain were observed, but no deaths occurred. Both food consumption and body weight remained unaffected at 10 mg/kg. The applicant, therefore, considered that the above findings were not attributable to the treatment. Findings in dams included abortion at ≥10 mg/kg; and decreases in body weight and food consumption, reduced body weight gain, emaciation, no-feces, anuria, and premature birth at 100 mg/kg. The applicant considered that premature birth and abortion were changes secondary to malnutrition, because continuously decreased food consumption or emaciation was observed in the animal with these findings. There were no treatment-related changes in fetuses. Based on the above, the NOAEL for maternal general toxicity was determined to be 10 mg/kg/day; that for reproductive toxicity was 1 mg/kg/day; and that for developmental toxicity was 100 mg/kg/day.

5.5.4 Rat study on pre- and postnatal development, including maternal function (a) (CTD 4.2.3.5.3-1)

Pemafibrate (0, 3, 10, or 30 mg/kg/day) was orally administered to pregnant SD rats from gestation day 7 to postpartum day 20 (n = 21-22/group). Death occurred in 3 animals in each of the groups treated at ≥3 mg/kg. Findings in dams included reduced lactation performance at ≥10 mg/kg; and decreased food consumption, reduced body weight gain, and cannibalism of neonates at 30 mg/kg. Findings in offspring included decreased body weight and a trend toward delayed physical development at ≥3 mg/kg; and reduced survival to postnatal day 4 and reduced arched back righting reflex at ≥10 mg/kg. Based on the above, the NOAEL for any of maternal general and reproductive toxicities as well as developmental toxicity was determined to be <3 mg/kg/day.

5.5.5 Rat study on pre- and postnatal development, including maternal function (b) (CTD 4.2.3.5.3-2)

Pemafibrate (0, 0.1, or 0.3 mg/kg/day) was orally administered to pregnant SD rats from gestation day 7 to postpartum day 20 (n = 22/group). No pemafibrate-related changes occurred in either dams or offspring. Based on the above, the NOAEL for any of maternal general and reproductive toxicities as well as developmental toxicity was determined to be 0.3 mg/kg/day.

5.6 Other toxicity studies

5.6.1 Mechanistic studies

5.6.1.1 Carcinogenicity mechanistic study (CTD 4.2.3.7.3-1, 4.2.3.7.3-2 [Reference data])

In order to identify causes of hepatocellular adenoma and hepatocellular carcinoma observed in the rat carcinogenicity study, the applicant conducted studies using liver specimens collected in the 26-week repeated-dose oral toxicity study in rats, 4-week repeated-dose oral toxicokinetics study in rats, and 52-week repeated-dose oral toxicity study in monkeys. Findings in rat specimens included elevated mRNA expression levels of genes involved in peroxisome proliferation; electron micrograph indicating increased periportal peroxisomes/mitochondria ratio; increased terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling (TUNEL)-staining positive cell count, elevated 8-hydroxydeoxyguanosine activity, and increased Ki67 immunostaining positive cell count. Findings in monkey specimens included increased peroxisomes/mitochondria ratio and increased mRNA expression levels of genes involved in peroxisome proliferation, but their degrees were smaller than those in rats. Either TUNEL-staining or Ki67 immunostaining positive cell count did not increase.

5.6.1.2 Study for evaluation for effects on blood CCK concentrations in rats (CTD 4.2.3.7.3-6 [reference data])

Effects on cholecystokinin (CCK) were examined to elucidate the mechanism of the increased incidence of pancreatic acinar cell tumor in rats receiving pemafibrate. Pemafibrate 0 or 3 mg/kg/day or FF 200 mg/kg/day was orally administered to male and female SD rats for 13 weeks. Body weight in the pemafibrate 3 mg/kg/day group and FF group tended to be lower than that in the control group (−3% and −7%, respectively, relative to that in the control group). The mean plasma CCK concentrations on Days 28 and 91 tended to be high in the pemafibrate 3 mg/kg/day group, while the concerned concentrations were high in the FF group, and clearly increased plasma CCK concentration was found in 1 of 10 animals and 2 of 10 animals, respectively. The percentage of the animals with clearly increased plasma CCK concentration in the pemafibrate 3 mg/kg/day group was comparable to the incidence of pancreatic acinar cell tumor in the 104-week carcinogenicity study of pemafibrate in rats [see Section "5.4.2 A 104-week carcinogenicity study in rats"]. Based on the above, increased plasma CCK concentration was observed in rats receiving pemafibrate, but the applicant considered that the effect was not qualitatively different from that of FF.

5.6.2 Toxicity studies of metabolites (CTD 4.2.3.7.5-5 to 4.2.3.7.5-8)

Exposures to K-23467 and K-23605, metabolites of pemafibrate, in humans have been shown to account for >10% of total exposure to all the substances related to pemafibrate. Exposure to these metabolites were evaluated in the 52-week repeated dose toxicity study in monkeys, embryo-fetal development study in rats, carcinogenicity study in rats, and carcinogenicity study in mice. Exposures to the 2 metabolites in different animal species were compared with the $AUC_{0\text{-}24h}$ of the metabolites in humans at the maximum clinical dose. In the 52-week repeated dose toxicity study in monkeys, exposures to K-23467 in males in the 10 mg/kg group and in females in the 3 mg/kg group were 781- and 377-fold, respectively, the human $AUC_{0\text{-}24h}$ of K-23467; and exposures to K-23605 were 1621- and 296-fold, respectively, the human $AUC_{0\text{-}24h}$ of K-23605. In the embryo-fetal development study in rats, exposures to K-23467 and K-23605 in the 100 mg/kg group were 5.4- and 18-fold, respectively, the corresponding human $AUC_{0\text{-}24h}$. In the carcinogenicity study in rats, exposures to K-23467 in males in the 3 mg/kg group and in females in the 10 mg/kg group were 1.1- and 0.7-fold, respectively, the human $AUC_{0\text{-}24h}$ of K-23467, and exposures to K-23605 were 1.6- and 1.1-fold, respectively, the human $AUC_{0\text{-}24h}$ of K-23605. In the carcinogenicity study in mice, exposures to K-23467 in males in the 0.3 mg/kg group and in females in the 0.3 mg/kg group were 2.6- and 2.1-fold, respectively, the human $AUC_{0\text{-}24h}$ of K-23467. Based on the above, the applicant considered that the toxicity of K-23467 and K-23605, the metabolites of pemafibrate, was adequately evaluated in the toxicity studies.

5.6.3 Phototoxicity study (CTD 4.2.3.7.7-1)

In a phototoxicity study, rats given a single dose of pemafibrate by gavage were exposed to ultraviolet A (UVA) irradiation. macroscopic observation of auricles and back skin and tests including ophthalmological examination showed that pemafibrate is not phototoxic.

5.6.4 Thirteen-week pemafibrate/atorvastatin co-administration toxicity study in rats (CTD 4.2.3.7.7-2)

Pemafibrate and atorvastatin were co-administered to rats for 13 weeks by gavage to evaluate whether their co-administration increases toxic effects. There were no abnormalities shown by the clinical observation, urinalysis, haematology, clinical chemistry, organ weight, necropsy, histopathological examination, or electron microscopy. The applicant considered that the co-administration of the 2 drugs did not increase the toxicity in either additive or synergistic manner.

5.R Outline of the review conducted by PMDA

5.R.1 Effect on the liver

Since hepatic changes were observed in the repeated-dose toxicity studies, PMDA asked the applicant to explain the safety in humans, for example, by examining whether the findings in these studies differ from those with other drugs in the same class.

The applicant's explanation:

Hepatocellular hypertrophy observed in the repeated-dose toxicity studies of pemafibrate was accompanied by an eosinophilic change (eosinophil granule-like change together with peroxisome proliferation). The exposure at which pemafibrate-related hepatic changes were observed was higher in both dogs and monkeys than in rodents, and no toxic changes occurred in monkeys. Taking the above into account, pemafibrate-related hepatic changes represent peroxisome proliferation mediated by the PPARα agonistic effect, which is the pharmacological effect of pemafibrate. Hepatic impairment and hepatocarcinogenesis induced by PPARα agonists are specific to rodents, and thus the risk of such toxicity is deemed to be low in humans (*Toxicol Pathol.* 2012;40:971-94, *Toxicol Sci.* 2008;101:132-9). The changes related to pemafibrate were unlikely to occur in humans. Hepatocellular hypertrophy occurred in the periportal region in rats treated with pemafibrate, while it occurred in the centrilobular region in animals receiving FF, a drug in the same class. The difference was attributable to increased CYP expression in the centrilobular region that occurred with FF-related hepatocellular hypertrophy accompanied by peroxisome proliferation.

PMDA's view:

Hepatocellular hypertrophy observed in repeated-dose toxicity studies of pemafibrate is unlikely to pose clinically relevant problems, because the applicant's explanation was appropriate including discussion about a difference in the mechanism of hepatic changes between pemafibrate and other drugs in the same class.

5.R.2 Carcinogenicity

The applicant's explanation about neoplastic changes observed in the carcinogenicity studies in mice and rats:

Because pemafibrate did not directly exhibit genotoxicity in the genotoxicity studies, tumorigenesis observed in mice and rats was considered related to a mechanism independent from the genotoxicity. According to the examination of hepatocellular tumors observed in the carcinogenicity studies in rats and mice, findings in rats included multinucleation, apoptosis, increased mitosis, and regenerative hyperplasia, which were suggestive of precancerous lesions. These findings were considered as a result of an effect of PPARα-mediated oxidative stress or the secondary changes to a necrotic change. In addition, peroxisome proliferation was marked in rats. A gene expression analysis revealed species differences in the induction of expression of peroxisome-related genes between rats and monkeys. PPARα agonist-induced hepatocarcinogenesis is specific to rodents, and there are qualititative differences in hepatocyte proliferation and carcinogenicity in response to PPARα agonists between humans and rodents (*Carcinogenesis.* 2006;27:1074-80, *Toxicol Sci.* 2008;101:132-9). Results from a study for various potential factors leading to tumorigenesis in animals receiving pemafibrate [see Section "5.6.1.1 Carcinogenicity mechanistic study"] have shown that PPARα-mediated responses differ between rats and monkeys. Especially, when cell proliferation activity was measured as an indicator of

tumorigenesis, no changes were observed in monkeys in which exposure was t≥30-fold that in humans at the maximum clinical dose. Hepatocellular tumor is unlikely to be relevant to humans.

The mechanism of testicular interstitial cell tumor formation observed in the carcinogenicity study in rats was investigated. Enhanced aromatase activity in the liver and increased estradiol may be involved in PPARα agonist-induced testicular interstitial cell tumor formation in rats (*Crit Rev Toxicol.* 2003;33:655-780). In humans, however, aromatase in the liver is unlikely to be activated by a PPARα agonist for the following reasons: (1) An epidemiologic study in humans exposed to perfluorooctanoic acid (PFOA), a PPARα agonist, revealed that reproductive hormones such as testosterone, estradiol, follicle stimulating hormone (FSH), luteinizing hormone (LH), thyroid stimulating hormone (TSH), prolactin were not affected by the PPARα agonist (*J Occup Environ Med.* 1998;40:614-22); and (2) estradiol concentrations were not elevated in primate treated with a PPARα agonist (clofibrate, diethylhexyl phthalate [DEHP], or PFOA) (*Toxicol Sci.* 2002;69:244-57, *Toxicol Sci.* 1998;42:49-56). Based on the above, as with other PPARα agonists, the risk of pemafibrate-induced testicular interstitial cell tumor is unlikely to be relevant to humans.

The mechanism of thyroid follicular epithelial cell tumor formation observed in the carcinogenicity study in rats was investigated. The mechanism of drug-induced thyroid follicular epithelial cell tumors is known to involve secondary changes via a negative-feedback loop (enhanced TSH secretion), in which an increased hepatic T_4 UGT activity results in increased thyroid hormone metabolism (*Toxicol Pathol.* 1994;22:179-86). The above mechanism differs among animal species. Published literature indicates that half-life of plasma T_4 is remarkably short in rodents lacking thyroxin binding globulin, and thus the thyroid hormone is readily metabolized, resulting in tumorigenesis (*Toxicol Pathol.* 1997;25:39-48). In addition, examination of pituitary gland cell vacuolation observed in the 26-week repeated-dose toxicity study in rats produced positive results for staining with anti-TSH antibody, suggesting enhanced secretion of TSH from the pituitary gland. Based on the above, pemafibrate-induced thyroid tumor is specific to rodents, and thus its risk is unlikely to be relevant to humans.

PMDA asked the applicant to explain the mechanism of development of pancreatic acinar cell tumor observed in the carcinogenicity study in rats and whether the finding is relevant to humans.

The applicant's explanation:
PPARα agonists have been reported to inhibit the biosynthesis of bile acid in the liver, leading to reduced bile acid flow rate and composition changes of bile acid (*J Biol Chem.* 2000;275:28947-53, *J Lipid Res.* 2000;41:514-20). The reduced flow rate and composition changes of bile acid are thought to reduce intestinal trypsin activity and increase CCK, resulting in proliferative changes of pancreatic acinar cells. Pancreatic acinar cell tumor related to pemafibrate is considered to be a consequence of elevated blood CCK concentrations, as observed with other PPARα agonists. Plasma CCK concentrations increased in rats receiving repeated oral dose of pemafibrate for 13 weeks. The percentage of animals with increased plasma CCK concentrations was almost consistent with the incidence of pancreatic acinar cell tumor in the carcinogenicity study of pemafibrate in rats [see Section "5.6.1.2 Study for evaluation for effects on blood CCK concentrations in rats"]. Development of pancreatic acinar cell tumor mediated by increased CCK concentrations is considered to be specific to rodents, because there are species differences in the regulatory mechanism of exocrine pancreas in response to CCK between rodents and humans (*Cell Biol Int.* 2009;33:1-9, *Gastroenterology.* 2001;121:1380-90, etc.). In addition, a trypsin inhibitor increases CCK in rats, but an epidemiological study in humans has reported that a diet rich in trypsin inhibitors does not increase pancreatic acinar cell tumor (*Crit Rev Toxicol.* 2003;33:655-780, *J Natl Cancer Inst.* 1991;83:541-6). Based on the above, pancreatic acinar cell tumor observed in rats is unlikely to be relevant to humans. The package insert will include information on neoplastic changes observed in the carcinogenicity studies in mice and rats.

PMDA's view:
Based on applicant's explanation about hepatocellular tumor, testicular interstitial cell tumor, thyroid follicular epithelial cell tumor, and pancreatic acinar cell tumor observed in the carcinogenicity study in mice or rats, PMDA has concluded that these neoplastic changes related to pemafibrate are specific to rodents, and that they are unlikely to occur in humans. In addition, the applicant has decided to provide information on the neoplastic changes in the package insert. The applicant's decision is appropriate.

5.R.3 Effect on myocardium

Myocardial changes were observed in repeated-dose toxicity studies in rats and dogs. PMDA therefore asked the applicant to clarify whether findings similar to myocardial ones were also observed in skeletal muscles and to explain the mechanism of the findings and the risk of the findings in humans.

The applicant's explanation:
No changes in skeletal muscles were observed in the 4-week repeated-dose toxicity study in rats. The observed myocardial degeneration and necrosis accompanied by inflammatory cell infiltration were focal changes because they were also observed in the control group; the findings are considered to be spontaneous cardiomyopathy (*Guides for Toxicologic Pathology*. STP/ARP/AFIP; 2000). However, the reason for the increased incidence of such findings in animals treated with pemafibrate remains unclear. The myocardial vacuolation observed in dogs, on the other hand, is inferred to be a consequence of lipid accumulation due to the excessive pharmacological effect of pemafibrate, because reports indicate that PPARα plays an important role in mitochondrial fatty acid β-oxidation in myocardial cells (*J Biol Chem.* 1998;273:23786-92), and that PPARα is involved in lipid metabolism and toxicity in the heart (*Cell Metab.* 2012;15:805-12, *FASEB J.* 2004;18:1692-700). These cardiac findings, however, were observed at the exposure >100 fold that in humans at the maximum clinical dose, and there were no findings in the heart in either carcinogenicity study in rats or 52-week repeated-dose toxicity study in monkeys. Thus, these findings are unlikely to be relevant to humans.

PMDA's view:
The mechanism of the myocardium findings in the repeated-dose toxicity study in rats remains unclear, while no similar findings were observed in the carcinogenicity study in rats or 52-week repeated-dose toxicity study in monkeys. The finding in the repeated-dose toxicity study in dogs is inferred to be a consequence of lipid accumulation due to the excessive pharmacological effect of pemafibrate, but the exposure at which the finding was observed was higher than that in humans at the maximum clinical dose. In consideration of the applicant's explanation about no effects on the skeletal muscles observed in non-clinical studies, these myocardial findings are unlikely to be relevant to humans.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

Formulation A different from the to-be-marketed formulation was used in a phase I study at the early clinical development stage. Formulations used in Japanese and foreign clinical studies in patients with hypertriglyceridemia and some clinical pharmacology studies were Formulations B and C, which were both the same as the to-be-marketed formulation, except for ingredients for film coating. Formulation B and C were used in confirmatory studies comparing pemafibrate with FF (Studies K-877-09 and K-877-17). Bioequivalence between Formulation C and the to-be-marketed formulation has been demonstrated by dissolution tests. The tests were conducted in accordance with the Guideline for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms (PMSB/ELD Notification No. 67 dated February 14, 2000; partially revised by PFSB/ELD Notification No. 0229-10 dated February 29, 2012).

Plasma pemafibrate concentrations were determined by LC-MS-MS, and the LLOQ was 0.05 ng/mL.

6.1.1 Absolute bioavailability study (Study K-877-07, CTD 5.3.1.1-1)

Following a single oral dose of pemafibrate (0.2 mg) and a single intravenous dose of ^{14}C-pemafibrate (0.002 mg) to 8 healthy non-Japanese adults, the geometric mean $AUC_{0\text{-}inf}$ of pemafibrate was 6.977 and 0.106 ng·h/mL, respectively. The absolute bioavailability (BA) (ratio of dose-adjusted $AUC_{0\text{-}inf}$ [oral dose/intravenous dose]) was 61.5%.

6.1.2 Food effect (Study K-877-20, CTD 5.3.3.4-6)

A two-treatment, two-period crossover study was conducted in 16 healthy Japanese adults to evaluate the food effect on pharmacokinetics of pemafibrate following a single oral dose of pemafibrate 0.1 mg (one 0.1-mg tablet of the to-be marketed formulation) (with a washout period of 3 days). The geometric mean ratios [90% confidence interval (CI)] of C_{max} and $AUC_{0\text{-}t}$ under fed conditions to those under fasted conditions were 0.873 [0.803, 0.950] and 0.911 [0.863, 0.961], respectively.

6.2 Summary of clinical pharmacology studies

Unless otherwise specified, the pharmacokinetic parameters are expressed as the mean or mean ± SD.

6.2.1 *In vitro* studies using human biomaterials

6.2.1.1 Plasma protein binding and distribution in blood cells (CTD 4.2.2.3-4)

When ^{14}C-pemafibrate at a final concentrations of 0.5 to 10 μg/mL was added to human plasma, human serum albumin, or α_1-acid glycoprotein, the fraction of unbound ^{14}C-pemafibrate was 0.15% to 0.17%, 0.17% to 0.20%, and 25.0% to 45.8%, respectively.

When ^{14}C-pemafibrate at a final concentrations of 0.5 to 10 μg/mL was added to human blood, 1.7% to 13.1% of the added radioactivity was distributed in blood cells.

6.2.1.2 *In vitro* metabolism

6.2.1.2.1 Metabolism of pemafibrate (CTD 4.2.2.4-7 to 11)

Pemafibrate (10 μmol/L) was incubated with human liver microsomes at 37°C. K-15823, K-15824, K-15825, K-15827, K-15828, K-15830, and K-15834 were detected after incubation.

^{14}C-pemafibrate (10 μmol/L) was incubated with human liver microsomes at 37°C. The major metabolite detected after incubation was K-15828.

When ^{14}C-pemafibrate (0.5 μmol/L) was incubated with human liver microsomes at 37°C, the metabolic clearance in the phase I and II reactions was 135.4 and 84.8 μL/min/mg protein, respectively. When ^{14}C-pemafibrate (0.5 to 100 μmol/L) was incubated with human liver microsomes at 37°C, K-15828 and K-15834 were mainly generated by the phase I reaction, and their maximum velocity/Michaelis-Menten constant (V_{max}/K_m) was 101.6 and 15.3 μL/min/mg protein, respectively. A glucuronide conjugate of pemafibrate was generated by the phase II reaction, and their V_{max}/K_m was 38.7 μL/min/mg protein.

^{14}C-pemafibrate (5 μmol/L) was incubated with human hepatic cytosols, hepatic S9 fraction, or hepatocytes at 37°C. The reaction hardly occurred in the hepatic cytosols. The reaction pattern in the hepatic S9 fraction was similar to that in the liver microsomes, and K-15827, K-15828, and K-15834 were mainly detected. A glucuronide conjugate of pemafibrate was detected in the hepatocytes, and its deconjugation resulted in an increased level of K-15828.

Pemafibrate, K-15823, K-15827, K-15828, K-15834, K-23467, K-23469, or K-23605 (5 μmol/L for each) was incubated with human liver microsomes or hepatocytes at 37°C to investigate the metabolic pathway of pemafibrate. K-15827, K-15828, and K-15834 were mainly detected after incubation of pemafibrate with human liver microsomes. K-15827 was mainly detected after incubation of K-15823 or K-15828 with human liver microsomes. No known metabolites were detected after incubation of K-15834, K-15827, K-23467, K-23469, or K-23605 with human liver microsomes. K-15828, K-15834, and K-23467 were mainly detected after incubation of pemafibrate with human hepatocytes. K-15827 was detected after incubation of K-15828 with human hepatocytes. Furthermore, K-23469 was detected after incubation of K-15827 with human hepatocytes. No known metabolites were detected after incubation of K-15823, K-15834, K-23467, K-23469, or K-23605 with human hepatocytes.

6.2.1.2.2 Identification of enzymes involved in metabolism of pemafibrate (CTD 4.2.2.4-9)

^{14}C-pemafibrate (0.5 μmol/L) was incubated with each of human CYP isoform expression systems (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9*1, CYP2C19, CYP2D6*1, CYP2E1, CYP3A4, CYP3A5, CYP3A7, or CYP4A11) or human UGT isoform expression systems (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B4, UGT2B7, UGT2B15, or UGT2B17) at 37°C. Pemafibrate was metabolized through CYP2C8, CYP2C9*1, CYP3A4, and CYP3A7 expression systems as well as UGT1A1, UGT1A3, and UGT1A8 expression systems. The contribution rates of CYP2C8, CYP2C9, and CYP3A4 isoforms to the metabolic reactions were 31.2%, 20.6%, and 31.2%, respectively, for K-15282, and 29.1%, 33.9%, and 61.4%, respectively, for K-15834.

6.2.1.2.3 Inhibition of CYP isoforms (CTD 4.2.2.6-2 to 4.2.2.6-4)

Inhibitory effects of pemafibrate, K-23467, K-23469, and K-23605 (0.1-30 μmol/L for each) on metabolic reactions by CYP isoforms were investigated using human liver microsomes and substrates

of various CYP isoforms (CYP1A2, CYP2A6 [only for pemafibrate], CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4/5). Pemafibrate inhibited tolbutamide 4-methyl hydroxylase (CYP2C9) activity with an IC_{50} of 17.7 μmol/L. The activity of any of other CYP isoforms was not inhibited (IC_{50} >30 μmol/L). In addition, pre-incubation of pemafibrate or its metabolite with liver microsomes hardly increased the inhibitory effect.

6.2.1.2.4 Induction of CYP isoforms (CTD 4.2.2.6-5, 4.2.2.6-6)

Pemafibrate (0.7 to 70 nmol/L) was added to human hepatocytes to investigate the induction of each CYP isoform. The results showed that pemafibrate increased phenacetin *O*-de-ethylase (CYP1A2) and bupropion hydroxylase (CYP2B6) activities up to 2.7- and 2.1-fold, respectively, those with vehicle, but hardly induced a testosterone 6β- hydroxylase (CYP3A4) activity.

Pemafibrate, K-23467, K-23469, or K-23605 (0.2 to 20 μmol/L for each) was added to human hepatocytes. mRNA expression levels of CYP1A2, CYP2B6, and CYP3A4 increased up to 1.83 fold; pemafibrate hardly induced mRNA expression of the isoform genes.

6.2.1.2.5 Inhibition of UGT isoforms (CTD 4.2.2.6-11)

Inhibitory effects of pemafibrate, K-23467, K-23469, and K-23605 (0.1-30 μmol/L for each) against metabolic reactions by UGT isoforms were investigated using human liver microsomes and substrates of UGT isoforms (UGT1A1 or UGT2B7). The results showed that pemafibrate inhibited UGT1A1 activity (IC_{50} 5.91 μmol/L), but did not inhibit UGT2B7 activity (IC_{50} >30 μmol/L). K-23467, K-23469, and K-23605 did not inhibit UGT1A1 or UGT2B7 activity (IC_{50} >30 μmol/L).

6.2.1.3 Transport via transporters (CTD 4.2.2.3-5 to 4.2.2.3-8)

^{14}C-pemafibrate (1 μmol/L) was added to Caco-2 cells. Apparent permeability coefficient (P_{app}) was calculated for both apical-to-basolateral direction (A→B) and basolateral-to-apical direction (B→A). The P_{app} A→B and P_{app} B→A were 4.9×10^{-6} cm/s and 28.2×10^{-6} cm/s, respectively, and the efflux ratio of pemafibrate calculated from the P_{app} (P_{app} B→A/P_{app} A→B) values was 5.8. After addition of verapamil hydrochloride or cyclosporine, a P-glycoprotein (P-gp) inhibitor, or Ko143, a breast cancer resistance protein (BCRP) inhibitor, the efflux ratio of pemafibrate (P_{app} B→A/P_{app} A→B) was reduced by both inhibitors. This indicates that pemafibrate is a substrate of P-gp and BCRP.

^{14}C-pemafibrate 1 to 300 μmol/L was added to cells expressing organic anion transporting polypeptide (OATP)1A2, OATP1B1, OATP1B3, OATP2B1, organic anion transporter (OAT)1, OAT2, OAT3, OAT4, OAT7, organic cation transporter (OCT)1, OCT2, OCT3, carnitine/organic cation transporter (OCTN)1, OCTN2, peptide transporter (PEPT)1, PEPT2, and sodium/taurocholate cotransporting polypeptide (NTCP). Pemafibrate was incorporated into cells expressing OATP1A2, OATP1B1, OATP1B3, OCT2, and NTCP. The K_m values for OATP1B1 and OCT2 were 232.3 and 29.8 μmol/L, respectively.

6.2.1.4 Inhibition of transporters (CTD 4.2.2.3-5, 4.2.2.6-9, 4.2.2.6-12)

^{3}H-digoxin, a substrate of P-gp, was added to Caco-2 cells to investigate the inhibitory effects of pemafibrate, K-23467, K-23469, and K-23605 against P-gp. The results showed that the IC_{50} of pemafibrate (0.1-62.5 μmol/L) was 20.8 μmol/L, and K-23467, K-23469, and K-23605 (0.2-20 μmol/L) did not inhibit P-gp activity (IC_{50} >20 μmol/L).

^{3}H-prazosin, a substrate of BCRP, was added to LLC-PK1 cells expressing BCRP to investigate the inhibitory effects of pemafibrate, K-23467, K-23469, and K-23605 against BCRP. The results showed that the IC_{50} of pemafibrate (0.02-12.5 μmol/L) was 4.42 μmol/L, and K-23467, K-23469, and K-23605 (0.2-20 μmol/L) did not inhibit BCRP (IC_{50} >20 μmol/L).

Membrane vesicles were prepared from HEK293 cells expressing OATP1B1, OATP1B3, OCT1, OCT2, multidrug and toxin extrusion (MATE)1, or MATE2-K; S_2 cells expressing OAT1 or OAT3; and cells expressing multidrug resistance-associated protein (MRP)2, MRP4, or bile salt export pump (BSEP). The inhibitory effects of pemafibrate, K-23467, K-23469, and K-23605 on the transporters was investigated by adding the following substrates of each transporter to the prepared membrane vesicles: ^{3}H-estradiol 17β-D-glucuronide for OATP1B1, OATP1B3, MRP2, and MRP4; ^{3}H-p-aminohippuric acid for OAT1; ^{3}H-estrone 3-sulfate for OAT3; ^{14}C-metformin for OCT1, OCT2, MATE1, and MATE2-K;

^{3}H-taurocholic acid for BSEP. The results showed that the IC_{50} of pemafibrate (0.02-20 μmol/L) against OATP1B1, OATP1B3, OAT1, OAT3, and MRP4 was 0.101, 1.84, 2.42, 0.0961, and 2 to 20 μmol/L, respectively; but pemafibrate did not inhibit MATE1, MATE2-K, OCT1, OCT2, MRP2, or BSEP (IC_{50} >20 μmol/L [>12.5 μmol/L for OCT2]). The IC_{50} of K-23467 (0.2-20 μmol/L) against both OAT1 and OAT3 were 2 to 20 μmol/L, and pemafibrate did not inhibit any of other transporters (IC_{50}, >20 μmol/L). The IC_{50} of K-23469 (0.2-20 μmol/L) against OAT1, OAT3, and MRP4 was 2 to 20, 0.2 to 2, and 2 to 20 μmol/L, respectively, and pemafibrate did not inhibit any of other transporters (IC_{50} >20 μmol/L). K-23605 did not inhibit any of the transporters tested (IC_{50}, >20 μmol/L).

6.2.1.5 Protein-binding drug interactions (CTD 4.2.2.6-7, 4.2.2.6-8, 4.2.2.6-13 [reference data])

Pemafibrate (4 or 40 ng/mL) was added to human plasma to investigate the effects of pemafibrate on plasma protein binding of ^{14}C-warfarin and ^{3}H-diazepam. The results showed that pemafibrate hardly affected the plasma protein binding of warfarin and diazepam.

Pemafibrate (10 ng/mL) was added to human plasma to investigate the effects of warfarin, diazepam, digitoxin, and pitavastatin on plasma protein binding of pemafibrate. The results showed that any of these drugs hardly affected the plasma protein binding of pemafibrate.

Pemafibrate (4 or 40 ng/mL) was added to human serum albumin to investigate the effects of pemafibrate on protein binding of sulfonylureas (glibenclamide, gliclazide, and glimepiride). The results showed that pemafibrate hardly affected the protein binding of these drugs.

6.2.2 Studies in healthy adults

6.2.2.1 Single-dose study (Study K-877-01, CTD 5.3.3.1-1)

A single oral dose of pemafibrate (0.3, 0.5, or 1 mg) was administered to 24 healthy Japanese adults (n = 8/group) (these subjects were evaluable for pharmacokinetic analysis). The pharmacokinetic parameters of pemafibrate are shown in Table 9.

Table 9. Pharmacokinetic parameters following a single oral dose of pemafibrate

Dose (mg)	C_{max} (ng/mL)	t_{max} (h)[a]	$AUC_{0\text{-}inf}$ (ng·h/mL)	$t_{1/2}$ (h)
0.3	4.504 ± 1.839	1.5	15.936 ± 7.247	2.061 ± 0.393
0.5	6.007 ± 2.162	1.5	24.031 ± 9.895	2.060 ± 0.525
1	14.325 ± 3.704	1.5	54.538 ± 12.457	2.435 ± 0.473

[a] Median

6.2.2.2 Multiple-dose studies

6.2.2.2.1 Study in Japanese subjects (Study K-877-03, CTD 5.3.3.1-2)

A total of 48 healthy Japanese adults (n = 8/group) orally received pemafibrate 0.1, 0.2, or 0.4 mg once daily after breakfast or twice daily after meals for 7 days. The pharmacokinetic parameters of pemafibrate are shown in Table 10.

Table 10. Pharmacokinetic parameters in healthy Japanese adults following multiple oral doses of pemafibrate

Daily dose (mg)	Dosing frequency	Sampling time point	C_{max} (ng/mL)	t_{max}[a] (h)	$AUC_{0\text{-}\tau}$ (ng·h/mL)	$t_{1/2}$ (h)
0.1	Once daily	Day 1	1.175 ± 0.284	2.0	4.468 ± 1.300	-
		Day 7	1.172 ± 0.312	1.75	4.040 ± 1.174	1.494 ± 0.181
0.2	Once daily	Day 1	2.328 ± 0.457	2.5	9.239 ± 2.017	-
		Day 7	2.524 ± 0.544	1.75	9.024 ± 1.956	1.562 ± 0.368
	Twice daily	Day 1	1.401 ± 0.249	2.0	4.884 ± 1.201	-
		Day 7	1.593 ± 0.366	2.0	5.404 ± 1.515	1.528 ± 0.402
0.4	Once daily	Day 1	6.374 ± 2.843	2.0	25.608 ± 8.015	-
		Day 7	6.775 ± 2.669	2.0	23.305 ± 8.207	1.806 ± 0.265
	Twice daily	Day 1	2.968 ± 0.905	2.0	10.975 ± 2.335	-
		Day 7	3.572 ± 1.021	2.0	12.207 ± 2.900	1.708 ± 0.158
0.8	Twice daily	Day 1	6.334 ± 1.597	2.0	25.858 ± 6.562	-
		Day 7	7.229 ± 1.956	2.0	29.768 ± 8.759	2.088 ± 0.206

-, Not calculated

[a] Median

6.2.2.2.2 Study in non-Japanese subjects (Study K-877-101, CTD 5.3.3.1-4)

A total of 70 healthy non-Japanese adults (n = 10/group) orally received pemafibrate 0.4, 0.8, or 1.6 mg once daily after breakfast or 0.05, 0.1, 0.2, or 0.4 mg twice daily after meals for 7 days. The pharmacokinetic parameters of pemafibrate are shown in Table 11.

Table 11. Pharmacokinetic parameters in healthy non-Japanese adults following multiple oral doses of pemafibrate

Daily dose (mg)	Dosing frequency	Sampling time point	C_{max} (ng/mL)	t_{max}[a] (h)	$AUC_{0-\tau}$ (ng·h/mL)	$t_{1/2}$ (h)
0.1	Twice daily	Day 1	0.50 ± 0.232	1.5	1.36 ± 0.548	1.26 ± 0.243
		Day 7	0.52 ± 0.253	2.03	1.63 ± 0.788	1.51 ± 0.346
0.2	Twice daily	Day 1	0.87 ± 0.403	2.53	2.74 ± 0.991	1.43 ± 0.378
		Day 7	0.86 ± 0.317	3.0	3.46 ± 1.445	1.78 ± 0.462
0.4	Once daily	Day 1	4.59 ± 1.881	1.5	12.69 ± 4.751	1.42 ± 0.391
		Day 7	4.27 ± 1.733	3.0	13.85 ± 4.185	1.68 ± 0.405
	Twice daily	Day 1	2.36 ± 0.600	1.53	7.27 ± 2.190	1.91 ± 0.811
		Day 7	2.38 ± 0.737	2.0	9.17 ± 2.696	2.09 ± 0.638
0.8	Once daily	Day 1	8.86 ± 3.239	2.0	30.71 ± 11.499	2.20 ± 0.818
		Day 7	9.25 ± 3.143	2.0	35.16 ± 14.214	2.29 ± 0.630
	Twice daily	Day 1	5.57 ± 2.375	1.5	17.07 ± 7.725	2.05 ± 0.752
		Day 7	5.96 ± 3.965	2.5	22.67 ± 15.752	2.44 ± 0.878
1.6	Once daily	Day 1	17.11 ± 6.313	2.0	53.52 ± 8.355	3.99 ± 3.010
		Day 7	17.94 ± 7.789	2.0	59.98 ± 13.342	3.04 ± 1.164

[a] Median

6.2.2.3 Mass balance study (Study K-877-07, CTD 5.3.1.1-1)

A total of 8 healthy non-Japanese adults orally received a single dose of ^{14}C-pemafibrate 0.8 mg. The peak plasma radioactivity level (14.366 ± 4.732 ng eq/mL) was reached at 1.75 hours post-dose. AUC_{0-inf} was 166.625 ± 57.699 ng eq·h/mL, and $t_{1/2}$ was 31.529 ± 42.628 hours. Radioactivity excreted in urine and feces up to 216 hours post-dose accounted for 14.53% and 73.29% of the administered radioactivity, respectively. The major metabolites identified in plasma were K-23605, K-23467, and a glucuronide conjugate of K-23469. The metabolites identified in urine were a glucuronide conjugate of K-23469 and K-23467. The major metabolite identified in feces was K-15828, and other metabolites identified were K-15830 and K-15834.

6.2.3 Studies in patients

6.2.3.1 Multiple-dose study (Study K-877-03, CTD 5.3.3.1-2)

A total of 19 Japanese patients with hypertriglyceridemia (9 for once-daily regimen, 10 for twice-daily regimen) orally received pemafibrate 0.2 mg once daily after breakfast or 0.1 mg twice daily after meals for 15 days. The pharmacokinetic parameters of pemafibrate are shown in Table 12.

Table 12. Pharmacokinetic parameters in Japanese patients with hypertriglyceridemia following multiple oral doses of pemafibrate

Daily dose (mg)	Dosing frequency	Sampling time point	C_{max} (ng/mL)	t_{max}[a] (h)	$AUC_{0-\tau}$ (ng·h/mL)	$t_{1/2}$ (h)
0.2	Once daily	Day 1	2.420 ± 0.659	2.0	10.232 ± 2.710	-
		Day 15	2.264 ± 0.771	2.0	10.499 ± 3.526	2.295 ± 0.470
	Twice daily	Day 1	1.517 ± 0.766	2.0	5.590 ± 2.049	-
		Day 15	1.478 ± 0.664	2.0	6.301 ± 2.280	2.043 ± 0.413

-, Not calculated
[a] Median

6.2.3.2 Dose-finding study (Study K-877-04, CTD 5.3.5.1-1)

Japanese patients with hypertriglyceridemia orally received pemafibrate 0.025, 0.05, 0.1, or 0.2 mg twice daily after meals (n = 26, 24, 21, and 25, respectively). C_{max} at Week 12 of treatment was 0.352 ± 0.129, 0.640 ± 0.214, 1.295 ± 0.354, and 3.059 ± 1.332 ng/mL, respectively; and AUC_{0-6h} was 1.297 ± 0.394, 2.286 ± 0.867, 4.861 ± 1.520, and 11.496 ± 4.978 ng·h/mL, respectively.

6.2.3.3 Dose-response study of pemafibrate in combination with pitavastatin (Study K-877-13, CTD 5.3.5.1-3)

Japanese patients with hypertriglyceridemia on pitavastatin therapy orally received pemafibrate 0.05, 0.1, or 0.2 mg twice daily after meals (n = 20, 25, and 17, respectively). C_{max} at Week 12 of treatment was 0.898 ± 0.794, 2.026 ± 1.276, and 3.857 ± 2.217 ng/mL, respectively; and $AUC_{0\text{-}6h}$ was 3.170 ± 2.525, 7.129 ± 5.302, and 13.018 ± 6.191 ng·h/mL, respectively.

6.2.4 PPK analysis (K-877-AP07, CTD 5.3.3.5-2)

Population pharmacokinetic (PPK) analysis was performed using 13,695 plasma pemafibrate concentration data from a total of 995 subjects including healthy adults, patients with hepatic impairment, patients with renal impairment, and patients with hypertriglyceridemia in Studies K-877-01, K-877-02, K-877-03, K-877-04, K-877-05, K-877-06, K-877-07, K-877-08, K-877-10, K-877-12, K-877-13, K-877-14, K-877-16, K-877-18, K-877-20, K-877-101, K-877-102, K-877-103, K-877-104, K-877-105, K-877-107, and K-877-201.

Characteristics of subjects included in the analysis as follows: sex, 794 males and 201 females; age, 43 [21, 70] years old (median [5th percentile, 95th percentile],); age group, 855 non-elderly subjects, 140 elderly subjects; body weight, 71.0 [53.5, 100.8] kg; body mass index (BMI) 25.1 [19.2, 33.5] kg/m^2; region, 629 subjects in Japan, 366 subjects overseas; race, 288 Caucasians, 66 Black or African Americans, 637 Asians, 4 subjects with unknown race; diet, 870 subjects treated under fed conditions, 463 subjects treated under fasted conditions; number of doses, 493 subjects treated with a single dose, 840 subjects treated with multiple doses; dosing frequency, 396 subjects treated with once-daily dosing, 599 subjects treated with twice-daily dosing; daily dose, 30 subjects on pemafibrate 0.05 mg, 161 subjects on pemafibrate 0.1 mg, 409 subjects on pemafibrate 0.2 mg, 8 subjects on pemafibrate 0.3 mg, 577 subjects on pemafibrate 0.4 mg, 8 subjects on pemafibrate 0.5 mg, 56 subjects on pemafibrate 0.8 mg, 8 subjects on pemafibrate 1.0 mg, 76 subjects on pemafibrate 1.6 mg; type of formulation, 104 subjects treated with Formulation A, 456 subjects treated with Formulation B, 419 subjects treated with Formulation C, 16 subjects treated with the to-be-marketed formulation; AST (IU/L), 20.0 [12.0, 45.0]; ALT (IU/L), 20.0 [8.0, 61.0]; γ-GTP (IU/L), 25.0 [10.0, 126.0]; total bilirubin (mg/dL), 0.64 [0.3, 1.3]; estimated glomerular filtration rate (eGFR) (mL/min/1.73 m^2), 407 subjects with eGFR ≥90, 496 subjects with eGFR ≥60 and <90, 63 subjects with eGFR ≥30 and <60, 10 subjects with eGFR ≥15 and <30, 15 subjects with eGFR <15 or on hemodialysis; creatinine clearance (CCr), 113.4 [59.07, 168.74] mL/min; total protein (g/dL), 7.2 [6.4, 73.0]; 506 subjects with hyperlipidemia, 489 subjects without hyperlipidemia; 184 subjects with comorbid type 2 diabetes mellitus, 811 subjects without comorbid type 2 diabetes mellitus; 280 subjects with comorbid hypertension, 715 subjects without comorbid hypertension; comorbid hepatobiliary disorders, 169 subjects with comorbid hepatic steatosis or alcoholic liver injury, 15 subjects with comorbid hepatic impairment, 15 subjects with comorbid hepatic cirrhosis, 796 subjects with other comorbidities or without any comorbidity; comorbid hepatobiliary disorders (except for hepatitis), 168 subjects with comorbid hepatic steatosis or alcoholic liver injury, 15 subjects with comorbid hepatic impairment, 15 subjects with comorbid hepatic cirrhosis, 797 subjects with other comorbidities or without any comorbidity; 2 subjects with hepatitis, 993 subjects without hepatitis; 110 subjects with concomitant pitavastatin, 1223 subjects without concomitant pitavastatin; 96 subjects with concomitant rosuvastatin, 1237 subjects without concomitant rosuvastatin; 86 subjects with concomitant atorvastatin, 1247 subjects without concomitant atorvastatin; 21 subjects with concomitant fluvastatin, 1312 subjects without concomitant fluvastatin; 30 subjects with concomitant pravastatin, 1303 subjects without concomitant pravastatin; 49 subjects with concomitant simvastatin, 1284 subjects without concomitant simvastatin; 5 subjects with concomitant polyunsaturated fatty acids, 990 subjects without concomitant polyunsaturated fatty acids; and 4 subjects with concomitant ezetimibe, 991 subjects without concomitant ezetimibe. The above characteristic factors were potential covariates for pharmacokinetic parameters. Some subjects were counted multiple times in terms of diet, dosing frequency, daily dose, and concomitant pitavastatin, rosuvastatin, atorvastatin, fluvastatin, pravastatin, and simvastatin.

The pharmacokinetics of pemafibrate was described in a 1-compartment model with first-order absorption. In the final model of PPK, covariates selected for clearance (CL) were race (Asian, other races), hyperlipidemia, daily dose, and concomitant rosuvastatin; covariates selected for volume of distribution were race (Asian, the other races), concomitant rosuvastatin, number of doses, and diet; and

covariates selected for absorption rate constant (k_a) were dosing frequency, daily dose, and type of formulation.

6.2.5 Intrinsic factors

6.2.5.1 Study in subjects with hepatic impairment (Study K-877-10, CTD 5.3.3.3-1)

Japanese subjects with normal hepatic function, those with mild hepatic cirrhosis (Child-Pugh class A), those with moderate hepatic cirrhosis (Child-Pugh class B), and those with hepatic steatosis (n = 8, 8, 6, and 10, respectively) orally received a single dose of pemafibrate 0.2 mg. The pharmacokinetic parameters of pemafibrate are shown in Table 13.

Table 13. Pharmacokinetic parameters in subjects with hepatic impairment following a single oral dose of pemafibrate

	C_{max} (ng/mL)	t_{max} (h)[a]	$AUC_{0\text{-}inf}$ (ng·h/mL)	$t_{1/2}$ (h)
Normal hepatic function	3.015 ± 1.165	1.5	9.311 ± 2.718	1.637 ± 0.306
Mild hepatic cirrhosis	6.780 ± 1.632	1.0	20.320 ± 6.555	2.035 ± 0.350
Moderate hepatic cirrhosis	11.564 ± 3.656	1.0	40.445 ± 18.360	3.515 ± 1.669
Hepatic steatosis	4.010 ± 2.079	1.5	12.112 ± 5.772	2.031 ± 0.913

[a] Median

6.2.5.2 Study in subjects with renal impairment (Study K-877-12, CTD 5.3.3.3-2)

Japanese subjects with normal renal function (CCr ≥80 mL/min, calculated according to the Cockcroft-Gault formula), those with mild renal impairment (CCr ≥50 mL/min and <80 mL/min), those with moderate renal impairment (CCr ≥30 mL/min and <50 mL/min), those with severe renal impairment (CCr <30 mL/min), and those with end-stage renal failure (n = 8, 8, 8, 7, and 7, respectively) orally received a single dose of pemafibrate 0.2 mg. The pharmacokinetic parameters of pemafibrate are shown in Table14.

Table 14. Pharmacokinetic parameters in subjects with renal impairment following a single oral dose of pemafibrate

	C_{max} (ng/mL)	t_{max} (h)[a]	$AUC_{0\text{-}inf}$ (ng·h/mL)	$t_{1/2}$ (h)
Normal renal function	2.983 ± 0.713	1.5	9.953 ± 2.861	2.371 ± 0.966
Mild renal impairment	4.986 ± 1.533	1.25	16.500 ± 5.391	2.873 ± 0.497
Moderate renal impairment	3.504 ± 1.619	1.5	12.041 ± 5.868	2.498 ± 0.918
Severe renal impairment	5.229 ± 3.748	1.0	11.032 ± 2.993	2.961 ± 1.578
End-stage renal failure	3.928 ± 1.633	1.5	16.788 ± 7.583	2.978 ± 0.839

[a] Median

6.2.6 Drug-drug interaction

6.2.6.1 Pitavastatin (Study K-877-05, CTD 5.3.3.4-2)

A six-treatment, three-period crossover study was conducted in 18 healthy Japanese adults. Subjects were assigned to one of 6 sequences of the following 3 treatments (separated by a washout period of ≥7 days): (1) oral pemafibrate 0.2 mg twice daily after meals for 7 days; (2) oral pitavastatin 4 mg once daily after breakfast for 7 days; and (3) co-administration of oral pemafibrate 0.2 mg twice daily after meals and oral pitavastatin 4 mg once daily after breakfast for 7 days. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0\text{-}\tau}$ of pemafibrate following co-administration of pemafibrate and pitavastatin to those following administration of pemafibrate alone were 1.061 [0.970, 1.160] and 1.122 [1.041, 1.209], respectively. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0\text{-}\tau}$ of pitavastatin following co-administration of pitavastatin and pemafibrate to those following administration of pitavastatin alone were 1.011 [0.973, 1.050] and 1.036 [1.007, 1.066], respectively.

6.2.6.2 Atorvastatin (Study K-877-06, CTD 5.3.3.4-3)

A six-treatment, three-period crossover study was conducted in 18 healthy Japanese adults. Subjects were assigned to one of 6 sequences of the following 3 treatments (separated by a washout period of ≥7 days): (1) oral pemafibrate 0.2 mg twice daily after meals for 7 days; (2) oral atorvastatin 20 mg once daily after breakfast for 7 days; and (3) co-administration of oral pemafibrate 0.2 mg twice daily after meals and oral atorvastatin 20 mg once daily after breakfast for 7 days. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0\text{-}\tau}$ of pemafibrate following co-administration of pemafibrate and atorvastatin to those following administration of pemafibrate alone were 1.166 [1.069, 1.272] and 1.098 [1.016, 1.187], respectively. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0\text{-}\tau}$ of atorvastatin following co-

administration of atorvastatin and pemafibrate to those following administration of atorvastatin alone were 1.032 [0.960, 1.109] and 0.934 [0.851, 1.024]. The geometric mean ratios (co-administration/alone) [90% CI] of C_{max} and $AUC_{0-\tau}$ of *o*-hydroxy atorvastatin were 0.875 [0.826, 0.927] and 0.784 [0.736, 0.836], respectively.

6.2.6.3 Pravastatin, simvastatin, fluvastatin (Study K-877-18, CTD 5.3.3.4-4)

A six-treatment, three-period crossover study was conducted in 18 healthy Japanese adults. Subjects were assigned to one of 6 sequences of the following 3 treatments (separated by a washout period of ≥7 days): (1) oral pemafibrate 0.2 mg twice daily after meals for 7 days; (2) oral pravastatin 20 mg once daily after breakfast for 7 days; and (3) co-administration of oral pemafibrate 0.2 mg twice daily after meals and oral pravastatin 20 mg once daily after breakfast for 7 days. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0-\tau}$ of pemafibrate following co-administration of pemafibrate and pravastatin to those following administration of pemafibrate alone were 1.058 [0.964, 1.162] and 1.057 [1.013, 1.102], respectively. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0-\tau}$ of pravastatin following co-administration of pravastatin and pemafibrate to those following administration of pravastatin alone [90% CI] were 1.107 [0.908, 1.351] and 1.065 [0.922, 1.231], respectively.

A six-treatment, three-period crossover study was conducted in 19 healthy Japanese adults. Subjects were assigned to one of 6 sequences of the following 3 treatments (separated by a washout period of ≥7 days): (1) oral pemafibrate 0.2 mg twice daily after meals for 7 days; (2) oral simvastatin 20 mg once daily after breakfast for 7 days; and (3) co-administration of oral pemafibrate 0.2 mg twice daily after meals and oral simvastatin 20 mg once daily after breakfast for 7 days. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0-\tau}$ of pemafibrate following co-administration of pemafibrate and simvastatin to those following administration of pemafibrate alone were 1.230 [1.090, 1.388] and 1.125 [0.997, 1.270], respectively. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0-\tau}$ of simvastatin following co-administration of simvastatin and pemafibrate to those following administration of simvastatin alone were 0.858 [0.660, 1.114] and 0.846 [0.722, 0.992]. The geometric mean ratios (co-administration/alone) [90% CI] of C_{max} and $AUC_{0-\tau}$ of the open-acid form of simvastatin were 0.626 [0.541, 0.725] and 0.405 [0.345, 0.475], respectively.

A six-treatment, three-period crossover study was conducted in 19 healthy Japanese adults. Subjects were assigned to one of 6 sequences of the following 3 treatments (separated by a washout period of ≥7 days): (1) oral pemafibrate 0.2 mg twice daily after meals for 7 days; (2) oral fluvastatin 60 mg once daily after breakfast for 7 days; and (3) co-administration of oral pemafibrate 0.2 mg twice daily after meals and oral fluvastatin 60 mg once daily after breakfast for 7 days. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0-\tau}$ of pemafibrate following co-administration of pemafibrate and fluvastatin to those following administration of pemafibrate alone were 1.181 [1.080, 1.290] and 1.207 [1.144, 1.274], respectively. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0-\tau}$ of fluvastatin following co-administration of fluvastatin and pemafibrate to those following administration of fluvastatin alone were 0.989 [0.790, 1.239] and 1.151 [1.057, 1.253], respectively.

6.2.6.4 Rosuvastatin (Study K-877-08, CTD 5.3.3.4-5)

A six-treatment, three-period crossover study was conducted in 24 healthy non-Japanese adults. Subjects were assigned to one of 6 sequences of the following 3 treatments (separated by a washout period of ≥7 days): (1) oral pemafibrate 0.2 mg twice daily after meals for 7 days; (2) oral rosuvastatin 20 mg once daily after breakfast for 7 days; and (3) co-administration of oral pemafibrate 0.2 mg twice daily after meals and oral rosuvastatin 20 mg once daily after breakfast for 7 days. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0-\tau}$ of pemafibrate following co-administration of pemafibrate and rosuvastatin to those following administration of pemafibrate alone were 1.106 [1.048, 1.167] and 1.110 [1.046, 1.177], respectively. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0-\tau}$ of rosuvastatin following co-administration of rosuvastatin and pemafibrate to those following administration of rosuvastatin alone were 1.092 [1.016, 1.174] and 1.025 [0.964, 1.091], respectively.

6.2.6.5 Cyclosporine (Study K-877-103, CTD 5.3.3.4-7)

A total of 20 healthy non-Japanese adults orally received a single dose of pemafibrate 0.4 mg on Day 1 and then orally received pemafibrate 0.4 mg concomitantly with cyclosporine 600 mg on Day 4. The geometric mean ratios [90% CI] of C_{max} and AUC_{0-inf} of pemafibrate following co-administration of

pemafibrate and cyclosporine to those following administration of pemafibrate alone were 8.964 [7.515, 10.693] and 13.995 [12.618, 15.522], respectively.

6.2.6.6 Clarithromycin (Study K-877-104, CTD 5.3.3.4-8)

A total of 19 healthy non-Japanese adults orally received a single dose of pemafibrate 0.4 mg on Days 1 and 9, and also orally received clarithromycin 500 mg twice daily from Day 4 to Day 11. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0\text{-}inf}$ of pemafibrate following co-administration of pemafibrate and clarithromycin to those following administration of pemafibrate alone were 2.425 [2.163, 2.717] and 2.098 [1.916, 2.296], respectively.

6.2.6.7 Fluconazole (Study K-877-105, CTD 5.3.3.4-9)

A total of 20 healthy non-Japanese adults orally received a single dose of pemafibrate 0.4 mg on Days 1 and 12, and also orally received fluconazole 400 mg once daily from Day 4 to Day 14. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0\text{-}inf}$ of pemafibrate following co-administration of pemafibrate and fluconazole to those following administration of pemafibrate alone were 1.441 [1.290, 1.610] and 1.789 [1.664, 1.924], respectively.

6.2.6.8 Digoxin (Study K-877-106, CTD 5.3.3.4-10)

A total of 19 healthy non-Japanese adults orally received digoxin 0.25 mg twice daily on Day 1 and digoxin 0.25 mg once daily from Day 2 to Day 16, and also orally received pemafibrate 0.4 mg twice daily from Day 11 to Day 16. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0\text{-}\tau}$ of digoxin following co-administration of digoxin and pemafibrate to those following administration of digoxin alone were 1.033 [0.951, 1.121] and 0.946 [0.909, 0.985], respectively.

6.2.6.9 Rifampicin (Study K-877-107, CTD 5.3.3.4-11)

A total of 20 healthy non-Japanese adults orally received a single dose of pemafibrate 0.4 mg on Days 1, 4, and 15, and also orally received rifampicin 600 mg once daily from Day 4 to Day 14. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0\text{-}inf}$ of pemafibrate following co-administration of a single dose of pemafibrate and rifampicin (Day 4) to those following administration of pemafibrate alone were 9.434 [8.363, 10.642] and 10.901 [9.915, 11.984], respectively. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0\text{-}inf}$ of pemafibrate following administration of pemafibrate alone (Day 15) after multiple doses of rifampicin to those following administration of pemafibrate alone were 0.379 [0.338, 0.426] and 0.222 [0.207, 0.239], respectively.

6.2.6.10 Warfarin (Study K-877-108, CTD 5.3.3.4-12)

A total of 19 healthy non-Japanese adults (these subjects were evaluable for pharmacodynamic and pharmacokinetic analyses) orally received warfarin 5 mg once daily on Days 1 and 2, and then continued treatment with warfarin at the dose individually adjusted to achieve a prothrombin time-international normalized ratio (PT-INR) of 1.2 to 2.2 from Day 3 to Day 9, then warfarin at the adjusted dose from Day 10 to Day 21, and also orally received pemafibrate 0.2 mg twice daily from Day 14 to Day 21. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0\text{-}\tau}$ of *R*-warfarin following co-administration of warfarin and pemafibrate to those following administration of warfarin alone were 1.004 [0.972, 1.037] and 1.029 [1.004, 1.055], and such ratios for *S*-warfarin were 0.929 [0.889, 0.970] and 0.951 [0.926, 0.976], respectively.

The ratios [90% CI] of least-squares mean PT-INR and PT following co-administration of warfarin and pemafibrate to those following administration of warfarin alone were 1.020 [0.988, 1.051] and 1.019 [0.987, 1.051], respectively.

6.2.6.11 QT evaluation study (Study K-877-102, CTD 5.3.4.1-1)

A four-treatment, four-period crossover study was conducted in 56 healthy non-Japanese adults (these subjects were included in pharmacodynamic and pharmacokinetic analyses) to investigate an effect of pemafibrate on QT interval. Subjects received a single oral dose of pemafibrate 0.4 or 1.6 mg, moxifloxacin 400 mg, or placebo in each period (treatments separated by a 4-day washout period).

Following a single dose of pemafibrate 0.4 or 1.6 mg, the median t_{max} of pemafibrate was 1.208 and 1.425 hours, respectively; geometric mean C_{max} (coefficient of variation[CV]) was 4.511 (58.0) and

16.276 (37.7) ng/mL, respectively; and geometric mean $AUC_{0\text{-inf}}$ (CV) was 14.967 (64.8) and 58.602 (42.0) ng·h/mL, respectively.

The least-squares mean of differences in a change in QTcI (QT interval corrected for each subject) from baseline between pemafibrate 0.4 or 1.6 mg and the placebo (ΔΔQTcI) was 1.16 and 1.43 ms at the maximum, and the upper bound of one-sided 95% CI of ΔΔQTcI did not exceed 4 ms at any time point. In addition, the mean ΔΔQTcI following administration of moxifloxacin was 11.03 ms at the maximum, and the lower limit of one-sided 98.33% of ΔΔQTcI exceeded 7 ms at any time point (2, 3, and 4 hours after administration of moxifloxacin).

6.R Outline of the review conducted by PMDA

6.R.1 Use in patients with hepatic impairment

A study in subjects with hepatic impairment (Study K-877-10) showed that exposure to pemafibrate in subjects with hepatic cirrhosis was higher than that in subjects with normal hepatic function. PMDA therefore asked the applicant to explain whether the use of pemafibrate is acceptable in patients with hepatic impairment and whether it is necessary to provide relevant advice.

The applicant's explanation:
The package insert specifies that pemafibrate is contraindicated in patients with serious hepatic impairment, Child-Pugh class B or C hepatic cirrhosis, or biliary obstruction, for the following reasons: (1) Pemafibrate is excreted in bile; (2) exposure to pemafibrate in subjects with Child-Pugh class B or C hepatic cirrhosis was approximately 4-fold higher than that in subjects with normal hepatic function in Study K-877-10; and (3) there is no experience with the use of pemafibrate in patients with serious hepatic impairment because such patient population was excluded from clinical studies. In addition, the applicant decided to provide advice stating that a reduced dose of pemafibrate should be used in patients with Child-Pugh class A hepatic cirrhosis, because (i) exposure to pemafibrate in subjects with such hepatic impairment was approximately 2-fold higher than that in subjects with normal hepatic function; and (ii) pemafibrate has not been used in patients with hypertriglyceridemia who concurrently have Child-Pugh class A hepatic cirrhosis.

PMDA's view:
It is appropriate to contraindicate pemafibrate in patients with Child-Pugh class B or C hepatic cirrhosis, in whom the exposure was markedly higher than that in subjects with normal hepatic function. In addition, pemafibrate exposure in subjects with Child-Pugh class A hepatic cirrhosis and those with hepatic steatosis was higher than that in subjects with normal hepatic function. This suggests that exposure to pemafibrate is potentially increased not only in patients with hepatic cirrhosis but also in patients with mild hepatic impairment. Therefore, the package insert should include advice stating that careful administration is necessary in patients with mild hepatic impairment, and the applicant should provide physicians with information on increased exposure in such patients, and advise the physicians to consider dose reduction where necessary.

6.R.2 Use in patients with renal impairment

For use of the existing fibrates in patients with renal impairment, warnings and precautions for contraindication or careful administration are applicable depending on severity of renal impairment. In a study in subjects with renal impairment (Study K-877-12), exposure to pemafibrate in such subjects was higher than that in subjects with normal renal function. PMDA therefore asked the applicant to explain the use of pemafibrate in patients with renal impairment and the necessity of providing advice.

The applicant's explanation:
Exposure to pemafibrate in subjects with renal impairment was 1.1- to 1.6-fold higher than that in subjects with normal renal function, but the increased exposure was not considered clinically relevant. Furthermore, the increase in exposure was not dependent on the severity of renal impairment. In addition, the safety profile of pemafibrate at a dose up to 0.4 mg/day was favorable in hypertriglyceridemia patients with renal impairment with eGFR <60 mL/min/1.73 m^2 [see Section "7.R.6.3 Use in patients with renal impairment"], and no dose-dependent safety concern has been raised at up to 0.4 mg. Based on the above, no special precautions are needed for patients with renal impairment.

PMDA's view:
At present, there is no evidence of adverse events occurring at a clearly increased incidence in hypertriglyceridemia patients with renal impairment with eGFR <60 mL/min/1.73 m^2 after treatment with pemafibrate at a dose up to 0.4 mg/day, compared with patients with normal renal function. However, advice for the use of pemafibrate in patients with renal impairment should be provided in the package insert, taking into account that (1) pemafibrate exposure in subjects with renal impairment was higher than that in subjects with normal renal function; and (2) an increased risk of rhabdomyolysis associated with the use of pemafibrate cannot be excluded in patients with renal impairment [see Section "7.R.6.3 Use in patients with renal impairment"]. In addition, more specific contents of the advice should be discussed in consideration of clinical study data [see Section "7.R.6.3 Use in patients with renal impairment"].

6.R.3 Interactions mediated by metabolic enzymes
PMDA asked the applicant to explain the major metabolic enzymes of pemafibrate, and then explain the necessity of advice for co-administration of pemafibrate and inhibitors or inducers of these metabolic enzymes.

The applicant's explanation:
Results from human mass balance and *in vitro* studies (CTD 4.2.2.4-9) showed that metabolism of pemafibrate to K-15828 has the largest impact on clearance of pemafibrate, and contribution rates of CYP2C8, CYP2C9, and CYP3A4 to its clearance were 0.38, 0.25, and 0.38. The contributions of these isoforms were similar. Drug interaction studies were conducted to evaluate interaction between pemafibrate and several inhibitors of these CYP isoforms. Cyclosporine (inhibitor of CYP2C8, CYP2C9, and CYP3A) is listed in the "Contraindications for Co-administration" section, and clarithromycin (inhibitor of CYP3A) is listed in the "Precautions for Co-administration" section with advice stating that a reduced dose of pemafibrate be used, based on the increase in exposure to pemafibrate seen in drug interaction studies with cyclosporine (Study K-877-103) and with clarithromycin (Study K-877-104). For fluconazole (inhibitor of CYP2C9 and CYP3A), on the other hand, advice for its co-administration with pemafibrate was unnecessary, because the increase in exposure to pemafibrate observed in an interaction study (Study K-877-105) was not relevant enough to affect the safety.

In addition, a clinical drug-drug interaction study of pemafibrate with clopidogrel (CYP2C8 inhibitor) is currently underway. Advice will be added, if necessary, based on results from this study.

Furthermore, the applicant's consideration on co-administration of pemafibrate and CYP2C8, CYP2C9, or CYP3A inducers is as follows:
A drug-drug interaction study with rifampicin (which induces CYP2C8, CYP2C9, and CYP3A when administered in multiple doses) (Study K-877-107) showed that the C_{max} and $AUC_{0\text{-}inf}$ of pemafibrate co-administered with rifampicin (in multiple doses) were 0.4- and 0.2-fold, respectively, those of pemafibrate alone. According to the literature (*Clin Pharmacokinet.* 2008;47:669-80) reporting that the reduction of AUC could be estimated from the contribution of metabolic enzymes to clearance, exposure to pemafibrate co-administered with a potent inducer of CYP2C8, CYP2C9, or CYP3A is estimated to be 0.3- to 0.5-fold that to pemafibrate alone; and exposure to pemafibrate co-administered with a moderate enzyme inducer is estimated to be 0.7- to 0.8-fold that to pemafibrate alone. Therefore, potent inducers of CYP2C8, CYP2C9, or CYP3A are listed in the "Precautions for Co-administration" section, because co-administration with such enzyme inducers potentially reduces the efficacy of pemafibrate. In contrast, moderate enzyme inducers do not have to be listed for special precautions, because co-administration with such moderate enzyme inducers is unlikely to have effects requiring dose adjustment, etc.

PMDA's view:
Data were reviewed concerning co-administration with inhibitors of CYP isoforms involved in the metabolism of pemafibrate. The following measures on the use of cyclosporine and clarithromycin are appropriate in consideration of the increase in exposure to pemafibrate following co-administration of pemafibrate and relevant CYP inhibitors: Cyclosporine is listed in the "Contraindications for Co-administration" section, and clarithromycin is listed in the "Precautions for Co-administration" section with advice stating that a reduced dose should be considered where necessary. Whether the extent of

increase in exposure to pemafibrate co-administered with fluconazole is unlikely to cause clinically relevant problems remains unknown, and thus fluconazole should be listed in the "Precautions for Co-administration" section.

Data were reviewed concerning co-administration with inducers of CYP isoforms involved in the metabolism of pemafibrate. The applicant's following consideration are appropriate in consideration of potential decrease in exposure to pemafibrate following co-administration of pemafibrate and relevant CYP inhibitors: Potent inducers of the above CYP isoforms are listed in the "Precautions for Co-administration" section; and drugs that moderate enzyme inducers are not listed in any precaution section.

The conclusion of PMDA, taking into account results from a clinical drug-drug interaction study of pemafibrate with clopidogrel, is presented in Review Report (2).

6.R.4 Interactions mediated by transporters

PMDA asked the applicant to explain the appropriateness of the advice for co-administration of pemafibrate with drugs that inhibit transporters, based on results from drug-drug interaction studies of pemafibrate.

The applicant's explanation:
Results from *in vitro* studies indicated that pemafibrate is transported through P-gp, BCRP, OATP1B1, and OATP1B3. Rifampicin (inhibitor of OATP1B1 and OATP1B3 [following a single dose]) and cyclosporine (inhibitor of P-gp, OATP1B1, and OATP1B3) are listed in the "Contraindications for Co-administration" section, and clarithromycin (inhibitor of P-gp, OATP1B1, and OATP1B3) is listed in the "Precautions for Co-administration" section, in consideration of the increases in exposure to pemafibrate in drug-drug interaction studies with rifampicin (Study K-877-107), with cyclosporine (Study K-877-103), and with clarithromycin (Study K-877-104).

Results from a human mass balance study showed that the absorption rate of pemafibrate was as high as 92.6% (calculated from $AUC_{0\text{-inf}}$ in Study K-877-07), suggesting that the exposure is unlikely to increase even if the absorption of pemafibrate is increased as a consequence of inhibition of P-gp and BCRP in the gastrointestinal tract. Furthermore, pemafibrate is scarcely excreted in urine, and thus the inhibition of P-gp in the renal tubular is considered to have little effect on the exposure to pemafibrate. Studies were conducted to evaluate drug-drug interactions mediated by OATP1B1 and OATP1B3. Eexposure to pemafibrate was elevated in drug-drug interaction studies of pemafibrate with rifampicin, cyclosporine, or clarithromycin. However, in terms of the R value (1 + the unbound fraction of the test drug in periportal blood × the maximum drug concentration in periportal blood/inhibition constant determined in an *in vitro* study) used as an index of inhibitory potential against transporter, no drugs are known to have higher R values against OATP1B1 or OATP1B3 than those of the above drugs against OATP1B1. Thus, exposure to pemafibrate after co-administration of pemafibrate with OATP1B1 or OATP1B3 inhibitors other than rifampicin, cyclosporine, and clarithromycin is unlikely to be higher than that after co-administration with the above 3 drugs. The applicant, therefore, considers it unnecessary to list other OATP1B1 and OATP1B3 inhibitors in the "Precautions for Co-administration" section.

PMDA's view:
Rifampicin and cyclosporine should be listed in the "Contraindications for Co-administration" section and clarithromycin in the "Precautions for Co-administration" section, in consideration of the increased exposure to pemafibrate in drug-drug interaction studies. There is, however, a limitation to estimating the degree of increase in drug exposure in humans based on results from *in vitro* co-administration studies. The results of the drug-drug interaction study of pemafibrate with rifampicin indicated that OATP1B1 and OATP1B3 highly contribute to the pharmacokinetics of pemafibrate. Therefore, the package insert should advice the co-administration of pemafibrate with OATP1B1 or OATP1B3 inhibitors other than rifampicin, cyclosporine, and clarithromycin as well. No special precautions regarding co-administration with P-gp and BCRP inhibitors are necessary at present, because inhibition of P-gp and BCRP, if any, is unlikely to elevate exposure to pemafibrate, based on the applicant's explanation.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted the evaluation data, namely the results from 11 phase I studies (including clinical pharmacology studies in patients with hypertriglyceridemia), 1 phase II study, and 6 phase III studies conducted in Japan as well as 1 phase I study conducted overseas [for pharmacokinetics, see Section "6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA"]. Main study results are shown in sections below. Lipid parameters were determined using fasted serum samples.

7.1 Phase I studies

7.1.1 Single-dose study (Study K-877-01, CTD 5.3.3.1-1 [[redacted] to [redacted]])

A randomized, double-blind study was conducted at 1 site in Japan to investigate the safety and pharmacokinetics of pemafibrate in 70 healthy Japanese adults (n = 10/group [8 for pemafibrate and 2 for placebo]). Subjects received a single oral dose of pemafibrate 0.3, 0.5, or 1 mg, or placebo under fasted conditions. The study initially included groups in which subjects orally received a single dose of pemafibrate 2, 4, 8, or 16 mg under fasted conditions or a single dose of pemafibrate 4 mg after breakfast, but these regimens were discontinued immediately after the start of this study because these regimens resulted in higher pemafibrate exposure than expected. A total of 30 subjects who received the study drug (8 in the pemafibrate 0.3 mg group, 8 in the pemafibrate 0.5 mg group, 8 in the pemafibrate 1 mg group, and 6 in the placebo group) were included in the safety analysis set.

Adverse events were reported by 1 subject in the pemafibrate 0.3 mg group (blood ALP increased), 1 subject in the pemafibrate 0.5 mg group (blood bilirubin increased), 4 subjects in the pemafibrate 1 mg group (APTT prolonged, blood fibrinogen increased [2 subjects]; blood bilirubin increased, blood fibrinogen decreased [1 subject]; blood fibrinogen decreased [1 subject]), and 2 subjects in the placebo group (blood bilirubin increased, bilirubin conjugated increased [1 subject]; headache [1 subject]). Adverse events for which a causal relationship to study drug could not be ruled out were reported by 1 subject in the pemafibrate 1 mg group (blood bilirubin increased) and in 1 subject in the placebo group (headache). No deaths, serious adverse events, or adverse events leading to discontinuation of the study drug were reported.

7.1.2 Multiple-dose study (Study K-877-03, CTD 5.3.3.1-2 [[redacted] to [redacted]])

A randomized, double-blind study was conducted at 1 site in Japan to investigate the safety and pharmacokinetics of pemafibrate following multiple doses of pemafibrate. In this study, 60 healthy Japanese adults(n = 10/group [8 for pemafibrate and 2 for placebo]) received multiple oral doses of pemafibrate 0.1, 0.2, or 0.4 mg or placebo once daily (QD) or twice daily (BID), and 30 Japanese patients with hypertriglyceridemia (n = 10/group) received multiple oral doses of pemafibrate 0.1 mg or placebo twice daily (BID) or pemafibrate 0.2 mg once daily (QD). A total of 90 subjects who received the study drug (8 in the pemafibrate 0.1 mg QD group, 8 in the pemafibrate 0.1 mg BID group, 8 in the pemafibrate 0.2 mg QD group, 8 in the pemafibrate 0.2 mg BID group, 8 in the pemafibrate 0.4 mg QD group, 8 in the pemafibrate 0.4 mg BID group, and 12 in the placebo group [healthy adults]; and 10 in the pemafibrate 0.1 mg BID group, 10 in the pemafibrate 0.2 mg QD group, and 10 subjects in the placebo group [patients with hypertriglyceridemia]) were included in the safety analysis set.

Tables 15 and 16 show adverse events reported by >1 subject in any group of healthy adults and in any group of patients with hypertriglyceridemia, respectively.

Table 15. Adverse events reported by >1 subject in any group (healthy adults, safety analysis set)

	Placebo (N = 12)	Pemafibrate					
		0.1 mg QD (N = 8)	0.1 mg BID (N = 8)	0.2 mg QD (N = 8)	0.2 mg BID (N = 8)	0.4 mg QD (N = 8)	0.4 mg BID (N = 8)
Adverse event	50.0 (6)	12.5 (1)	25.0 (2)	0 (0)	62.5 (5)	50.0 (4)	87.5 (7)
Blood fibrinogen decreased	25.0 (3)	12.5 (1)	12.5 (1)	0 (0)	50.0 (4)	37.5 (3)	87.5 (7)
APPT prolonged	16.7 (2)	0 (0)	0 (0)	0 (0)	37.5 (3)	0 (0)	12.5 (1)
Blood iron decreased	8.3 (1)	0 (0)	0 (0)	0 (0)	0 (0)	25.0 (2)	0 (0)
Adverse events for which a causal relationship could not be ruled out	41.7 (5)	12.5 (1)	12.5 (1)	0 (0)	62.5 (5)	37.5 (3)	87.5 (7)
Blood fibrinogen decreased	25.0 (3)	12.5 (1)	12.5 (1)	0 (0)	50.0 (4)	25.0 (2)	87.5 (7)
APTT prolonged	16.7 (2)	0 (0)	0 (0)	0 (0)	37.5 (3)	0 (0)	12.5 (1)

% (n)

Table 16. Adverse events reported by >1 subject in any group (patients with hypertriglyceridemia, safety analysis set)

	Placebo (N = 10)	Pemafibrate	
		0.1 mg BID (N = 10)	0.2 mg QD (N = 10)
Adverse event	50.0 (5)	40.0 (4)	70.0 (7)
Blood insulin increased	30.0 (3)	0 (0)	10.0 (1)
Blood fibrinogen decreased	10.0 (1)	20.0 (2)	10.0 (1)
Adverse events for which a causal relationship could not be ruled out	0 (0)	10.0 (1)	20.0 (2)

% (n)

No deaths occurred in either healthy adults or patients with hypertriglyceridemia. A serious adverse event was reported by 1 patient with hypertriglyceridemia in the pemafibrate 0.2 mg QD group (lymphoma), but its causal relationship to pemafibrate was ruled out.

Adverse events leading to discontinuation of the study drug were reported by 1 patient with hypertriglyceridemia in the pemafibrate 0.2 mg QD group (lymphoma).

7.2 Phase II studies

7.2.1 Dose-finding study (Study K-877-04, CTD 5.3.5.1-1 [November 2010 to July 2011])

A randomized, double-blind, parallel-group study was conducted at 19 sites in Japan to investigate the efficacy and safety of pemafibrate in Japanese patients with dyslipidemia characterized by high TG and low HDL-C levels (target sample size, a total of 192 subjects [n = 32/group]).

Subjects were to orally receive placebo, or pemafibrate 0.025, 0.05, 0.1, or 0.2 mg twice daily after breakfast and supper (daily dose of 0.05, 0.1, 0.2, or 0.4 mg; hereinafter expressed as a daily dose), or FF 100 mg (pulverized capsule formulation) once daily after breakfast during the 12-week treatment period after a screening period of ≤8 weeks.

This study included patients with dyslipidemia aged ≥20 and <75 years who met the following key eligibility criteria:

- TG ≥200 mg/dL on 2 consecutive measurements at screening
- TG <500 mg/dL on 2 consecutive measurements at screening
- HDL-C <50 mg/dL for males or <55 mg/dL for females on 2 consecutive measurements at screening

The concomitant use of other therapeutic drugs for dyslipidemia including statins, anion exchange resin, probucol, fibrates, nicotinate derivatives, phytosterol (unsaponifiable matter of soybean oil, gamma-oryzanol), and other medications (elastase, dextran sulfate sodium sulfur, ethyl icosapentate, pantothenic acid, polyenephosphatidylcholine, ezetimibe) was prohibited during the study period. Subjects were randomized to each group by the minimization method using the study site and mean HDL-C at screening (<40 mg/dL or ≥40 mg/dL) as factors.

All of the 224 randomized subjects (36 in the placebo group, 37 in the pemafibrate 0.05 mg group, 37 in the pemafibrate 0.1 mg group, 38 in the pemafibrate 0.2 mg group, 39 in the pemafibrate 0.4 mg group, and 37 in the FF group) received the study drug and were included in the safety analysis set. Of these, 223 subjects (36 subjects, 37 subjects, 37 subjects, 38 subjects, 38 subjects, and 37 subjects, respectively) were included in the full analysis set (FAS), and the remaining 1 subject (pemafibrate 0.4 mg group) without initial data evaluable for the efficacy endpoint (TG) were excluded from the analysis. Furthermore, 214 subjects (35 subjects, 34 subjects, 37 subjects, 36 subjects, 36 subjects, and 36 subjects, respectively) were included in the per protocol set (PPS), and the following subjects were excluded from the analysis: 3 subjects who did not provide end-of-treatment data for the efficacy endpoint (TG), 3 subjects who used prohibited concomitant medications, 3 subjects who had a change in the state of compliance with the diet/exercise advice, 2 subjects who changed restricted concomitant drugs, and 1 subject who was not evaluable due to discontinuation (some subjects were excluded due to more than one reason). The PPS was used as the primary efficacy analysis population. Treatment was discontinued in 1 subject in the FF group because the discontinuation criterion was met (aggravated hepatic function).

The primary efficacy endpoint of this study was percentage change in TG from Week 0 to end of treatment (EOT). The results are shown in Table 17. The results of the primary endpoint presented a significant dose-response relationship (adjusted $P < 0.001$, maximum contrast method using contrasts of [–2, –1, 0, 1, 2], [–9, –4, 1, 6, 6], [–7, –2, 3, 3,3], [–4, 1, 1, 1, 1], [–6, –6, –1, 4, 9], [–3, –3, –3, 2, 7], and [–1, –1, 0, 1, 1] for the placebo group, the pemafibrate 0.05 mg group, the pemafibrate 0.1 mg group, the pemafibrate 0.2 mg group, and the pemafibrate 0.4 mg group). Selected contrast was (−4, 1, 1, 1, 1).

Table 17. Percentage change in TG from Week 0 to EOT (PPS)

	Placebo (n = 35)	Pemafibrate				FF (n = 36)
		0.05 mg (n = 34)	0.1 mg (n = 37)	0.2 mg (n = 36)	0.4 mg (n = 36)	
Week 0 (mg/dL)[a]	309.2 ± 129.8	333.5 ± 220.2	294.6 ± 110.9	290.9 ± 119.5	302.9 ± 208.9	325.2 ± 204.3
EOT (mg/dL)[a]	382.3 ± 272.6	193.2 ± 66.5	182.9 ± 96.8	166.1 ± 102.8	150.7 ± 68.3	195.1 ± 82.0
% Change[b] (95% CI)	28.687 ± 7.155 [14.564, 42.810]	−30.783 ± 7.279 [−45.151, −16.414]	−36.147 ± 6.962 [−49.889, −22.405]	−42.365 ± 7.061 [−56.301, −28.428]	−42.468 ± 7.055 [−56.393, −28.543]	-

[a] Mean ± SD
[b] Least-squares mean ±SE (ANCOVA using treatment group as a factor and TG at Week 0 as a covariate)

In addition, percentage changes in lipid parameters from Week 0 to EOT (the secondary efficacy endpoint) are shown in Table 18.

Table 18. Percentage changes in lipid parameter from Week 0 to EOT (PPS)

		Placebo (n = 35)	Pemafibrate				FF (n = 36)
			0.05 mg (n = 34)	0.1 mg (n = 37)	0.2 mg (n = 36)	0.4 mg (n = 36)	
LDL-C (direct method)	Week 0[a]	140.1 ± 30.1	136.6 ± 33.0	133.6 ± 37.7	141.7 ± 39.5	156.7 ± 39.3	145.7 ± 38.5
	% Change[b]	−5.2 ± 16.4	5.9 ± 19.8	−1.1 ± 22.6	−0.8 ± 24.8	0.2 ± 29.7	1.4 ± 26.3
TC	Week 0[a]	224.9 ± 30.5	221.8 ± 36.7	216.8 ± 38.8	224.1 ± 39.6	239.4 ± 38.6	231.6 ± 41.9
	% Change [b]	0.1 ± 9.8	−2.7 ± 11.4	−6.5 ± 11.9	−7.0 ± 11.3	−5.3 ± 12.9	−6.0 ± 11.8
HDL-C (direct method)	Week 0[a]	40.3 ± 6.3	40.4 ± 8.0	40.8 ± 6.9	40.9 ± 7.3	41.4 ± 7.1	40.1 ± 7.3
	% Change [b]	−2.0 ± 13.5	12.0 ± 14.3	16.4 ± 16.9	16.1 ± 16.7	20.5 ± 22.5	14.6 ± 16.3
non-HDL-C	Week 0[a]	184.6 ± 29.7	181.4 ± 36.0	175.9 ± 36.8	183.3 ± 36.4	198.0 ± 38.0	191.5 ± 39.1
	% Change [b]	0.7 ± 12.8	−5.8 ± 12.4	−11.8 ± 14.0	−12.2 ± 13.8	−10.5 ± 14.2	−10.1 ± 14.2

Mean ± SD
[a] mg/dL
[b] %

Safety data were analyzed. Adverse events occurred in 47.2% (17 of 36) of subjects in the placebo group, 56.8% (21 of 37) of subjects in the pemafibrate 0.05 mg group, 32.4% (12 of 37) of subjects in the pemafibrate 0.1 mg group, 47.4% (18 of 38) of subjects in the pemafibrate 0.2 mg group, 41.0% (16 of

39) of subjects in the pemafibrate 0.4 mg group, and 56.8% (21 of 37) of subjects in the FF group. Adverse events reported by ≥3 subjects in any group are shown in Table 19.

Table 19. Adverse events reported by ≥3 subjects in any group (safety analysis set)

	Placebo (N = 36)	Pemafibrate				FF (N = 37)
		0.05 mg (N = 37)	0.1 mg (N = 37)	0.2 mg (N = 38)	0.4 mg (N = 39)	
Upper respiratory tract inflammation	8.3 (3)	5.4 (2)	2.7 (1)	5.3 (2)	5.1 (2)	5.4 (2)
Seasonal allergy	5.6 (2)	5.4 (2)	10.8 (4)	7.9 (3)	7.7 (3)	5.4 (2)
Seasonal rhinitis	2.8 (1)	2.7 (1)	2.7 (1)	2.6 (1)	0 (0)	8.1 (3)
Nasopharyngitis	0 (0)	5.4 (2)	8.1 (3)	10.5 (4)	5.1 (2)	13.5 (5)

% (n)

Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 8.3% (3 of 36) of subjects in the placebo group, 5.4% (2 of 37) of subjects in the pemafibrate 0.05 mg group, 2.7% (1 of 37) of subjects in the pemafibrate 0.1 mg group, 5.3% (2 of 38) of subjects in the pemafibrate 0.2 mg group, 5.1% (2 of 39) of subjects in the pemafibrate 0.4 mg group, and 10.8% (4 of 37) of subjects in the FF group. Adverse events reported by ≥3% of subjects in any group were constipation (5.6% [2 of 36] of subjects in the placebo group, 0% of subjects in all of the pemafibrate 0.05 mg group, pemafibrate 0.1 mg group, pemafibrate 0.2 mg group, pemafibrate 0.4 mg group, and FF group).

No deaths occurred. Other serious adverse events were reported by 1 subject in the pemafibrate 0.05 mg group (appendicitis) and 1 subject in the pemafibrate 0.4 mg group (ureterolithiasis). A causal relationship between study drug and ureterolithiasis reported in the pemafibrate 0.4 mg group could not be ruled out.

Adverse events leading to discontinuation of the study drug were reported by 1 subject in the FF group (hepatic function abnormal).

7.3 Phase III studies

7.3.1 Confirmatory study comparing pemafibrate with FF (Study K-877-09, CTD 5.3.5.1-2, [May 2012 to December 2012])

A randomized, double-blind, FF-controlled, parallel-group study was conducted at 32 sites in Japan to investigate the efficacy and safety of pemafibrate in Japanese patients with dyslipidemia characterized by high TG and low HDL-C levels (target sample size, a total of 480 subjects [40 in the placebo group, 40 in the pemafibrate 0.1 mg group, 120 in the pemafibrate 0.2 mg group, 80 in the pemafibrate 0.4 mg group, 80 in the FF 100 mg (pulverized capsule formulation) group, 120 in the FF 200 mg group]).

Subjects were to orally receive placebo, or pemafibrate 0.05, 0.1, or 0.2 mg twice daily after breakfast and supper (daily dose of 0.1, 0.2, or 0.4 mg; hereinafter expressed as a daily dose), or FF 100 or 200 mg once daily after breakfast during the 12-week treatment period after a screening period of ≤8 weeks.

The concomitant use of other therapeutic drugs for dyslipidemia including statins, anion exchange resin, probucol, fibrates, nicotinate derivatives, phytosterol (unsaponifiable matter of soybean oil, gamma-oryzanol), and other medications (elastase, dextran sulfate sodium sulfur, ethyl icosapentate, pantothenic acid, polyenephosphatidylcholine, ezetimibe) was prohibited during the study period.

This study included patients with dyslipidemia aged ≥20 and <75 years who met the following key eligibility criteria:

- TG ≥200 mg/dL on 2 consecutive measurements at screening
- TG ≤1000 mg/dL at screening
- HDL-C <50 mg/dL for males or <55 mg/dL for females on 2 consecutive measurements at screening

All of the 526 randomized subjects (43 in the placebo group, 45 in the pemafibrate 0.1 mg group, 128 in the pemafibrate 0.2 mg group, 85 in the pemafibrate 0.4 mg group, 85 in the FF 100 mg group, and

140 in the FF 200 mg group) received the study drug and were included in the safety analysis set. Of these, 525 subjects (43 subjects, 45 subjects, 128 subjects, 84 subjects, 85 subjects, and 140 subjects) were included in the FAS, and the remaining 1 subject (pemafibrate 0.4 mg group) was excluded from the analysis because the subject's post-treatment efficacy data were not available due to death. The FAS was used as the primary efficacy analysis population. Study treatment was discontinued in 37 subjects (0 subjects, 3 subjects, 7 subjects, 5 subjects, 7 subjects, and 15 subjects) and the main reason for discontinuation was adverse events (22 subjects [0 subjects, 2 subjects, 2 subjects, 1 subject, 3 subjects, and 14 subjects]).

The primary efficacy endpoint was percentage changes in TG from baseline to Weeks 8, 10, or 12. Baseline TG was defined as the mean of values measured at 2 screening examinations and at Week 0. The results of the primary endpoint were initially evaluated for a dose-response trend. If a significant dose-response relationship was observed, then the superiority of pemafibrate 0.1 mg, 0.2 mg, and 0.4 mg to placebo was to be evaluated. If the superiority of pemafibrate to placebo was observed, then the non-inferiority of pemafibrate 0.4 mg to FF 200 mg was to be evaluated. If the non-inferiority of pemafibrate 0.4 mg to FF 200 mg was then presented, then the non-inferiority of pemafibrate 0.2 mg to FF 200 mg was to be evaluated.

TG at baseline and at Weeks 8, 10, and 12 in each group are shown in Table 20.

Table 20. TG at baseline and at Weeks 8, 10, and 12 (FAS)

	Placebo	Pemafibrate			FF	
		0.1 mg	0.2 mg	0.4 mg	100 mg	200 mg
Baseline	346.1 ± 130.9 (43)	332.4 ± 106.1 (45)	367.2 ± 153.6 (128)	362.6 ± 158.5 (84)	362.0 ± 135.1 (85)	347.3 ± 123.8 (140)
Week 8	321.4 ± 143.2 (43)	177.2 ± 72.4 (43)	175.8 ± 73.4 (124)	166.0 ± 84.4 (83)	205.7 ± 89.9 (81)	173.7 ± 109.0 (136)
Week 10	331.1 ± 164.3 (43)	176.5 ± 76.8 (42)	188.4 ± 124.7 (122)	163.0 ± 70.5 (81)	218.7 ± 106.1 (81)	155.3 ± 72.9 (130)
Week 12	360.9 ± 270.5 (43)	162.6 ± 72.8 (42)	179.2 ± 84.4 (121)	161.8 ± 75.1 (80)	217.2 ± 97.7 (79)	156.3 ± 77.3 (128)

mg/dL
Mean ± SD (n)

Percentage changes in TG from baseline to Weeks 8, 10, or 12 (least-squares mean ± standard error [SE], repeated measures analysis of covariance [ANCOVA] using treatment group as a factor, baseline TG as a covariate, and Weeks 8, 10, and 12 as repeated time point) in the placebo group, the pemafibrate 0.1 mg group, the pemafibrate 0.2 mg group, and the pemafibrate 0.4 mg group were –2.775 ± 4.463, 46.342 ± 2.763, –46.766 ± 1.634, and –51.902 ± 2.000, respectively, presenting a significant dose-response relationship (adjusted $P < 0.001$, maximum contrast method using contrasts of [–3, –1, 1, 3], [–5, –1, 3, 3], and [–3, 1, 1, 1] for the placebo group, the pemafibrate 0.1 mg group, the pemafibrate 0.2 mg group, and the pemafibrate 0.4 mg group). Selected contrast was (–5, –1, 3, 3).

Because a significant dose-response relationship was observed, the percentage change in TG from baseline in each pemafibrate group was then compared with that in the placebo group. Differences between each pemafibrate group and the placebo group (differences in least-squares mean [95% CI]) were –43.567 [–54.011, –33.124], –43.991 [–53.524, –34.458], and −49.127 [–58.912, –39.343] for the pemafibrate 0.1 mg group, pemafibrate 0.2 mg group, and pemafibrate 0.4 mg group, respectively, showing the superiority of pemafibrate 0.1 mg, pemafibrate 0.2 mg, and pemafibrate 0.4 mg to placebo ($P < 0.001$ for all comparisons, Dunnett test).

Because the superiority of each pemafibrate dose to placebo was demonstrated, the percentage change in TG from baseline in the pemafibrate 0.4 mg group was then compared with that in the FF 200 mg group. Percentage changes in TG from baseline were –51.836 ± 2.001 in the pemafibrate 0.4 mg group (least-squares mean ± SE, repeated measures ANCOVA using treatment group as a factor, baseline TG as a covariate, and Weeks 8, 10, and 12 as repeated time points) and –51.534 ± 1.568 in the FF 200 mg group. The difference [95% CI] between the pemafibrate 0.4 mg group and FF 200 mg group was –0.302 [–5.300, 4.696], and the upper bound of 95% CI was below the pre-determined non-inferiority margin (10%), showing the non-inferiority of pemafibrate 0.4 mg to FF 200 mg.

Because the non-inferiority of pemafibrate 0.4 mg to FF 200 mg was demonstrated, the percentage change in TG from baseline in the pemafibrate 0.2 mg group was compared with that in the FF 200 mg group. Percentage changes in TG from baseline were –46.690 ± 1.635 in the pemafibrate 0.2 mg group and −51.534 ± 1.568 in the FF 200 mg group. The difference [95% CI] between the pemafibrate 0.2 mg group and FF 200 mg group was 4.844 [0.388, 9.299], and the upper bound of 95% CI was below the pre-determined non-inferiority margin (10%), showing the non-inferiority of pemafibrate 0.2 mg to FF 200 mg.

In addition, changes in lipid parameters over time (the secondary efficacy endpoint) are shown in Table 21.

Table 21. Lipid parameters at baseline and at Weeks 4, 8, and 12 (FAS)

		Placebo	Pemafibrate			FF	
			0.1 mg	0.2 mg	0.4 mg	100 mg	200 mg
LDL-C (direct method)	Baseline	133.8 ± 33.9 (43)	128.5 ± 36.9 (45)	131.4 ± 35.5 (128)	125.9 ± 33.5 (84)	133.8 ± 35.9 (85)	133.8 ± 36.1 (140)
	Week 4	130.2 ± 32.0 (43)	138.9 ± 32.0 (44)	143.2 ± 33.0 (127)	139.5 ± 29.6 (83)	142.2 ± 34.1 (83)	136.5 ± 30.5 (139)
	Week 8	137.8 ± 32.3 (43)	139.8 ± 32.2 (43)	147.8 ± 35.7 (124)	141.7 ± 30.6 (83)	148.2 ± 32.6 (81)	135.8 ± 30.9 (136)
	Week 12	131.8 ± 33.3 (43)	139.1 ± 30.7 (42)	149.1 ± 33.3 (122)	144.8 ± 32.2 (80)	148.8 ± 32.5 (79)	137.0 ± 32.3 (128)
TC	Baseline	222.4 ± 33.1 (43)	214.9 ± 36.8 (45)	224.6 ± 36.2 (128)	216.2 ± 36.6 (84)	225.3 ± 34.4 (85)	224.2 ± 35.4 (140)
	Week 4	218.4 ± 32.3 (43)	210.7 ± 34.9 (44)	218.8 ± 37.4 (127)	210.3 ± 31.8 (83)	220.9 ± 35.5 (83)	209.2 ± 33.7 (139)
	Week 8	223.2 ± 35.4 (43)	212.6 ± 34.0 (43)	221.9 ± 40.3 (124)	212.6 ± 32.6 (83)	224.1 ± 35.1 (81)	211.1 ± 34.0 (136)
	Week 12	220.9 ± 30.1 (43)	210.9 ± 33.3 (42)	224.4 ± 37.4 (122)	216.5 ± 35.6 (80)	226.6 ± 35.7 (79)	211.9 ± 35.2 (128)
HDL-C (direct method)	Baseline	39.2 ± 4.9 (43)	38.4 ± 5.4 (45)	39.4 ± 5.8 (128)	37.8 ± 5.5 (84)	39.7 ± 5.6 (85)	39.7 ± 5.3 (140)
	Week 4	39.1 ± 6.0 (43)	46.3 ± 7.7 (44)	46.4 ± 9.3 (127)	46.1 ± 8.9 (83)	45.4 ± 8.3 (83)	48.6 ± 9.2 (139)
	Week 8	39.9 ± 5.7 (43)	46.3 ± 7.9 (43)	48.2 ± 8.9 (124)	46.9 ± 9.5 (83)	47.0 ± 9.8 (81)	50.5 ± 10.4 (136)
	Week 12	39.9 ± 5.7 (43)	48.6 ± 9.0 (42)	49.6 ± 9.4 (122)	47.0 ± 9.7 (80)	47.0 ± 9.4 (79)	52.0 ± 10.2 (128)
Non-HDL-C	Baseline	183.2 ± 32.0 (43)	176.5 ± 34.9 (45)	185.2 ± 34.7 (128)	178.4 ± 34.8 (84)	185.6 ± 31.7 (85)	184.6 ± 33.9 (140)
	Week 4	179.3 ± 32.0 (43)	164.5 ± 33.7 (44)	172.4 ± 37.6 (127)	164.2 ± 31.7 (83)	175.5 ± 33.6 (83)	160.6 ± 33.3 (139)
	Week 8	183.3 ± 35.3 (43)	166.3 ± 33.0 (43)	173.7 ± 39.7 (124)	165.7 ± 32.5 (83)	177.1 ± 32.6 (81)	160.6 ± 34.2 (136)
	Week 12	181.0 ± 29.8 (43)	162.3 ± 33.3 (42)	174.8 ± 38.1 (122)	169.4 ± 35.7 (80)	179.6 ± 33.8 (79)	159.9 ± 35.2 (128)

mg/dL
Mean ± SD (n)

Safety data were analyzed. Adverse events occurred in 41.9% (18 of 43) of subjects in the placebo group, 33.3% (15 of 45) of subjects in the pemafibrate 0.1 mg group, 38.3% (49 of 128) of subjects in the pemafibrate 0.2 mg group, 40.0% (34 of 85) of subjects in the pemafibrate 0.4 mg group, 42.4% (36 of 85) of subjects in the FF 100 mg group, and 56.4% (79 of 140) of subjects in the FF 200 mg group. Adverse events reported by ≥5% of subjects in any group are shown in Table 22.

Table 22. Adverse events reported by ≥5% of subjects in any group (safety analysis set)

	Placebo (N = 43)	Pemafibrate			FF	
		0.1 mg (N = 45)	0.2 mg (N = 128)	0.4 mg (N = 85)	100 mg (N = 85)	200 mg (N = 140)
Nasopharyngitis	9.3 (4)	2.2 (1)	9.4 (12)	5.9 (5)	8.2 (7)	10.7 (15)
Blood creatine phosphokinase increased	7.0 (3)	2.2 (1)	0.8 (1)	1.2 (1)	2.4 (2)	2.1 (3)
Liver function test abnormal	2.3 (1)	4.4 (2)	1.6 (2)	4.7 (4)	12.9 (11)	15.7 (22)

% (n)

Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 7.0% (3 of 43) of subjects in the placebo group, 4.4% (2 of 45) of subjects in the pemafibrate 0.1 mg group, 7.8% (10 of 128) of subjects in the pemafibrate 0.2 mg group, 11.8% (10 of 85) of subjects in the pemafibrate 0.4 mg group, 14.1% (12 of 85) of subjects in the FF 100 mg group, and in 26.4% (37 of 140) of subjects in the FF 200 mg group. Adverse events reported by ≥3% of subjects in any group were liver function test abnormal (2.3% [1 of 43] of subjects in the placebo group, 0% [0 of 45] of subjects in the pemafibrate 0.1 mg group, 1.6% [2 of 128] of subjects in the pemafibrate 0.2 mg group, 3.5% [3 of 85] of subjects in the pemafibrate 0.4 mg group, 8.2% [7 of 85] of subjects in the FF 100 mg group, and 12.9% [18 of 140] of subjects in the FF 200 mg group).

Adverse events leading to deaths were observed in 1 subject in the pemafibrate 0.4 mg group (pulmonary embolism), but its causal relationship to the study drug was ruled out. Other serious adverse events were reported by 1 subject in the pemafibrate 0.1 mg group (acute myocardial infarction), 2 subjects in the pemafibrate 0.2 mg group (lung neoplasm malignant, enterocolitis), and 3 subjects in the FF 200 mg group (gastrooesophageal reflux disease, adjustment disorder, humerus fracture), but these adverse events were considered unrelated to the study drug.

Adverse events leading to discontinuation of the study drug were reported by 2 subjects in the pemafibrate 0.1 mg group (acute myocardial infarction, dyspepsia), 2 subjects in the pemafibrate 0.2 mg group (lung neoplasm malignant, ALT increased), 1 subject in the pemafibrate 0.4 mg group (pulmonary embolism), 3 subjects in the FF 100 mg group (liver function test abnormal in 2 subjects, hepatic function abnormal), and 14 subjects in the FF 200 mg group (liver function test abnormal in 8 subjects, hepatic function abnormal in 3 subjects, humerus fracture, eczema, rash).

7.3.2 Pitavastatin combination therapy study (Study K-877-13, CTD 5.3.5.1-3, [May 2012 to October 2013])

A randomized, double-blind, parallel-group study was conducted at 26 sites in Japan to investigate the efficacy and safety of pemafibrate in combination with pitavastatin in Japanese patients with dyslipidemia characterized by high TG and high non-HDL-C levels (target sample size, a total of 168 subjects [42 per group]).

Subjects received pitavastatin 2 mg once daily after supper during the run-in and screening periods of ≤16 weeks, and then placebo or pemafibrate 0.05, 0.1, or 0.2 mg twice daily after breakfast and supper (daily dose of 0.1, 0.2, or 0.4 mg, hereinafter expressed as a daily dose) during the 12-week treatment period. The regimen of pitavastatin remained the same as that during the screening period.

This study included patients with dyslipidemia aged ≥20 years <75 years who met the following key eligibility criteria:

- TG ≥200 mg/dL and ≤1000 mg/dL on 2 consecutive measurements at screening
- Non-HDL-C ≥150 mg/dL at screening

All of the 188 randomized subjects (46 in the placebo group, 45 in the pemafibrate 0.1 mg group, 49 in the pemafibrate 0.2 mg group, 48 in the pemafibrate 0.4 mg group) received the study drug and were included in the safety analysis set and FAS. Of these, 170 subjects (41 subjects, 42 subjects, 45 subjects, 42 subjects) were included in the PPS and the primary efficacy analysis population, and the remaining 18 subjects were excluded from the analyses: 5 subjects who did not meet the inclusion criteria or met the exclusion criteria (2 subjects, 1 subject, 1 subject, 1 subject), 3 subjects who were unevaluable and withdrawn from the study (0 subjects, 1 subject, 2 subjects, 0 subjects), 3 subjects who changed restricted concomitant drugs (0 subject, 1 subject, 1 subject, 1 subject), 2 subjects who used prohibited concomitant medications (1 subject, 0 subject, 0 subject, 1 subject), 2 subjects with missing data of TG at Week 12 (0 subjects, 0 subjects, 0 subjects, 2 subjects), 2 subjects who had a change in the state of compliance with the diet/exercise advice (2 subjects, 0 subjects, 0 subjects, 0 subjects), and 1 subject with poor compliance (0 subject, 0 subject, 0 subject, 1 subject). Study treatment was discontinued in 5 subjects (1 subject, 2 subjects, 2 subjects, 0 subjects) mainly due to the judgment of the investigator or subinvestigator (cough, blood potassium increased, and LDL-C increased in 1 subject each).

The primary efficacy endpoint was the percentage change in TG from baseline to Week 12, and baseline TG was defined as the mean of values measured at 2 screening examinations and at Week 0. The results of the primary endpoint were initially evaluated for a dose-response trend. If a significant dose-response relationship was observed, the superiority of pemafibrate 0.1 mg, 0.2 mg, and 0.4 mg to placebo was to be evaluated.

Percentage changes in TG from baseline to Week 12 in each group is shown in Table 23, in which a significant dose-response relationship was presented (adjusted $P < 0.001$, maximum contrast method using contrasts of [−3,−1, 1, 3], [−5,−1, 3, 3], [−3, 1, 1, 1], [−1,−1, 1, 1], and [−3,−3, 1, 5] for the placebo group, the pemafibrate 0.1 mg group, the pemafibrate 0.2 mg group, and the pemafibrate 0.4 mg group, respectively). Selected contrast was (−3, 1, 1, 1).

Table 23. Percentage change in TG from baseline to Week 12 (PPS)

	Placebo (n = 41)	Pemafibrate		
		0.1 mg (n = 42)	0.2 mg (n = 45)	0.4 mg (n = 42)
Baseline (mg/dL)[a]	382.0 ± 176.0	347.1 ± 122.9	353.3 ± 160.0	368.6 ± 116.1
Week 12 (mg/dL)[a]	339.9 ± 180.1	189.5 ± 111.3	154.5 ± 76.1	168.2 ± 89.6
% Change[b]	−6.898 ± 3.964	−46.062 ± 3.913	−53.353 ± 3.777	−52.003 ± 3.909

[a] Mean ± SD
[b] Least-squares mean ± SE (ANCOVA using treatment group as a factor and baseline TG as a covariate)

Because a significant dose-response relationship was observed, the percentage changes in TG from baseline to Week 12 in each pemafibrate group were then compared with that in the placebo group. Differences (%) between each pemafibrate group and the placebo group (differences in least-squares mean [95% CI]) were –39.164 [–50.181, –28.147], –46.455 [–57.277, –35.632], and –45.105 [–56.088, –34.121] for the pemafibrate 0.1 mg group, pemafibrate 0.2 mg group, and pemafibrate 0.4 mg group, respectively, showing the superiority of each pemafibrate dose to placebo ($P < 0.001$ for all comparisons, Dunnett test). Similar results were also obtained in the FAS.

In addition, percentage changes in lipid parameters from baseline to Week 12 (the secondary efficacy endpoint) are shown in Table 24.

Table 24. Percentage changes in lipid parameters from baseline to Week 12 (PPS)

		Placebo (n = 41)	Pemafibrate		
			0.1 mg (n = 42)	0.2 mg (n = 45)	0.4 mg (n = 42)
LDL-C (direct method)	Baseline (mg/dL)	115.7 ± 34.1	124.9 ± 20.4	121.0 ± 30.7	120.1 ± 22.2
	% Change	−2.30 ± 18.01	0.97 ± 21.55	6.60 ± 32.09	2.94 ± 25.81
TC	Baseline (mg/dL)	213.2 ± 28.9	218.6 ± 24.1	213.8 ± 25.3	214.3 ± 24.5
	% Change	−3.86 ± 11.52	−5.27 ± 13.66	−6.16 ± 12.75	−7.85 ± 13.76
HDL-C (direct method)	Baseline (mg/dL)	46.9 ± 12.0	48.3 ± 9.0	45.5 ± 10.8	44.2 ± 8.4
	% Change	2.06 ± 12.20	16.35 ± 17.42	22.71 ± 22.10	15.15 ± 22.30
Non-HDL-C	Baseline (mg/dL)	166.3 ± 24.1	170.4 ± 22.2	168.2 ± 20.3	170.0 ± 22.8
	% Change	−5.38 ± 14.53	−11.66 ± 17.82	−13.99 ± 17.62	−13.56 ± 19.26

Mean ± SD

Safety data were analyzed. Adverse events occurred in 52.2% (24 of 46) of subjects in the placebo group, 64.4% (29 of 45) of subjects in the pemafibrate 0.1 mg group, 55.1% (27 of 49) of subjects in the pemafibrate 0.2 mg group, and 58.3% (28 of 48) of subjects in the pemafibrate 0.4 mg group. Adverse events reported by ≥5% of subjects in any group are shown in Table 25.

Table 25. Adverse events reported by ≥5% of subjects in any group (safety analysis set)

	Placebo (N = 46)	Pemafibrate		
		0.1 mg (N = 45)	0.2 mg (N = 49)	0.4 mg (N = 48)
Nasopharyngitis	10.9 (5)	15.6 (7)	16.3 (8)	14.6 (7)
Seasonal allergy	6.5 (3)	6.7 (3)	2.0 (1)	6.3 (3)
Liver function test abnormal	4.3 (2)	6.7 (3)	2.0 (1)	2.1 (1)
Blood CK increased	4.3 (2)	0 (0)	2.0 (1)	6.3 (3)
Type 2 diabetes mellitus	2.2 (1)	2.2 (1)	8.2 (4)	0 (0)
Blood uric acid increased	0 (0)	2.2 (1)	6.1 (3)	4.2 (2)

% (n)

Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 8.7% (4 of 46) of subjects in the placebo group, 6.7% (3 of 45) of subjects in the pemafibrate 0.1 mg group, 10.2% (5 of 49) of subjects in the pemafibrate 0.2 mg group, and 4.2% (2 of 48) of subjects in the pemafibrate 0.4 mg group. There were no adverse events reported by ≥3% of subjects in any group.

No deaths occurred. Other serious adverse events were reported by 2 subjects in the pemafibrate 0.1 mg group (cervix carcinoma, upper limb fracture), but both events were considered unrelated to the study drug.

Adverse events leading to discontinuation of the study drug were reported by 2 subjects in the pemafibrate 0.1 mg group (cough, blood potassium increased) and 2 subjects in the pemafibrate 0.2 mg group (LDL increased, blood CK increased).

7.3.3 Confirmatory study comparing pemafibrate with FF (Study K-877-17, CTD 5.3.5.1-4, [August 2014 to May 2015])

A randomized, double-blind, FF-controlled, parallel-group study was conducted at 10 sites in Japan to investigate the efficacy and safety of pemafibrate in Japanese patients with dyslipidemia characterized by high TG and low HDL-C levels (target sample size, a total of 225 subjects [75 per group]).

Subjects were to orally receive pemafibrate 0.1 or 0.2 mg twice daily after breakfast and supper (daily dose of 0.2 or 0.4 mg; hereinafter expressed as a daily dose), or FF 106.6 mg (tablets[4)]) once daily after breakfast during the 24-week treatment period after a screening period of ≤8 weeks.

This study included patients with dyslipidemia aged ≥20 years who met the following key eligibility criteria:

- TG ≥150 mg/dL on 2 consecutive measurements at screening
- TG ≤500 mg/dL at screening
- HDL-C <50 mg/dL for males or <55 mg/dL for females on 2 consecutive measurements at screening

In addition, the use of other fibrates was prohibited, and other therapeutic drugs for dyslipidemia were allowed to be concomitantly used, but in principle, addition or discontinuation of such drugs or changes of the dosing regimen was prohibited from the start of screening examination to the end of the study.

Of 225 the randomized subjects (75 in the pemafibrate 0.2 mg group, 74 in the pemafibrate 0.4 mg group, and 76 in the FF 106.6 mg group), 224 subjects (74 subjects, 74 subjects, and 76 subjects) received the study drug, and the remaining 1 subject who withdrew the consent or requested discontinuation was excluded. Of those who received the study drug, 223 subjects (73 subjects, 74 subjects, 76 subjects) were included in the safety analysis set and FAS, and the remaining 1 subject who did not provide post-treatment data was excluded from the analyses. In addition, the FAS was used as the primary efficacy analysis population. Study treatment was discontinued in 13 subjects (5 subjects, 1 subject, 7 subjects) and reasons for discontinuation were adverse events (5 subjects [2 subjects, 1 subject, 2 subjects]),

4) FF 106.6 mg (tablets) has been shown to be bioequivalent to FF 134 mg (pulverized capsule formulation).

aggravated hepatic function (5 subjects [1 subject, 0 subjects, 4 subjects]), consent withdrawal or request for discontinuation (2 subjects [2 subjects, 0 subjects, 0 subjects]), and judgment of investigator or subinvestigator (1 subject [0 subject, 0 subject, 1 subject]).

The primary efficacy endpoint was percentage change in TG from baseline to Weeks 8, 12, 16, 20, and 24. Baseline TG was defined as the mean of values measured at 2 screening examinations and at Week 0. The results of the primary endpoint were initially evaluated for the non-inferiority of pemafibrate 0.4 mg to FF 106.6 mg. If the non-inferiority of pemafibrate 0.4 mg to FF 106.6 mg was observed, then the non-inferiority of pemafibrate 0.2 mg to FF 106.6 mg was to be evaluated.

TG levels at baseline and at Weeks 8, 12, 16, 20, and 24 in each group are shown in Table 26.

Table 26. TG levels at baseline and at Weeks 8, 12, 16, 20, and 24 (FAS)

	Pemafibrate 0.2 mg	Pemafibrate 0.4 mg	FF 106.6 mg
Baseline	242.4 ± 55.3 (73)	233.3 ± 60.8 (74)	235.6 ± 71.7 (76)
Week 8	125.8 ± 53.2 (72)	117.8 ± 45.9 (74)	140.5 ± 54.4 (76)
Week 12	128.2 ± 67.8 (71)	128.1 ± 59.3 (73)	145.0 ± 68.5 (72)
Week 16	137.0 ± 72.1 (71)	120.7 ± 49.6 (74)	137.7 ± 58.7 (71)
Week 20	121.5 ± 44.4 (70)	126.7 ± 56.2 (74)	137.0 ± 78.8 (70)
Week 24	137.4 ± 108.8 (69)	133.8 ± 84.5 (73)	133.4 ± 56.7 (68)

mg/dL
Mean ± SD (n)

Percentage changes in TG from baseline to Weeks 8, 12, 16, 20, and 24 are shown in Table 27. The difference (%) between the pemafibrate 0.4 mg group and FF 106.6 mg group (difference in least-squares mean [95% CI], repeated measures ANCOVA using treatment group as a factor, baseline TG as a covariate, and Weeks 8, 12, 16, 20, and 24 as repeated time points) was –6.166 [–11.576, –0.755], and the upper bound of 95% CI was below the pre-determined non-inferiority margin (10%), showing the non-inferiority of pemafibrate 0.4 mg to FF 106.6 mg.

Because the non-inferiority of pemafibrate 0.4 mg to FF 106.6 mg group was demonstrated, the percentage change in TG from baseline in the pemafibrate 0.2 mg group was compared with that in the FF 106.6 mg group. The difference [95% CI] between the pemafibrate 0.2 mg group and FF 106.6 mg group was –6.541 [–12.004, –1.078], and the upper bound of 95% CI was below the pre-determined non-inferiority margin (10%), showing the non-inferiority of pemafibrate 0.2 mg to FF 106.6 mg.

Table 27. Percentage change in TG from baseline to Weeks 8, 12, 16, 20, and 24 (FAS)

	Pemafibrate 0.2 mg	Pemafibrate 0.4 mg	FF 106.6 mg
% Change	−46.226 ± 1.977	−45.850 ± 1.942	−39.685 ± 1.942

Least-squares mean ± SE (repeated measures ANCOVA using treatment group as a factor, baseline TG as a covariate, and Weeks 8, 12, 16, 20, and 24 as repeated time points)

In addition, changes in lipid parameters over time (the secondary efficacy endpoint) are shown in Table 28 and Table 29.

Table 28. LDL-C at baseline and at Weeks 4, 8, 12, 16, 20, and 24 (direct method) (FAS)

	Pemafibrate 0.2 mg	Pemafibrate 0.4 mg	FF 106.6 mg
Baseline	157.8 ± 29.2 (73)	154.0 ± 27.4 (74)	152.6 ± 26.1 (76)
Week 4	145.4 ± 23.0 (73)	144.2 ± 30.6 (74)	142.8 ± 27.2 (76)
Week 8	145.4 ± 24.6 (72)	145.7 ± 32.3 (74)	139.7 ± 28.8 (76)
Week 12	146.3 ± 23.9 (71)	144.0 ± 33.4 (74)	143.6 ± 27.9 (72)
Week 16	144.4 ± 25.0 (71)	142.0 ± 33.0 (74)	138.8 ± 30.0 (71)
Week 20	145.1 ± 21.5 (70)	143.1 ± 31.5 (74)	139.0 ± 29.4 (70)
Week 24	144.6 ± 26.5 (69)	147.0 ± 32.2 (73)	141.4 ± 31.7 (68)
Week 24 (LOCF)	144.7 ± 25.8 (73)	146.7 ± 32.0 (74)	142.2 ± 31.5 (76)

mg/dL
Mean ± SD (n)

Table 29. Lipid parameters at baseline and Week 24 (LOCF) (FAS)

		Pemafibrate 0.2 mg (n = 73)	Pemafibrate 0.4 mg (n = 74)	FF 106.6 mg (n = 76)
TC	Baseline	232.7 ± 30.1	228.8 ± 29.2	226.3 ± 28.9
	Week 24	218.4 ± 26.9	219.7 ± 34.3	212.1 ± 32.8
HDL-C (direct method)	Baseline	41.4 ± 5.2	42.2 ± 4.5	41.7 ± 5.2
	Week 24	50.6 ± 9.3	49.4 ± 8.6	48.8 ± 7.9
Non-HDL-C	Baseline	191.3 ± 27.1	186.6 ± 29.0	184.7 ± 27.6
	Week 24	167.7 ± 27.6	170.2 ± 36.0	163.3 ± 33.6

mg/dL
Mean ± SD

Safety data were analyzed. Adverse events occurred in 38.4% (28 of 73) of subjects in the pemafibrate 0.2 mg group, 50.0% (37 of 74) of subjects in the pemafibrate 0.4 mg group, and 59.2% (45 of 76) of subjects in the FF 106.6 mg group. Adverse events reported by ≥5% of subjects in any group are shown in Table 30.

Table 30. Adverse events reported by ≥5% of subjects in any group (safety analysis set)

	Pemafibrate 0.2 mg (N = 73)	Pemafibrate 0.4 mg (N = 74)	FF 106.6 mg (N = 76)
Nasopharyngitis	8.2 (6)	21.6 (16)	10.5 (8)
ALT increased	5.5 (4)	0 (0)	18.4 (14)
AST increased	5.5 (4)	0 (0)	17.1 (13)
Diabetes mellitus	5.5 (4)	2.7 (2)	0 (0)
γ-GTP increased	4.1 (3)	0 (0)	22.4 (17)
Myalgia	0 (0)	0 (0)	5.3 (4)
Upper respiratory tract inflammation	2.7 (2)	4.1 (3)	5.3 (4)
Liver function test abnormal	0 (0)	0 (0)	7.9 (6)

% (n)

Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 2.7% (2 of 73) of subjects in the pemafibrate 0.2 mg group, 6.8% (5 of 74) of subjects in the pemafibrate 0.4 mg group, and 23.7% (18 of 76) of subjects in the FF 106.6 mg group. Adverse events reported by ≥3% of subjects in any group were ALT increased (1.4% [1 of 73] subjects in the pemafibrate 0.2 mg group, 0% [0 of 74] subjects in the pemafibrate 0.4 mg group, 10.5% [8 of 76] subjects in the FF 106.6 mg group), AST increased (1.4% [1 of 73] subjects in the pemafibrate 0.2 mg group, 0% [0 of 74] subjects in the pemafibrate 0.4 mg group, 10.5% [8 of 76] subjects in the FF 106.6 mg group), and γ-GTP increased (1.4% [1 of 73] subjects in the pemafibrate 0.2 mg group, 0% [0 of 74] subjects in the pemafibrate 0.4 mg group, 13.2% [10 of 76] subjects in the FF 106.6 mg group).

No deaths occurred. Other serious adverse events were reported by 1 subject in the pemafibrate 0.4 mg group (hypopharyngeal cancer) and 1 subject in the FF 106.6 mg group (ankle fracture), but both events were considered unrelated to the study drug.

Adverse events leading to discontinuation of the study drug were reported by 3 subjects in the pemafibrate 0.2 mg group (arthritis; cholelithiasis; and ALT increased, AST increased, and γ-GTP increased in 1 subject each), 1 subject in the pemafibrate 0.4 mg group (hypopharyngeal cancer), 6 subjects in the FF 106.6 mg group (ALT increased, AST increased, and γ-GTP increased in 3 subjects; liver function test abnormal; abdominal discomfort, dizziness, hot flush, and diarrhoea; and hepatic dysfunction in 1 subject each).

7.3.4 Long-term treatment study in patients on statin therapy (Study K-877-15, CTD 5.3.5.1-5, [February 2013 to April 2014])

A randomized, double-blind, parallel-group study was conducted at 53 sites in Japan to investigate the efficacy and safety of pemafibrate in combination with statin in Japanese patients with hypertriglyceridemia (target sample size, a total of 400 subjects [100 in the placebo group, 150 in each pemafibrate group]).

The study drug was administered for a total of 24 weeks after a screening period of ≤8 weeks. The treatment period consisted of 2 periods of 12 weeks each: Periods 1 and 2. Subjects assigned to the placebo group and pemafibrate 0.2 mg group were to receive placebo and pemafibrate 0.2 mg (daily

dose), respectively, throughout the treatment period (Periods 1 and 2). Subjects assigned to the pemafibrate 0.2/0.4 mg (dose-increase) group were to receive pemafibrate 0.2 mg in Period 1, and then subjects with TG ≥150 mg/dL at Week 8 of Period 1 were to receive an increased dose of pemafibrate 0.4 mg in Period 2. The increased dose had to be continued in Period 2, irrespective of TG levels at the subsequent visits. The study drug was to be orally administered twice daily in the morning and evening, and the timing of administration of the study drug (before or after meals) was to be kept unchanged throughout the study period.

This study included patients with dyslipidemia aged ≥20 years who met the following key eligibility criteria:

- TG ≥200 mg/dL on 2 consecutive measurements at screening
- TG ≤1000 mg/dL at screening

All of the 423 randomized subjects (108 in the placebo group, 150 in the pemafibrate 0.2 mg group, 165 in the pemafibrate 0.2/0.4 mg group) received the study drug and were included in the safety analysis set and FAS. In addition, the FAS was used as the primary efficacy analysis population. Study treatment was discontinued in 28 subjects (5 subjects, 10 subjects, 13 subjects) mainly due to adverse events (17 subjects [2 subjects, 6 subjects, 9 subjects]).

Percentage changes in TG from baseline to end of treatment (EOT), the primary efficacy endpoint, are shown in Table 31. Baseline TG was defined as the mean of values measured at 2 screening examinations and at Week 0.

Table 31. Percentage change in TG from baseline to EOT (FAS)

	Placebo (n = 108)	Pemafibrate 0.2 mg (n = 150)	Pemafibrate 0.2/0.4 mg (n = 165)
Baseline (mg/dL)[a]	329.0 ± 135.0	333.3 ± 132.2	324.5 ± 133.4
EOT (LOCF) (mg/dL)[a]	307.7 ± 154.1	176.6 ± 124.9	156.8 ± 108.5
% Change[b]	−0.841 ± 3.037	−46.821 ± 2.577	−50.848 ± 2.457
Difference from the placebo	-	−45.981 [−53.810, −38.151]	−50.007 [−57.686, −42.328]

[a] Mean ± SD
[b] Least-squares mean ± SE (ANCOVA using treatment group as a factor and baseline TG as a covariate)

In addition, changes in lipid parameters over time (the secondary efficacy endpoint) are shown in Table 32.

Table 32. Lipid parameters at baseline and EOT (LOCF) (FAS)

		Placebo (n = 108)	Pemafibrate 0.2 mg (n = 150)	Pemafibrate 0.2/0.4mg (n = 165)
LDL-C (direct method)	Baseline	108.7 ± 28.9	108.2 ± 29.1	106.9 ± 30.7
	EOT	111.2 ± 30.8	113.6 ± 30.6	114.0 ± 31.1
TC	Baseline	196.9 ± 30.3	199.7 ± 29.8	195.8 ± 32.0
	EOT	197.3 ± 34.2	194.1 ± 32.0	189.7 ± 34.2
HDL-C (direct method)	Baseline	45.1 ± 10.1	46.6 ± 9.7	44.9 ± 10.2
	EOT	46.8 ± 10.2	54.8 ± 14.2	52.0 ± 12.4
Non-HDL-C	Baseline	151.8 ± 27.3	153.1 ± 28.9	150.9 ± 29.7
	EOT	150.5 ± 33.3	139.3 ± 33.7	137.7 ± 35.1

mg/dL
Mean ± SD

Safety data were analyzed. Adverse events occurred in 57.4% (62 of 108) of subjects in the placebo group, 56.0% (84 of 150) of subjects in the pemafibrate 0.2 mg group, and 63.6% (105 of 165) of subjects in the pemafibrate 0.2/0.4 mg group. Adverse events reported by ≥5% of subjects in any group were nasopharyngitis (22.2% [24 of 108] subjects in the placebo group, 12.7% [19 of 150] subjects in the pemafibrate 0.2 mg group, 17.0% [28 of 165] subjects in the pemafibrate 0.2/0.4 mg group) and diabetes mellitus (3.7% [4 of 108] subjects in the placebo group, 3.3% [5 of 150] subjects in the pemafibrate 0.2 mg group, 7.9% [13 of 165] subjects in the pemafibrate 0.2/0.4 mg group).

Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 15.7% (17 of 108) of subjects in the placebo group, 19.3% (29 of 150) of subjects in the pemafibrate 0.2 mg group, and 19.4% (32 of 165) of subjects in the pemafibrate 0.2/0.4 mg group. Of these, adverse events reported by ≥3% of subjects in any group were diabetes mellitus (0.9% [1 of 108 subjects] in the placebo group, 2.0% [3 of 150 subjects] in the pemafibrate 0.2 mg group, 4.8% [8 of 165 subjects] in the pemafibrate 0.2/0.4 mg group).

No deaths occurred. Other serious adverse events were reported by 2 subjects in the placebo group (embolic stroke and cataract in 1 subject each), 6 subjects in the pemafibrate 0.2 mg group (angina pectoris, abdominal wall haematoma, colon cancer, ankle fracture, gallbladder cancer, and lumbar spinal stenosis in 1 subject each), 5 subjects in the pemafibrate 0.2/0.4 mg group (large intestine polyp, diabetes mellitus, bile duct cancer, cerebral infarction, enterocolitis). Except for embolic stroke in the placebo group, abdominal wall haematoma in the pemafibrate 0.2 mg group, and diabetes mellitus in the pemafibrate 0.2/0.4 mg group, all the above events were considered unrelated to the study drug.

Adverse events leading to discontinuation of the study drug were reported by 2 subjects in the placebo group (embolic stroke and rash in 1 subject each), 6 subjects in the pemafibrate 0.2 mg group (abdominal wall haematoma; dizziness and hypertension; malaise; cholelithiasis; eczema; and ankle fracture in 1 subject each), and 9 subjects in the pemafibrate 0.2/0.4 mg group (diabetes mellitus in 2 subjects; rash, urticaria, malaise, blood CK increased and myoglobin blood increased, bile duct cancer, bronchitis chronic, and blood fibrinogen decreased in 1 subject each).

7.3.5 Long-term treatment study in patients with dyslipidemia and comorbid type 2 diabetes mellitus (Study K-877-16, CTD 5.3.5.1-6-1, 5.3.5.1-6-2, [February 2014 to December 2015])

A randomized, double-blind, parallel-group study was conducted at 34 sites in Japan to investigate the efficacy and safety of pemafibrate in Japanese patients with hypertriglyceridemia and comorbid type 2 diabetes mellitus (target sample size, a total of 165 subjects [55 per group]).

The study drug was administered for a total of 52 weeks after a screening period of ≤8 weeks. The entire treatment period consisted of 24 weeks of treatment (Period 1) followed by 28 weeks of treatment (Period 2). During Period 1, subjects were to orally receive placebo or pemafibrate 0.1 or 0.2 mg twice daily in the morning and evening (daily dose of 0.2 or 0.4 mg; hereinafter expressed as a daily dose). During Period 2, subjects assigned to receive pemafibrate 0.2 or 0.4 mg/day in Period 1 were to receive pemafibrate at the same dose as that in Period 1, and subjects assigned to the placebo group in Period 1 were to receive pemafibrate 0.2 mg/day instead of placebo. The timing of administration of the study drug (before or after meals) was to be kept unchanged throughout the study period.

This study included patients with dyslipidemia and comorbid type 2 diabetes mellitus aged ≥20 years who met the following key eligibility criteria:

- TG ≥150 mg/dL on 2 consecutive measurements at screening
- TG ≤1000 mg/dL at screening
- Hemoglobin A1c ≥6.2% and <8.0% on 2 consecutive measurements at screening

7.3.5.1 Period 1 (until Week 24)

Of 167 randomized subjects (57 in the placebo group, 54 in the pemafibrate 0.2 mg group, 56 in the pemafibrate 0.4 mg group), 166 subjects (57 subjects, 54 subjects, 55 subjects) received the study drug and were included in the safety analysis set and FAS, and the remaining 1 subject who discontinued study participation due to adverse events before the first dose of the study drug was excluded. In addition, the FAS was used as the primary efficacy analysis population. Study treatment was discontinued in 6 subjects (2 subjects, 0, subjects 4 subjects) due to adverse events (4 subjects [0 subjects, 0 subjects, 4 subjects]) and consent withdrawal (2 subjects [2 subjects, 0 subjects, 0 subjects]).

Percentage changes in TG from baseline to end of Period 1 (Week 24 or at the time of discontinuation in Period 1) (the primary efficacy endpoint) are shown in Table 33. Baseline TG was defined as the mean of values measured at 2 screening examinations and at Week 0.

Table 33. Percentage change in TG from baseline to end of Period 1 (FAS)

	Placebo (n = 57)	Pemafibrate 0.2 mg (n = 54)	Pemafibrate 0.4 mg (n = 55)
Baseline (mg/dL)[a]	284.3 ± 117.6	240.3 ± 93.5	260.4 ± 95.9
End of Period 1 (mg/dL)[a] (LOCF)	242.0 ± 92.2	129.0 ± 71.5	135.8 ± 71.2
% Change[b]	−10.814 ± 3.605	−44.347 ± 3.701	−45.093 ± 3.641
Difference from the placebo	-	−33.534 [−43.814, −23.253]	−34.280 [−44.403, −24.156]

[a] Mean ± SD
[b] Least-squares mean ± SE (ANCOVA using treatment group as a factor and baseline TG as a covariate)

In addition, changes in lipid parameters over time (the secondary efficacy endpoint) are shown in Table 34.

Table 34. Lipid parameters at baseline and end of Period 1 (LOCF) (FAS)

		Placebo (n = 57)	Pemafibrate 0.2 mg (n = 54)	Pemafibrate 0.4 mg (n = 55)
LDL-C (direct method)	Baseline	131.2 ± 33.9	129.9 ± 32.4	124.6 ± 29.8
	End of Period 1	131.9 ± 33.5	120.9 ± 30.1	124.1 ± 34.5
TC	Baseline	218.2 ± 34.1	211.1 ± 33.7	210.6 ± 37.4
	End of Period 1	215.4 ± 34.3	197.5 ± 36.4	201.7 ± 36.1
HDL-C (direct method)	Baseline	47.1 ± 10.7	46.6 ± 10.2	50.3 ± 27.7
	End of Period 1	49.1 ± 11.7	54.5 ± 14.8	52.9 ± 16.1
Non-HDL-C	Baseline	171.1 ± 33.0	164.5 ± 32.3	160.3 ± 32.7
	End of Period 1	166.3 ± 34.8	143.0 ± 31.5	148.8 ± 37.5

mg/dL
Mean ± SD

Safety data were analyzed. Adverse events occurred in 71.9% (41 of 57) of subjects in the placebo group, 66.7% (36 of 54) of subjects in the pemafibrate 0.2 mg group, and 60.0% (33 of 55) of subjects in the pemafibrate 0.4 mg group. Of these, adverse events reported by ≥5% of subjects in any group are shown in Table 35.

Table 35. Adverse events reported by ≥5% subjects in any group (safety analysis set)

	Placebo (N = 57)	Pemafibrate 0.2 mg (N = 54)	Pemafibrate 0.4 mg (N = 55)
Nasopharyngitis	22.8 (13)	20.4 (11)	9.1 (5)
Diabetes mellitus	7.0 (4)	5.6 (3)	3.6 (2)
Diabetic retinopathy	1.8 (1)	3.7 (2)	9.1 (5)
Cystitis	5.3 (3)	1.9 (1)	0 (0)
Arthralgia	5.3 (3)	3.7 (2)	0 (0)
Upper respiratory tract inflammation	5.3 (3)	9.3 (5)	3.6 (2)

% (n)

Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 12.3% (7 of 57) of subjects in the placebo group, 11.1% (6 of 54) of subjects in the pemafibrate 0.2 mg group, and 16.4% (9 of 55) of subjects in the pemafibrate 0.4 mg group. Adverse events reported by ≥3% of subjects in any group were malaise (3.5% [2 of 57 subjects] in the placebo group, 0% [0 of 54 subjects] in the pemafibrate 0.2 mg group, 0% [0 of 55 subjects] in the pemafibrate 0.4 mg group), diabetes mellitus (0% [0 of 57 subjects], 3.7% [2 of 54 subjects], 1.8% [1 of 55 subjects]), and hyperhomocysteinaemia (0% [0 of 57 subjects], 0% [0 of 54 subjects], 3.6% [2 of 55 subjects]).

No deaths occurred. Other serious adverse events were reported by 3 subjects in the placebo group (dyspnoea exertional, angina pectoris, and prostatitis in 1 subject each), 4 subjects in the pemafibrate 0.2 mg group (appendicitis, ureterolithiasis, varicose vein operation, and bile duct stone in 1 subject each), and 2 subjects in the pemafibrate 0.4 mg group (intervertebral disc disorder, myocardial

infarction). Except for bile duct stone in the pemafibrate 0.2 mg group, all these events were considered unrelated to the study drug.

Adverse events leading to discontinuation of the study drug were reported by 4 subjects in the pemafibrate 0.4 mg group (nasopharyngitis, dizziness, acute renal failure, and hepatic function abnormal in 1 subject each).

7.3.5.2 Period 2 (until Week 52)

A total of 160 subjects (55 in the placebo/pemafibrate 0.2 mg group, 54 in the pemafibrate 0.2 mg group, 51 in the pemafibrate 0.4 mg group) completed Period 1, and all of the subjects entered into Period 2. Of these, 150 subjects (51 subjects, 49 subjects, 50 subjects) completed Period 2. Study treatment was discontinued in 10 subjects (4 subjects, 5 subjects, 1 subject) due to adverse events (7 subjects [4 subjects, 2 subjects, 1 subject]), AST >5 fold the upper limit of normal (ULN) (1 subject [0 subjects, 1 subject, 0 subjects]), and consent withdrawal (2 subjects [0 subjects, 2 subjects, 0 subjects]).

Percentage changes in TG from baseline to end of Period 2 (Week 52 or at the time of discontinuation) are shown in Table 36.

Table 36. Percentage changes in TG from baseline to end of Period 2 (FAS)

	Placebo/pemafibrate 0.2 mg (n = 57)	Pemafibrate 0.2 mg (n = 54)	Pemafibrate 0.4 mg (n = 55)
Baseline (mg/dL)[a]	284.3 ± 117.6	240.3 ± 93.5	260.4 ± 95.9
End of Period 2 (mg/dL)[a] (LOCF)	141.7 ± 74.5	130.1 ± 64.8	133.8 ± 63.3
% Change[b]	−46.835 ± 3.105	−43.629 ± 3.188	−46.552 ± 3.136

[a] Mean ± SD
[b] Least-squares mean ± SE (ANCOVA using treatment group as a factor and baseline TG as a covariate)

In addition, changes in lipid parameters over time are shown in Table 37.

Table 37. Lipid parameters at baseline and end of Period 2 (LOCF) (FAS)

		Placebo/pemafibrate 0.2 mg (n = 57)	Pemafibrate 0.2 mg (n = 54)	Pemafibrate 0.4 mg (n = 55)
LDL-C (direct method)	Baseline	131.2 ± 33.9	129.9 ± 32.4	124.6 ± 29.8
	End of Period 2	122.9 ± 37.4	120.8 ± 32.3	121.8 ± 35.5
TC	Baseline	218.2 ± 34.1	211.1 ± 33.7	210.6 ± 37.4
	End of Period 2	199.1 ± 37.3	195.4 ± 37.6	196.7 ± 38.2
HDL-C (direct method)	Baseline	47.1 ± 10.7	46.6 ± 10.2	50.3 ± 27.7
	End of Period 2	51.7 ± 12.3	51.2 ± 12.0	49.9 ± 17.7
Non-HDL-C	Baseline	171.1 ± 33.0	164.5 ± 32.3	160.3 ± 32.7
	End of Period 2	147.4 ± 39.7	144.2 ± 33.7	146.7 ± 40.2

mg/dL
Mean ± SD

Safety data were analyzed. During Period 2, adverse events occurred in 81.8% (45 of 55) of subjects in the placebo/pemafibrate 0.2 mg group, 50.0% (27 of 54) of subjects in the pemafibrate 0.2 mg group, and 51.0% (26 of 51) of subjects in the pemafibrate 0.4 mg group. Adverse events reported by ≥5% of subjects in any group are shown in Table 38.

Table 38. Adverse events reported by ≥5% of subjects in any group (safety analysis set)

	Placebo/pemafibrate 0.2 mg (N = 55)	Pemafibrate 0.2 mg (N = 54)	Pemafibrate 0.4 mg (N = 51)
Nasopharyngitis	16.4 (9)	3.7 (2)	5.9 (3)
Diabetes mellitus	10.9 (6)	1.9 (1)	7.8 (4)
Upper respiratory tract inflammation	10.9 (6)	5.6 (3)	0 (0)

% (n)

During Period 2, adverse events for which a causal relationship to the study drug could not be ruled out occurred in 21.8% (12 of 55) of subjects in the placebo/pemafibrate 0.2 mg group, 11.1% (6 of 54) of subjects in the pemafibrate 0.2 mg group, and 11.8% (6 of 51) of subjects in the pemafibrate 0.4 mg group. Adverse events reported by ≥3% of subjects in any group were diabetes mellitus (3.6% [2 of 55

subjects] in the placebo/pemafibrate 0.2 mg group, 0% [0 of 54 subjects] in the pemafibrate 0.2 mg group, 3.9% [2 of 51 subjects] in the pemafibrate 0.4 mg group) and cholelithiasis (1.8% [1 of 55 subjects], 3.7% [2 of 54 subjects], 2.0% [1 of 51 subjects]).

No deaths occurred. During Period 2, other serious adverse events were reported by 6 subjects in the placebo/pemafibrate 0.2 mg group (prostatic operation, urinary retention, and urethral stenosis; anal fistula; coronary artery stenosis; psoas abscess; gastric cancer; and angina pectoris in 1 subject each), 2 subjects in the pemafibrate 0.2 mg group (vertigo, status asthmaticus), and 2 subjects in the pemafibrate 0.4 mg group (aortic valve stenosis, bradycardia, coronary artery stenosis, and cardiac failure acute; pyelonephritis). All events were considered unrelated to the study drug.

During Period 2, adverse events leading to discontinuation of the study drug occurred in 4 subjects in the placebo/pemafibrate 0.2 mg group (urethral stenosis, eczema, psoas abscess, and angina pectoris in 1 subject each), 3 subjects in the pemafibrate 0.2 mg group (status asthmaticus, rash, and bile duct stone in 1 subject each), and 1 subject in the pemafibrate 0.4 mg group (depression).

7.3.6 Fifty-two-week long-term treatment study in patients with hypertriglyceridemia (Study K-877-14, CTD 5.3.5.2-1-1, 5.3.5.2-1-2, [May 2014 to November 2015])

An open-label, uncontrolled study was conducted at 32 sites in Japan to evaluate the long-term safety and efficacy of pemafibrate in Japanese patients with hypertriglyceridemia (target sample size, 170 subjects).

The study drug was administered for 52 weeks after a screening period of ≤8 weeks. During the treatment period, subjects were to orally receive pemafibrate 0.1 mg twice daily in the morning and evening (daily dose of 0.2 mg; hereinafter expressed as a daily dose). A dose increase to pemafibrate 0.4 mg/day was allowed in subjects with inadequate response to the initial treatment (TG ≥150 mg/dL) at Week ≥12. The timing of administration of the study drug (before or after meals) was to be kept unchanged throughout the study period.

This study included patients with dyslipidemia aged ≥20 years who met the following key eligibility criteria:

- TG ≥150 mg/dL on 2 consecutive measurements at screening
- TG <500 mg/dL at screening

Of 190 subjects enrolled in the study, 189 received the study drug and the remaining 1 subject was withdrew from the study due to adverse events before the start of treatment. Except for the subject withdrawn, the 189 subjects treated were included in the safety analysis set and FAS. In addition, the FAS was used as the primary efficacy analysis population. A total of 170 subjects completed the 52-week treatment. Study treatment was discontinued in 19 subjects due to adverse events (10 subjects), consent withdrawal (6 subjects), and judgment of investigator or subinvestigator (3 subjects).

Percentage changes in TG from baseline to Week 52 are shown in Table 39.

Table 39. Percentage change in TG from baseline to Week 52 of treatment period (FAS)

	Pemafibrate (n = 189)
Baseline (mg/dL)	249.7 ± 77.5
Week 52 (LOCF) (mg/dL)	131.3 ± 61.2
% Change	−45.93 ± 21.84

Mean ± SD

In addition, changes in other lipid parameters over time are shown in Table 40.

Table 40. Lipid parameter at baseline and Week 52 (LOCF) (FAS)

		Pemafibrate (n = 189)
LDL-C (direct method)	Baseline	119.3 ± 31.7
	Week 52	116.6 ± 29.1
TC	Baseline	201.4 ± 33.0
	Week 52	191.7 ± 31.1
HDL-C (direct method)	Baseline	45.7 ± 10.6
	Week 52	51.4 ± 13.3
non-HDL-C	Baseline	155.8 ± 30.3
	Week 52	140.2 ± 32.2

mg/dL
Mean ± SD

Safety data were analyzed. Adverse events occurred in 82.0% (155 of 189) of subjects. Of these, adverse events reported by ≥5% of subjects were nasopharyngitis (28.0% [53 of 189 subjects]) and cholelithiasis (5.8% [11 of 189 subjects]).

Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 31.7% (60 of 189) of subjects. Of these, adverse events reported by ≥3% of subjects were cholelithiasis (5.3% [10 of 189 subjects]).

An adverse events leading to deaths occurred 1 subject (acute myocardial infarction), but its causal relationship to the study drug was ruled out. Other serious adverse events were reported by 15 subjects (myocardial ischaemia and pneumonia in 2 subjects each; diabetes mellitus; gastric adenoma and adenocarcinoma gastric (2 events); spinal compression fracture, aortic aneurysm, aortic dissection, and carotid artery dissection; aortic aneurysm; adenocarcinoma gastric; inguinal hernia and cryptorchism; sepsis; shunt occlusion and shunt stenosis; malaise; cerebral infarction; and shunt stenosis, cataract, and upper respiratory tract inflammation in 1 subject each). Except for cerebral infarction, the adverse events were considered unrelated to the study drug.

Adverse events leading to discontinuation of the study drug were reported by 11 subjects (cholelithiasis in 2 subjects; aortic aneurysm, aortic dissection, and carotid artery dissection; adenocarcinoma gastric; AST increased and ALT increased; chronic kidney disease; drug eruption; LDL increased and cholelithiasis; pneumonia; diabetes mellitus; and acute myocardial infarction in 1 subject each).

7.R Outline of the review conducted by PMDA

7.R.1 Clinical positioning of pemafibrate

The applicant's explanation:

Many clinical studies indicate that high fasting serum TG level is an independent risk factor of cardiovascular diseases. The "Japan Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2012" specify management target for TG. In addition, the JAS guidelines recommend that fibrates, nicotinate derivatives, and eicosapentaenoic acid preparations should be used in patients with uncontrolled TG levels according to the risk of coronary artery diseases, though improvement of life style should be given the first priority to treat hypertriglyceridemia.

Fibrates which exhibit potent TG-lowering effects are used as the first-line drugs to treat dyslipidemia characterized by high TG level and normal LDL-C level (Type IV hyperlipidemia according to the WHO classification),. In randomized comparative studies of gemfibrozil, Helsinki Heart Study (HHS) and Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT), fibrate-monotherapy was shown to prevent cardiovascular events (*N Engl J Med.* 1987;317:1237-45, *N Engl J Med.* 1999;341:410-8). In addition, subgroup analysis (*N Engl J Med.* 2011;365:481-4) of data from Bezafibrate Infarction Prevention (BIP) Study of bezafibrate (*Circulation.* 2000;102:21-7) and Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study of FF (*Lancet.* 2005;366:1849-61) suggests that fibrate-monotherapy can reduce cardiovascular events.

Statins are recommended for the treatment of dyslipidemia characterized by high TG levels and high LDL-C levels (Type IIb hyperlipidemia according to the WHO classification) because reduction of LDL-C is given the first priority. However, not only using statins to decrease abnormal LDL-C levels but also controlling abnormal levels of other lipid parameters such as TG is important to reduce the risk of cardiovascular events (*Diav Vasc Dis Res.* 2008;5:319-35). Fibrates that can control TG, non-HDL-

C, small dense LDL-C, and HDL-C levels are therefore expected to meet the treatment needs by reducing the residual risk of cardiovascular diseases in patients on statin therapy. A subgroup analysis in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid Trial of FF (*N Engl J Med.* 2010;362:1563-74) suggests that simvastatin in combination with FF can reduce the rate of cardiovascular events compared with simvastatin alone in patients with high TG level and low HDL-C level (*N Engl J Med.* 2011;365:481-4).

Based on the above, both pemafibrate alone and co-administration of pemafibrate and statins are expected to be effective.

In addition, because there may be an increased risk of rhabdomyolysis in patients with renal impairment, co-administration of statins and fibrates is, in principle, contraindicated in Japan. However, compared with the existing fibrates, pemafibrate is expected to be safe when used concomitantly with statins [see Section "7.R.6.1 Rhabdomyolysis"]. Furthermore, the use of the existing fibrates are restricted in patients with hepatic impairment due to safety concerns, but pemafibrate is considered to be safe even in such patients [see Section "7.R.6.2 Effect on the liver"]. On the above grounds, pemafibrate can be a new therapeutic option for patients with hypertriglyceridemia.

PMDA's view on the clinical positioning of pemafibrate:
The applicant decided to develop pemafibrate because the existing fibrates were shown to reduce cardiovascular events. According to the applicant, pemafibrate mainly lowers TG levels and is positioned as a drug used in patients for whom the approved fibrates are indicated. The applicant claimed that pemafibrate is expected to reduce cardiovascular events because the clinical study data of drugs in the same class indicated that the TG-lowering effect of such drugs was related to the reduced risk of cardiovascular events. There are, however, no clinical studies of fibrates except for gemfibrozil mainly showing that the drugs could reduce cardiovascular events, and therapeutic intervention with TG-lowering drugs has not been demonstrated to reduce cardiovascular events so far. In clinical development of pemafibrate as a new therapeutic drug for hypertriglyceridemia, therefore, reduction in the risk of cardiovascular events should have been verified as the true endpoint in clinical studies of pemafibrate. In clinical practices in Japan, however, fibrates have been used in patients with hypertriglyceridemia for a long time because the drugs are expected to lower TG levels, thereby reducing cardiovascular events. Given that pemafibrate is classified as a fibrate, pemafibrate may be made available in clinical practices as one of fibrates if clinical studies demonstrate that pemafibrate has TG-lowering effect and other effects on lipid parameters and that it has the safety profile equivalent to those of the approved fibrates [for comparison of the effects of pemafibrate on lipid parameters with those of the existing fibrates, see Section "7.R.3 Effects on lipid parameters other than TG"]. In addition, the safety of pemafibrate in combination with statins, effect on the liver, and safety in patients with renal impairment in comparison with the existing fibrates are discussed in Section "7.R.6 Safety."

7.R.2 Efficacy

7.R.2.1 Appropriateness of control drug and primary endpoint

The applicant's explanation about the appropriateness of design of the phase III study, in which FF was selected as the comparator and percentage change in fasting serum TG levels was chosen as the primary endpoint:
In Japan, 4 fibrates (FF, bezafibrate, clinofibrate, and clofibrate) are approved for the treatment of "hyperlipidemia" or "hyperlipemia." Of the 4 drugs, FF was considered to serve as the comparator in clinical studies to evaluate the clinical positioning of pemafibrate, because (1) FF has been widely prescribed in and outside Japan and (2) the effect of FF on cardiovascular events was evaluated in clinical studies, such as FIELD study and ACCORD Lipid Trial. In addition, pemafibrate would be positioned similarly to the existing fibrates, which are recommended as drugs lowering serum TG levels by both Japanese and foreign guidelines. Therefore, percentage change in fasting serum TG at the end of treatment was selected as the primary endpoint.

PMDA's view:
Phase III studies were designed to compare pemafibrate with other fibrates, and FF was then selected based on its use in clinical settings. The choice of the comparator is appropriate, because clinical development of pemafibrate was intended to demonstrate that it is a drug positioned similarly to the approved fibrates. In addition, taking into account that fibrates are recommended as TG-lowering drugs

by the JAS's "Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2012," it is acceptable to evaluate the efficacy of pemafibrate based on results from phase III studies in which percentage change in fasting serum TG was selected as the primary endpoint.

7.R.2.2 TG-lowering effect

The applicant's explanation about the TG-lowering effect of pemafibrate:
All of the studies evaluating pemafibrate monotherapy (Studies K-877-04, K-877-09, and K-877-17), combination therapy with pemafibrate and statins (Studies K-877-13, K-877-15, and K-877-201), and long-term treatment with pemafibrate (Studies K-877-14 and K-877-16) showed that pemafibrate reduced fasting serum TG levels. In these studies, the maximal TG-lowering effect of pemafibrate was seen at 0.2 to 0.4 mg (daily dose). In addition, Study K-877-09 demonstrated the non-inferiority of pemafibrate 0.2 and 0.4 mg to FF 200 mg (pulverized capsule formulation) in terms of percentage reduction in fasting serum TG. Study K-877-17 also demonstrated the non-inferiority of pemafibrate 0.2 and 0.4 mg to FF 106.6 mg (tablets) in terms of percentage reduction in fasting serum TG. The above findings have demonstrated that pemafibrate has TG-lowering effect equivalent to those of the existing fibrates.

PMDA's view:
The clinical study data submitted have demonstrated that the TG-lowering effect of pemafibrate is not inferior to that of FF. As described in Section "7.R.1 Clinical positioning of pemafibrate," however, pemafibrate has not yet sufficiently been evaluated for treatment of dyslipidemia, despite its TG-lowering effect demonstrated. The applicant should therefore evaluate the effects of pemafibrate on lipid parameters other than TG in comparison with FF to demonstrate that pemafibrate has equivalent effects on lipid parameters to those of the existing fibrates. Effects on lipid parameters other than TG are discussed in the subsequent sections.

7.R.3 Effects on lipid parameters other than TG

7.R.3.1 Effect on LDL-C

In Study K-877-09, LDL-C was elevated in all treatment groups at Week 12; percentage change in LDL-C from baseline to Week 12 (LOCF) (mean ± SD) was 18.6% ± 34.1% in the pemafibrate 0.2 mg (daily dose) group, 19.3% ± 30.9% in the pemafibrate 0.4 mg group, 14.0% ± 24.1% in the FF 100 mg (pulverized capsule formulation) group, and 6.6% ± 28.2% in the FF 200 mg (pulverized capsule formulation) group. The degrees of elevation in both pemafibrate 0.2 mg and 0.4 mg groups were greater than those in the FF groups [for measured LDL-C levels, see Table 21 in Section "7.3.1 Confirmatory study comparing pemafibrate with FF"]. In Study K-877-17 additionally conducted in response to the above results, however, decreases from baseline in LDL-C were observed in all of the pemafibrate 0.2 mg and 0.4 mg groups and FF 106.6 mg (tablets) group.

In consideration of the above results, PMDA asked the applicant to explain the effect of pemafibrate on LDL-C.

The applicant's explanation:
In Study K-877-09, LDL-C was elevated in many subjects treated with pemafibrate or FF, but none of these elevations were classified as adverse events. None of the subjects discontinued the study drug due to the elevated LDL-C. The characteristics of subjects showing markedly elevated LDL-C in this study were investigated in terms of sex, age, BMI, smoking, as well as the baseline levels of TG, non-HDL-C, TC, LDL-C, HDL-C, VLDL-C, ApoAI, ApoAII, ApoB, ApoB48, ApoCIII, and ApoE. As a result, baseline TG, VLDL-C, ApoB48, ApoCIII, and ApoE levels in these subjects tended to be higher than those in other subjects, while LDL-C and HDL-C levels tended to be lower. All the patients participating in this study were divided into 4 subgroups according to quartiles of baseline TG and LDL-C levels to perform subgroup analysis. The percentage of patients with LDL-C ≤107.3 mg/dL (first quartile) in the FF group was smaller than those in the pemafibrate group (27.3% [35 of 128] of subjects in the pemafibrate 0.2 mg group, 31.0% [26 of 84] of subjects in the pemafibrate 0.4 mg group, 20.0% [17 of 85] of subjects in the FF 100 mg group, 22.9% [32 of 140] of subjects in the FF 200 mg group). The percentage of the subjects with TG >411.5 mg/dL (third quartile) in the FF 200 mg group was smaller than those in the pemafibrate 0.2 and 0.4 mg groups (25.8% [33 of 128] of subjects in the pemafibrate 0.2 mg group, 26.2% [22 of 84] of subjects in the pemafibrate 0.4 mg group, 22.1% [31 of 140] of

subjects in the FF 200 mg group). The percentages of subjects with "baseline fasting serum TG ≥400 mg/dL or baseline LDL-C <100 mg/dL" in Studies K-877-09 and K-877-17 were calculated based on the cut-off values for this analysis. The percentages of such subjects in Studies K-877-09 and K-877-17 were 34.3% (180 of 525 subjects) and 2.2% (5 of 223 subjects), respectively. These biases of baseline TG and LDL-C levels may have partly contributed to the differences in the effect on LDL-C between groups or studies.

In Study K-877-09, LDL-C in the pemafibrate group tended to be elevated with time [see Table 21 in Section "7.3.1 Confirmatory study comparing pemafibrate with FF"]. PMDA therefore asked the applicant to explain a possibility of continued elevation of LDL-C in patients on long-term treatment with pemafibrate.

The applicant's explanation:
In the long-term treatment study (Study K-877-14), percentage change (mean ± SD) in LDL-C from baseline was 3.4 ± 28.9 at Week 4, 4.0 ± 28.4 at Week 8, and 7.5 ± 31.3 at Week 12, showing a time course similar to that in Study K-877-09. However, it declined to 5.7 ± 32.8 at Week 24 and 2.5 ± 31.2 at Week 52. In addition, only 2.1% (4 of 189) of treated subjects underwent a new intervention with therapeutic drugs for dyslipidemia such as statins or dose increase in response to the elevated LDL-C following administration of pemafibrate in Study K-877-14. Therefore, long-term treatment with pemafibrate does not raise clinically relevant concerns such as elevation in LDL-C.

PMDA's view:
In Study K-877-09, LDL-C was elevated at Week 12 compared with those at baseline in both pemafibrate and FF groups, and the degree of elevation in LDL-C in the pemafibrate group was greater than that in the FF group. In contrast, in Study K-877-17 additionally conducted, LDL-C was reduced at Week 24 compared with those at baseline in both pemafibrate and FF groups. As explained by the applicant, differences in the characteristics of subjects (baseline TG and LDL-C levels) between studies or groups may have partly contributed to the difference in changes in LDL-C. However, the reasons for the difference remain unclarified, because Study K-877-17 included only the small number of patients with low LDL-C and high TG levels, which may have affected the data on LDL-C, and other factors are possibly involved.

On the other hand, the difference in the percentage change in LDL-C between the pemafibrate and FF groups was not remarkable in Study K-877-09. In Study K-877-04 in which the use of other therapeutic drugs for dyslipidemia was prohibited as done in Study K-877-09, LDL-C in the pemafibrate group was reduced at Week 12, and the degree of the reduction was not greatly different from that in the FF group. In Study K-877-17, LDL-C in the pemafibrate group was reduced until Week 12, and the change was not largely different from that in the FF group. In addition, LDL-C was higher at Week 12 than at Week 8 in both pemafibrate and FF groups in Study K-877-09, but such a trend was not observed in Study K-877-04 or K-877-17. No trend toward elevation in LDL-C with time was observed in any of other long-term treatment studies.

Comprehensive evaluation of results from these studies could draw the following conclusion: the degree of elevation in LDL-C in patients receiving pemafibrate is unlikely to be clearly greater than that in patients receiving FF, and continued elevation in LDL-C is unlikely to occur in patients on long-term treatment with pemafibrate. However, since the true purpose of treatment for dyslipidemia is to reduce the risk of cardiovascular events, changes in LDL-C should be carefully monitored, and the effect of pemafibrate to reduce the risk of cardiovascular events should be investigated in the future. Then, based on the investigation results, the applicant should provide information on the risk-benefit balance of pemafibrate to healthcare professionals. As with other fibrates, patients on treatment with pemafibrate should be monitored periodically for changes in serum lipid parameters including LDL-C so that appropriate measures can be taken in each patient experiencing any change in lipid parameters. A final decision on the above evaluation of the effect of pemafibrate on LDL-C and specific post-marketing measures will be made, taking account of comments raised in the Expert Discussion.

7.R.3.2 Effects on the other lipid parameters
PMDA's view:

Percentage changes in non-HDL-C and HDL-C from baseline to the end of treatment in the pemafibrate groups were not markedly different from those in the FF groups in any of Studies K-877-04, K-877-09, and K-877-17 [see Sections "7.2.1 Dose-finding study," "7.3.1 Confirmatory study comparing pemafibrate with FF," and "7.3.3 Confirmatory study with FF"]. For this reason, pemafibrate is unlikely to raise new concerns about changes in these lipid parameters. In addition, data from Studies K-877-14 and K-877-16 showed no clear pemafibrate-related elevation in non-HDL-C and HDL-C at Week 52. At present, there is no evidence suggesting that the effects of pemafibrate on lipid parameters other than TG and LDL-C cause more significant problems compared with those of FF.

7.R.4 Indication

The applicant's explanation:

Pemafibrate is a selective PPARα agonist that reduces TG and increases HDL-C in fasting serum by regulating expression of genes involved in lipid and glucose metabolism. All of the studies in patients with hypertriglyceridemia evaluating pemafibrate monotherapy (Studies K-877-04, K-877-09, and K-877-17) and co-administration of pemafibrate and statins (Studies K-877-13, K-877-15, and K-877-201) showed that pemafibrate reduced fasting serum TG. In the studies, the maximal TG-lowering effect of pemafibrate was seen at 0.2 to 0.4 mg (daily dose). In terms of percentage reduction in fasting serum TG, Study K-877-09 demonstrated the non-inferiority of pemafibrate 0.2 and 0.4 mg to FF 200 mg (pulverized capsule formulation), and Study K-877-17 demonstrated the non-inferiority of pemafibrate 0.2 and 0.4 mg to FF 106.6 mg (tablets). In addition, pemafibrate improved lipid parameters other than TG (e.g., non-HDL-C, HDL-C). Based on the above, the applicant considered it appropriate to select hyperlipidemia (including familial hyperlipidemia) as the indication of pemafibrate. This indication is the same as that of FF.

PMDA's view:

Although results from Japanese clinical studies indicate that the effect of pemafibrate on LDL-C needs careful evaluation [see Section "7.R.3.1 Effect on LDL-C"], changes in other lipid parameters in pemafibrate-treated patients are almost comparable to those in patients treated with the existing fibrate, and the safety of pemafibrate is not markedly different from that of FF. Accordingly, pemafibrate can be made available in clinical practices as a drug in the same class as FF. The proposed indication of pemafibrate ("hyperlipidemia [including familial hyperlipidemia]," which is the same as that of FF) is appropriate.

7.R.5 Dosage and administration

The applicant's explanation:

Pemafibrate 0.2 mg/day (0.1 mg per dose, twice daily) was selected as the middle dose in a phase II study (Study K-877-04), because the TG-lowering effect of the middle dose was demonstrated in a phase I multiple-dose study in patients with hypertriglyceridemia (Study K-877-03). In addition, twice-daily administration was selected, because (i) the elimination half-life of pemafibrate is as short as approximately 2 hours and (ii) the TG-lowering effect was more favorable with the twice-daily regimen than with the once-daily regimen. In Study K-877-04, pemafibrate was administered at 0.05, 0.1, 0.2, or 0.4 mg (daily dose) twice daily under fed conditions. Results presented a significant dose-response relationship; the degrees of reduction in fasting serum TG were greater in the 0.2 mg and 0.4 mg groups than in the 0.05 mg and 0.1 mg groups. Furthermore, in all of the studies in patients with hypertriglyceridemia evaluating pemafibrate monotherapy (Studies K-877-04, K-877-09, and K-877-17) and co-administration of pemafibrate and statins (Studies K-877-13, K-877-15, and K-877-201), the maximal fasting serum TG-lowering effect of pemafibrate was observed at 0.2 to 0.4 mg. In addition, Study K-877-09 demonstrated the non-inferiority of pemafibrate 0.2 and 0.4 mg to FF 200 mg (pulverized capsule formulation), the maximum dose of FF, in terms of percentage reduction in fasting serum TG. Study K-877-17 demonstrated the non-inferiority of pemafibrate 0.2 and 0.4 mg to FF 106.6 mg (tablets) in terms of percentage reduction in fasting serum TG. Furthermore, in Study K-877-15, the starting dose of pemafibrate was 0.2 mg and then the dose was increased to 0.4 mg in subjects with inadequate response to the starting dose (TG ≥150 mg/dL at Week 8). In this study, the degree of reduction in fasting serum TG was greater in the 0.2/0.4 mg (dose-increase) group than in the 0.2 mg group (the dose maintained at 0.2 mg), and the percentage of patients who achieved fasting serum TG <150 mg/dL at the end of treatment tended to be higher in the 0.2/0.4 mg group than in the 0.2 mg group. In Study K-877-14, the starting dose of pemafibrate was 0.2 mg and then the dose was increased to 0.4

mg in subjects with inadequate response to the starting dose. Of 29 subjects who received the increased dose, 17 achieved further reduction in fasting serum TG. Safety data showed no significant differences between the groups treated pemafibrate ≤0.4 mg and the placebo group, nor was there any safety concern presenting dose-dependent changes. On the above grounds, the applicant selected the following dosage and administration of pemafibrate: The usual daily dose is 0.2 mg, and the daily dose may be increased to 0.4 mg according to the patient's condition.

PMDA's view:
Results from clinical studies have demonstrated that both pemafibrate 0.2 and 0.4 mg doses have TG-lowering effect equivalent to that of FF at the usual dose. Although not all the studies consistently showed a greater TG-lowering effect of pemafibrate 0.4 mg than that of pemafibrate 0.2 mg, pemafibrate 0.4 mg is expected to potentially reduce TG in patient with severe hypertriglyceridemia compared with pemafibrate 0.2 mg, according to the applicant's explanation. Therefore, selecting pemafibrate 0.2 mg as the usual dose and allowing dose increase up to 0.4 mg according to the patient's condition are appropriate.

7.R.6 Safety

7.R.6.1 Rhabdomyolysis

The applicant's explanation about the effects of pemafibrate on muscles:
The pooled analysis of 12-week data[5)] and 52-week data[6)] was performed. Adverse events coded to "Rhabdomyolysis/myopathy (SMQ)" are summarized in Table 41. No significant differences were observed between the pemafibrate group and the placebo or FF group. An analysis of adverse events by duration of treatment showed no increasing trend in the incidences of adverse events with increasing duration of treatment.

Table 41. Incidences of adverse events coded to "Rhabdomyolysis/myopathy (SMQ)" (safety analysis set)

	Week 12						Week 52
		Pemafibrate		FF			Pemafibrate
	Placebo (N = 298)	0.2 mg/day (N = 657)	0.4 mg/day (N = 320)	100 mg/day (N = 122)	106.6 mg/day (N = 76)	200 mg/day (N = 140)	0.2-0.4 mg/day (N = 298)
Rhabdomyolysis/myopathy (SMQ)	4.4 (13)	2.7 (18)	2.8 (9)	2.5 (3)	9.2 (7)	5.0 (7)	8.1 (24)
Blood CK increased	3.0 (9)	1.5 (10)	1.9 (6)	1.6 (2)	1.3 (1)	2.1 (3)	4.0 (12)
Blood Cr increased	0 (0)	0.3 (2)	0 (0)	0 (0)	2.6 (2)	2.9 (4)	0.3 (1)
Myalgia	0.7 (2)	0.6 (4)	0.3 (1)	0.8 (1)	5.3 (4)	0 (0)	1.7 (5)
Acute renal failure	0 (0)	0 (0)	0.3 (1)	0 (0)	1.3 (1)	0 (0)	0.3 (1)
Myoglobin blood increased	0 (0)	0.6 (4)	0.3 (1)	0 (0)	0 (0)	0 (0)	2.0 (6)
Myoglobin urine present	0.7 (2)	0.2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1.0 (3)
Chronic kidney disease	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1.0 (3)

% (n)
Adverse events reported by ≥1% of subjects in any group

Adverse events[7)] that occurred after administration of pemafibrate and led to discontinuation were reported by 5 subjects (6 events; 3 events of blood CK increased in 3 subjects, 1 event of myoglobin blood increased in 1 subject, 1 event of acute renal failure in 1 subject, 1 event of chronic kidney disease aggravated in 1 subject). All events were considered possibly related to the study drug, but they resolved without treatment or with outpatient treatment.

In addition, the incidences of adverse events coded to "Rhabdomyolysis/myopathy (SMQ)" in each of the subgroups with or without statin therapy and/or renal impairment are shown in Table 42. No significant differences in the incidence of adverse events between the pemafibrate and placebo groups were observed in the overall population or any of the subgroups investigated. No particular dose-response relationships were observed in the pemafibrate group. Furthermore, an analysis of adverse events by duration of treatment showed no increasing trend in the incidences of adverse events with increasing duration of treatment.

5) Data from Studies K-877-04, K-877-09, K-877-13, K-877-15, K-877-16 (only Period 1), K-877-17, and K-877-19
6) Data from Studies K-877-14 and K-877-16 (only patients who received pemafibrate in Periods 1 and 2)
7) Data from Studies K-877-04, K-877-09, K-877-11, K-877-13, K-877-14, K-877-15, K-877-16, K-877-17, and K-877-19

Table 42. Incidences of adverse events coded to "Rhabdomyolysis/myopathy (SMQ)" in each subgroup (safety analysis set)

		Week 12						Week 52
		Placebo	Pemafibrate		FF			Pemafibrate
			0.2 mg/day	0.4 mg/day	100 mg/day	106.6 mg/day	200 mg/day	0.2-0.4 mg/day
Overall population		4.4% (13/298)	2.7% (18/657)	2.8% (9/320)	2.5% (3/122)	9.2% (7/76)	5.0% (7/140)	8.1% (24/298)
Statin[a]	With	3.9% (7/178)	4.2% (16/382)	4.2% (3/72)	-	-	-	8.7% (13/150)
	Without	5.0% (6/120)	0.7% (2/275)	2.4% (6/248)	2.5% (3/122)	9.2% (7/76)	5.0% (7/140)	7.4% (11/148)
Renal impairment	With	4.5% (2/44)	8.1% (6/74)	3.6% (1/28)	0% (0/8)	22.2% (2/9)	20.0% (2/10)	18.8% (12/64)
	Without	4.3% (11/254)	2.1% (12/583)	2.7% (8/292)	2.6% (3/114)	7.5% (5/67)	3.8% (5/130)	5.1% (12/234)
Statin + renal impairment[a]	With	5.7% (2/35)	10.6% (5/47)	0% (0/8)	-	-	-	20.7% (6/29)
	Without	4.2% (11/263)	2.1% (13/610)	2.9% (9/312)	2.5% (3/122)	9.2% (7/76)	5.0% (7/140)	6.7% (18/269)

[a] Data from Studies K-877-04, K-877-09, and K-877-17 cannot be evaluated for the subgroups of patients who received FF concomitantly with statins, because patients on statin therapy were excluded from the studies.

The applicant added the following explanation about the risk of rhabdomyolysis:
Although the mechanism of fibrate-related muscle disorder remains unclarified, a drug alert was issued in Japan (November 1994) because of the risk of rhabdomyolysis in patients receiving bezafibrate. The alert stated that most of the reported cases developed in patients with creatinine (Cr) ≥2.5 mg/dL, in whom this drug was contraindicated. The risk of rhabdomyolysis in patients receiving a fibrate in combination with a statin is considered attributable to the effect of the concomitant fibrate on the metabolism of the stain. Particularly, gemfibrozil in combination with cerivastatin elevated blood concentrations of cerivastatin active form, resulting in the increased risk of rhabdomyolysis (*JAMA.* 2003;289:1681-90, *Am J Cardiol.* 2005;96:44K-9K; discussion 34K-5K). In contrast, FF does not affect the blood concentrations of a concomitant statin. The ACCORD study on co-administration of FF and statins did not indicate an increased risk of muscular symptoms including elevated CK and rhabdomyolysis (*N Engl J Med.* 2010;362:1563-74). According to the Guidelines for the management of dyslipidemias issued by the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) (*Atherosclerosis.* 2016;253:281-344), results from clinical studies for each of FF and gemfibrozil indicate that the risk of rhabdomyolysis was increased only in patients receiving gemfibrozil in combination with a statin, but not in those receiving any fibrate with a statin. Precautionary statements for patients with renal impairment differ among the Japanese package inserts of fibrates, and some fibrates are not contraindicated in such patients. Under the above circumstances, the increased risk of rhabdomyolysis in patients with renal impairment and patients receiving a fibrate combination with a statin is not commonly applicable to all fibrates. Treatment discontinuation due to elevated CK and other adverse events occurred in some subjects treated with pemafibrate (1 subject in Study K-877-13 [at 0.2 mg/day on Day 14], 1 subject in Study K-877-15 [at 0.2 mg/day, blood CK increased occurring on Day 15 and myoglobin blood increased occurring on Day 57], and 1 subject in Study K-877-19 [at 0.4 mg/day on Day 56]), but these events resolved without treatment after discontinuation of pemafibrate. Thus, elevated CK reported in clinical studies of pemafibrate are not considered clinically relevant. In addition, because pemafibrate is excreted in bile, the use of pemafibrate in patients with renal impairment and patients on statin therapy would result in a decreased risk of rhabdomyolysis, compared with the existing fibrates.

PMDA's view:
Based on the drug-drug interactions and excretion route of pemafibrate, the applicant infers that the use of pemafibrate in patients with renal impairment and patients on statin therapy results in a decreased risk of rhabdomyolysis, compared with other fibrates. The clinical study data submitted suggest that the incidence of adverse events related to rhabdomyolysis in patients receiving pemafibrate is not high compared with that in patients receiving FF, but there is little evidence indicating that pemafibrate pose a decreased risk of rhabdomyolysis compared with fibrates other than FF. Furthermore, it should be noted that adverse events such as renal impairment and myalgia were reported in clinical studies in Japan. Given that the incidences of adverse events coded to "Rhabdomyolysis/myopathy (SMQ)" were higher in the subgroups of patients with renal impairment and patients on statin therapy than in the

overall population, the same advice as that for the existing fibrates should be provide for the use of pemafibrate in patients with renal impairment and patients on statin therapy.

7.R.6.2 Effect on the liver

The applicant's explanation about the effect on the liver:
Table 43 shows the incidences of adverse events coded to "Drug related hepatic disorders - comprehensive search (SMQ)," obtained from the pooled analysis of 12-week data[5)] and 52-week data.[6)] Table 44 shows the percentage of subjects with liver function test values ≥3 fold the ULN, obtained from the pooled analysis of t12-week data.[5)] The data in both tables showed that the incidences of such events in the pemafibrate groups were lower than that in the FF groups, indicating that pemafibrate is less likely to cause liver disorders than FF. An analysis of adverse events by duration of treatment showed no increasing trend in the incidences of adverse events with increasing duration of treatment.

Table 43. Incidences of adverse events coded to "Drug related hepatic disorders - comprehensive search (SMQ)" (safety analysis set)

	Week 12						Week 52
	Placebo (N = 298)	Pemafibrate		FF			Pemafibrate
		0.2 mg/day (N = 657)	0.4 mg/day (N = 320)	100 mg/day (N = 122)	106.6 mg/day (N = 76)	200 mg/day (N = 140)	0.2-0.4 mg/day (N = 298)
Drug related hepatic disorders (SMQ)	2.7 (8)	2.7 (18)	3.8 (12)	13.9 (17)	35.5 (27)	24.3 (34)	6.7 (20)
Hepatic function abnormal	0 (0)	0.3 (2)	0.6 (2)	1.6 (2)	2.6 (2)	2.1 (3)	0.3 (1)
ALT increased	0.7 (2)	1.1 (7)	0.3 (1)	0 (0)	15.8 (12)	1.4 (2)	1.0 (3)
AST increased	0 (0)	0.8 (5)	0.3 (1)	0 (0)	13.2 (10)	0 (0)	1.3 (4)
γ-GTP increased	0.7 (2)	0.6 (4)	0 (0)	1.6 (2)	21.1 (16)	2.9 (4)	0 (0)
Liver function test abnormal	1.0 (3)	0.5 (3)	2.2 (7)	9.8 (12)	6.6 (5)	15.7 (22)	0.3 (1)
Hepatic steatosis	0 (0)	0.2 (1)	0 (0)	0 (0)	1.3 (1)	0 (0)	3.0 (9)

% (n)
Adverse events reported by ≥2% of subjects in any group

Table 44. Percentage of subjects with liver function test values ≥3 fold ULN (pooled analysis of 12-week data, safety analysis set)

	Placebo	Pemafibrate		FF		
		0.2 mg/day	0.4 mg/day	100 mg/day	106.6 mg/day	200 mg/day
AST ≥3 × ULN	0% (0/297)	0.2% (1/657)	0.6% (2/319)	0.8% (1/122)	3.9% (3/76)	2.1% (3/140)
ALT ≥3 × ULN	0.3% (1/298)	0% (0/657)	0.3% (1/319)	2.5% (3/122)	9.2% (7/76)	4.3% (6/140)

Adverse events[7)] coded to "Drug related hepatic disorders - comprehensive search (SMQ)" which led to discontinuation reported by 6 subjects (9 events; 3 events of ALT increased in 3 subjects, 2 events of AST increased in 2 subjects, 1 event each of blood fibrinogen decreased, hepatic function abnormal, γ-GTP increased, liver function test abnormal in 1 subject each). All events were considered possibly related to the study drug, but they were resolving or resolved without any treatment or with outpatient treatment.

The applicant's explanation about a risk of gallstone in patients receiving pemafibrate:
According the pooled analysis of 12-week data,[5)] adverse events coded to "Gallstone related disorders (SMQ)" occurred in 0.5% (3 of 657 subjects, cholelithiasis in 2 subjects and bile duct stone in 1 subject) of subjects in the pemafibrate 0.2 mg/day group only. A causal relationship to the study drug could not be ruled out for bile duct stone in 1 subject. According the pooled analysis of 52-week data[6)] from subjects treated with pemafibrate 0.2 mg or 0.4 mg, adverse events coded to "Gallstone related disorders (SMQ)" occurred in 6.0% (18 of 298 subjects, cholelithiasis in 16 subjects and bile duct stone in 2 subjects) of the analyzed subjects. Except for cholelithiasis in 1 subject, all the events were considered possibly related to the study drug. There was no increasing trend in the incidences of adverse events with increasing duration of treatment.

Of adverse events[7)] coded to "Gallstone related disorders (SMQ)," 1 event of bile duct stone in 1 subject was judged as severe or serious and led to discontinuation of the study drug. For this reason, pemafibrate should be carefully administered to patients with gallstone or its past history.

PMDA's view:
The clinical study data submitted does not suggest any increased risk of hepatic dysfunction in patients receiving pemafibrate compared with that in patients receiving FF, but it cannot be concluded that the risk of hepatic dysfunction with pemafibrate is lower than that with FF because the data were obtained from controlled studies that were conducted only in the limited number of patients for the limited period. Accordingly, the same advice as that for FF should be provided for the risk of hepatic dysfunction. In addition, it should be noted that adverse events related to gallstone did not occur in the FF group, while pemafibrate-treated subjects experienced these events, some of which led to discontinuation. However, these adverse events occurred only in a limited number of subjects, making it difficult to evaluate their risk in comparison with FF, and the risk of gallstone is common in patients receiving any fibrate. Thus, at present, the same advice as that for FF should be provided for the risk of gallstone.

7.R.6.3 Use in patients with renal impairment

The applicant's explanation about the use of pemafibrate in patients with renal impairment:
Table 45 shows the incidences of adverse events from the pooled analysis of 12-week data.[5)] In the subgroup of patients with renal impairment (eGFR <60 mL/min/1.73 m^2), the incidences of adverse events in the pemafibrate group were comparable with those in the placebo group. No increasing trend in the incidences of adverse events with increasing dose was observed in the pemafibrate group. Accordingly, the use of pemafibrate is allowed in patients with renal impairment, but pemafibrate should be carefully administered to this patient population because there was limited experience with the use of pemafibrate in patients with severe (serious) renal impairment on statin therapy in clinical studies. Therefore, the package insert will advise this issue.

Table 45. Incidences of adverse events in subgroups divided according to baseline eGFR (pooled analysis of 12-week data, safety analysis set)

	Placebo	Pemafibrate		FF		
		0.2 mg/day	0.4 mg/day	100 mg/day	106.6 mg/day	200 mg/day
eGFR <60 mL/min/1.73 m^2						
N	44	74	28	8	9	10
Adverse events	43.2 (19)	45.9 (34)	46.4 (13)	50.0 (4)	77.8 (7)	40.0 (4)
Serious adverse events	2.3 (1)	6.8 (5)	3.6 (1)	0 (0)	0 (0)	0 (0)
Adverse events leading to discontinuation	4.5 (2)	4.1 (3)	3.6 (1)	0 (0)	22.2 (2)	10.0 (1)
eGFR ≥60 mL/min/1.73 m^2						
N	254	583	292	114	67	130
Adverse events	42.9 (109)	39.5 (230)	37.3 (109)	46.5 (53)	49.3 (33)	57.7 (75)
Serious adverse events	0.4 (1)	0.9 (5)	0.3 (1)	0 (0)	0 (0)	2.3 (3)
Adverse events leading to discontinuation	0 (0)	2.4 (14)	1.7 (5)	3.5 (4)	6.0 (4)	10.0 (13)

% (n)

PMDA's view:
The clinical study data submitted did not indicate any clear trend toward an increased risk of adverse events in patients with renal impairment receiving pemafibrate compared with patients receiving FF. Rhabdomyolysis is a particular safety concern in patients with renal impairment. Given the incidence of rhabdomyolysis in patients receiving the approved fibrates, adequate comparison of the drugs is difficult at the scales of clinical studies included in this application. As described in Section "7.R.1 Clinical positioning of pemafibrate," pemafibrate has been developed to be made available in clinical practices as a drug in the same class as the existing fibrates, based on its mechanism of action and other data, by conducting controlled clinical studies and then demonstrating that pemafibrate is not inferior to the approved fibrates in terms of effects on lipid parameters including TG-lowering effect and the safety profile. In addition, the clinical study data showed that the incidences of adverse events related to rhabdomyolysis were higher in patients with renal impairment than in other patients [see Table 42 in Section "7.R.6.1 Rhabdomyolysis"]. Taking account of the above considerations, the same advice as that for the existing fibrates should be provided for the use of pemafibrate in patients with renal impairment.

Final decisions on PMDA's discussion about the safety and the appropriateness of proposed precautionary statements will be made, taking account of comments raised in the Expert Discussion.

7.R.7 Post-marketing investigations

The applicant's explanation about post-marketing investigations for pemafibrate:
The applicant plans to conduct a specified use-results survey with the follow-up period of 2 years to investigate the long-time safety and efficacy of pemafibrate used in patients with hyperlipidemia (including familial hyperlipidemia) in clinical settings. In addition, in view of the concern about changes in LDL-C in patients receiving pemafibrate [see Section "7.R.3.1 Effect on LDL-C"], the applicant will have Japanese patients participate in a multi-regional placebo-controlled study in patients with hypertriglyceridemia who are at a high risk of cardiovascular events to evaluate whether pemafibrate have an effect to reduce cardiovascular events. The multi-regional study is planned in European countries and the US. Furthermore, given that the multi-regional study is intended to include patients at a high risk of cardiovascular events, the applicant will separately conduct a specified use-results survey covering the patient population commonly seen in Japanese clinical practice to investigate the effect of pemafibrate on cardiovascular events in clinical settings in Japan. The investigation is planned as a concurrent-controlled cohort study.

PMDA's view:
How the changes in LDL-C in patients receiving pemafibrate affect the risk-benefit balance of pemafibrate should be investigated in the post-marketing setting. To this end, the participation of Japanese patients in the multi-regional study, which is designed as a randomized, double-blind, controlled study, is useful. In addition, it is acceptable for the applicant to conduct a cohort study in order to investigate the effect of pemafibrate on the risk of cardiovascular events in clinical settings in Japan, but the design of the study and other details should be further discussed. A final decision on the details of the post-marketing clinical study and surveillance will be made, taking account of comments raised in the Expert Discussion. The identification of safety specification, appropriateness of risk classification, pharmacovigilance activities, and appropriateness of risk minimization activities will also assessed in accordance with the "Risk Management Plan Guidance" (PFSB/SD Notification No. 0411-1 and PFSB/ELD Notification No. 0411-2, dated April 11, 2012).

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion on the results of document-based GLP/GCP inspection and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1-1, CTD 5.3.5.1-2, CTD 5.3.5.1-3, CTD 5.3.5.1-4, CTD 5.3.5.1-5, CTD 5.3.5.1-6-1, CTD 5.3.5.1-6-2, CTD 5.3.5.2-1-1, CTD 5.3.5.2-1-2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection showed that the clinical studies as a whole had been conducted in compliance with GCP. PMDA therefore concluded that there were no obstacles to conducting its review based on the application documents submitted. The following finding was observed in a study site (medical institution), although it did not significantly affect the overall evaluation of the study. The head of the medical institution was informed of this finding requiring corrective action.

Finding requiring corrective action
Study site

- Prior to the re-collection of blood samples, the investigator should inform the subject of details and confirm the subjects' willingness to continue participation in the study, and such communication should be recorded. However, there were no documents recording such communication for some subjects.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that pemafibrate has efficacy in the treatment of patients with hyperlipidemia, for whom fibrates are indicated, is equivalent to that of FF, an approved fibrate. The safety of pemafibrate is acceptable, because at present, there is no trend toward markedly higher incidences of adverse events in patients receiving pemafibrate than those in patients receiving FF, although the effect of pemafibrate on LDL-C should be carefully evaluated. In addition, the contents of precautionary statements in the package insert, post-marketing investigations, etc., should be further discussed.

PMDA has concluded that Parmodia (pemafibrate) may be approved if the product is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

May 16, 2017

Product Submitted for Approval	
Brand Name	Parmodia Tab. 0.1 mg
Non-proprietary Name	Pemafibrate
Applicant	Kowa Company, Ltd.
Date of Application	October 19, 2015

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized in the following. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Clinical positioning of pemafibrate

In clinical practice in Japan, fibrates have been already used as TG-lowering drugs in patients with hypertriglyceridemia for an extended period of time. Since Parmodia Tab. 0.1 mg (hereinafter referred to as pemafibrate) is classified as a fibrate, pemafibrate may be made available in clinical practice as one of fibrates, as long as clinical studies have demonstrated that pemafibrate's effects on lipid parameters including the TG-lowering effect and the safety profile are equivalent to those of the approved fibrates even though pre-approval clinical studies have not been conducted to verify pemafibrate's ability to reduce cardiovascular events. The above conclusion of PMDA was supported by the expert advisors.

1.2 Effect on LDL-C

Elevated low-density lipoprotein cholesterol (LDL-C) was observed in patients receiving pemafibrate in Study K-877-09. Concerning this finding, the expert advisors raised following comments:

- The risk-benefit balance of pemafibrate should be carefully determined because (i) elevated LDL-C potentially leads to cardiovascular events and (ii) pemafibrate's ability to reduce cardiovascular events has not been investigated in the studies.
- At present, elevated LDL-C, which was observed in Study K-877-09, does not necessarily result in an increased risk of cardiovascular events in patients receiving pemafibrate, for the following reasons: (i) The elevated LDL-C is possibly attributable to a relative increase in cholesterol content resulting from a decrease in TG content in LDL particles; (ii) there were no significant differences in percentage elevation in LDL-C between the pemafibrate and fenofibrate (FF) groups in Study K-877-09; and (iii) no elevation in LDL-C was observed in Study K-877-17.

After discussing in the Expert Discussion, expert advisers reached the following consensus:

- The applicant should conduct a post-marketing clinical study to investigate the effect of pemafibrate to reduce the risk of cardiovascular events [see Section "1.4 Risk management plan (draft)"], and should ensure that, based on the study results, information on the risk-benefit balance of pemafibrate is communicated appropriately to healthcare professionals.
- The applicant should advise healthcare professionals to periodically monitor serum lipid parameters including LDL-C in patients on pemafibrate and to take appropriate measures if any change is detected in these parameters.

The conclusion of PMDA described in Section "7.R.3.1 Effect on LDL-C" of the Review Report (1) was supported by the expert advisors.

1.3 Safety

1.3.1 Rhabdomyolysis as well as use of pemafibrate in patients with renal impairment and patients on statin therapy

The risk of rhabdomyolysis in patients with renal impairment and patients on therapy with a hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor (statin) was addressed in the discussion. The expert advisors raised the following comments:

- PMDA's conclusion is acceptable; the same advice as that for the existing fibrates should be provided at present.
- The appropriateness of use of the same advice as that for the existing fibrates should be reviewed because their metabolic pathways differ; pemafibrate is mainly metabolized in the liver while the metabolism of the existing fibrates mainly involves renal excretion.

Taking account of the above comments, PMDA reviewed the risk of rhabdomyolysis and has concluded as follows:
The clinical study data submitted [see Table 41 in Section "7.R.6.1 Rhabdomyolysis" of the Review Report (1)] indicate that the risk of rhabdomyolysis is unlikely to be higher in patients receiving pemafibrate than in patients receiving FF, but the number of patients evaluated was limited. There is no clear evidence demonstrating that the risk of rhabdomyolysis associated with pemafibrate is lower than that associated with the existing fibrates. In addition, adverse events such as renal impairment and myalgia were reported by subjects receiving pemafibrate in Japanese clinical studies, and the incidences of adverse events related to rhabdomyolysis in the subgroups of patients with renal impairment and patients on statin therapy were higher than that in the overall population. On the above grounds, the same advice as that for the existing fibrates should be provided for the use of pemafibrate in patients with renal impairment and patients on statin therapy.

Based on the above, PMDA requested the applicant to provide, in the package inserts, the same advice as that for the existing fibrates should be provided for the risk of rhabdomyolysis associated with the use of pemafibrate in patients with renal impairment and patients on statin therapy for, and the applicant responded appropriately.

1.3.2 Effect on the liver

The following conclusion of PMDA was supported by the expert advisors: The risk of hepatic dysfunction in patients receiving pemafibrate does not seem to be higher than that in patients receiving FF, but it is not possible to conclude that the risk of hepatic dysfunction associated with pemafibrate is lower than that with FF; and thus the same advice as that for FF should be provided for the risk of hepatic dysfunction. In addition, the following PMDA's conclusion on the risk of gallstone was supported by the expert advisors: The same advice as that for FF should be provided for the risk of gallstone, because the clinical study data of pemafibrate indicate the risk of gallstone, and the risk is commonly found in patients receiving any fibrate.

Based on the above, PMDA requested the applicant to provide necessary advice on the risk of hepatic dysfunction and cholelithiasis in the package insert, and the applicant responded appropriately.

1.4 Risk management plan (draft)

In view of the review in Section "7.R.7 Post-marketing investigations" of the Review Report (1) and discussion at the Expert Discussion, PMDA has concluded that the current risk management plan (draft) for pemafibrate should include the safety and efficacy specifications presented in Table 46, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 47 as well as a post-marketing clinical study presented in Table 48 and specified use-results surveys presented in Tables 49 and 50.

Table 46. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
- Rhabdomyolysis	- Elevated LDL-C level	- Patients with renal impairment - Patients with hepatic impairment - Elderly patients aged ≥75 years - Long-term safety of pemafibrate
Efficacy specification		
- Long-term efficacy of pemafibrate in routine clinical use - Reduction of cardiovascular events		

Table 47. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft) as well as summary of surveys and study on efficacy

Additional pharmacovigilance activities	Additional risk minimization activities	Surveys and study on efficacy
- Early post-marketing phase vigilance - Specified use-results survey (long-term use) - Specified use-results survey (reduction of cardiovascular events) - Post-marketing clinical study	- Information provision through post-marketing phase vigilance	- Specified use-results survey (long-term use) - Specified use-results survey (reduction of cardiovascular events) - Post-marketing clinical study

Table 48. Outline of post-marketing clinical study plan (draft)

Study design	Randomized, double-blind, placebo-controlled study
Population	Patients with hyperlipidemia and comorbid diabetes mellitus at a high risk of cardiovascular events TG ≥200 mg/dL and <500 mg/dL, and high-density lipoprotein cholesterol (HDL-C) ≤40 mg/dL
Sample size	10,000 patients (5000 each for the pemafibrate and placebo groups) Including 300 to 500 Japanese patients
Dosage regimen	Pemafibrate 0.2 mg or placebo twice daily
Study period	5 years
Primary endpoint	Time to first onset of any of the following cardiovascular events: "non-fatal myocardial infarction," "non-fatal ischaemic stroke," "hospitalization due to unstable angina requiring unscheduled coronary revascularization," and "cardiovascular death"

Table 49. Outline of specified use-results survey (reduction of cardiovascular events) plan (draft)

Survey design	No-treatment, non-randomized, concurrent-controlled cohort study
Population	Patients with hyperlipidemia (TG ≥150 mg/dL)
Sample size	30,000 patients (15,000 each for the pemafibrate and no-TG-lowering drug treatment groups)
Survey period	6.5 years (2 years of enrollment, 4 years of follow-up after the end of enrollment)
Primary endpoint	Time to first onset of any of the following cardiovascular events: "non-fatal myocardial infarction," "non-fatal ischaemic stroke," "hospitalization due to unstable angina undergoing coronary revascularization," and "cardiovascular death"

Table 50. Outline of specified use-results survey (long-term use) plan (draft)

Objective	Investigation of long-term safety and efficacy of pemafibrate in routine clinical use
Survey method	Central registry system
Population	Patients with hyperlipidemia
Observation period	2 years after the first dose of pemafibrate
Planned sample size	3000 patients for safety evaluation
Main survey items	Incidences of events related to rhabdomyolysis, changes in LDL-C, etc.

1.5 Others

1.5.1 Co-administration of pemafibrate and clopidogrel

A clinical drug-drug interaction study of pemafibrate and clopidogrel (Study K-877-109, CTD 5.3.3.4-13) was underway at the time of preparation of the Review Report (1). Data from the study were submitted for review. The summary of the data is shown below.

In the study, a total of 20 healthy non-Japanese adults orally received a single dose of pemafibrate 0.4 mg on Days 1, 4, and 7, and also orally received a single dose of clopidogrel 300 mg on Day 4 followed by oral dose of clopidogrel 75 mg once daily from Day 5 to Day 9. The geometric mean ratios (90% CIs) of the C_{max} and $AUC_{0\text{-}inf}$ of pemafibrate following co-administration of pemafibrate and clopidogrel 300 mg to those following administration of pemafibrate alone were 1.486 [1.392, 1.586] and 2.373 [2.247, 2.505], respectively. The geometric mean ratios [90% CIs] of the C_{max} and $AUC_{0\text{-}inf}$ of pemafibrate following co-administration of pemafibrate and clopidogrel 75 mg to those following administration of pemafibrate alone were 1.342 [1.258, 1.430] and 2.088 [1.981, 2.200], respectively.

The applicant's explanation about co-administration of pemafibrate and clopidogrel:
Among metabolic enzyme and transporters potentially involved in the pharmacokinetics of pemafibrate [see Section "6.2.1 *In vitro* studies using human biomaterials" of the Review Report (1)], cytochrome P450 (CYP) 2C8 and organic anion transport polypeptide (OATP) 1B1 are inhibited by clopidogrel. Elevated exposure to pemafibrate following co-administration of pemafibrate and clopidogrel is therefore considered attributable to the inhibition of CYP2C8 and OATP1B1 by clopidogrel. In

consideration of the elevated exposure to pemafibrate observed in Study K-877-109, the applicant plans to list clopidogrel in the "Precautions for Co-administration" section and to provide advice stating that the use of a reduced dose of pemafibrate be considered for co-administration with clopidogrel.

PMDA's view
In consideration of the elevation in exposure to pemafibrate following co-administration of pemafibrate and clopidogrel, the applicant's actions are appropriate.

2. Overall Evaluation
As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indication and the dosage and administration as shown below, with the following condition for approval. Since Parmodia (pemafibrate) is a drug with a new active ingredient, the re-examination period is 8 years. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug. The product is not classified as a biological product or a specified biological product.

Indication
Hyperlipidemia (including familial hyperlipidemia)

Dosage and Administration
The usual adult dosage is 0.1 mg of pemafibrate orally administered twice daily in the morning and evening. The dose may be adjusted according to the patient's age and symptoms. The maximum dose should be 0.2 mg twice daily.

Condition of Approval
The applicant is required to develop and appropriately implement a risk management plan.