Long-term safety and efficacy of pemafibrate to treat hyperlipidemia: post-marketing surveillance over a 24-month observation period in Japan

Authors: Mao Watanabe[1], Michiko Nakanishi[2], Wataru Shingaki[2], Ryoji Gunji[2], Yuichi Makinose[2], Takashi Kanno[2], Shun Ishibashi[3,4]

Affiliations: [1]Medical Affairs Department, Kowa Company, Ltd., Tokyo, Japan

[2]Postmarketing Surveillance Department, Kowa Company, Ltd., Tokyo, Japan

[3]Division of Endocrinology and Metabolism, Department of Internal Medicine, School of Medicine, Jichi Medical University, Tochigi, Japan

[4]Ishibashi Diabetes and Endocrine Clinic, Saitama, Japan

Corresponding author: Mao Watanabe. E-mail: m-watanabe@kowa.co.jp

Supplementary material

Supplementary Table S1. Important safety considerations according to the Pharmaceutical Risk Management Plan by preferred term (PT) included in the safety assessment

Assessment item	Included events (PT)		
Rhabdomyolysis-related events	Muscle necrosis	Myoglobin blood increased	Myoglobin blood present
	Myoglobin urine present	Myoglobinemia	Myoglobinuria
	Myopathy	Myopathy toxic	Necrotizing myositis
	Rhabdomyolysis	AKI	Anuria
	Biopsy muscle abnormal	Blood calcium decreased	Blood CPK abnormal
	Blood CPK increased	Blood CPK MM* increased	Blood creatinine abnormal
	Blood creatinine increased	Chromaturia	CKD
	Compartment syndrome	Creatinine renal clearance abnormal	Creatinine renal clearance decreased
	Diaphragm muscle weakness	Electromyogram abnormal	GFR abnormal
	GFR decreased	Hypercreatinemia	Hypocalcemia
	Muscle disorder	Muscle enzyme increased	Muscle fatigue
	Muscle hemorrhage	Muscle rupture	Muscular weakness
	Musculoskeletal discomfort	Musculoskeletal disorder	Musculoskeletal pain
	Myalgia	Myalgia intercostal	Myositis
	Oliguria	Renal failure	Renal impairment
	Renal tubular necrosis	Tendon discomfort	
Renal-related events	Blood creatinine increased	GFR decreased	AKI
	CKD	Diabetic nephropathy	Renal impairment
Elevation of LDL-C	Low density lipoprotein increased	Hypercholesterolemia	Blood cholesterol increased

*skeletal muscle fraction.

AKI acute kidney injury, *CKD* chronic kidney disease, *CPK* creatine phosphokinase, *GFR* glomerular filtration rate, *LDL-C* low-density lipoprotein cholesterol

Supplementary Table S2. Observation period and reason for discontinuation of observation in the safety analysis set (N=3610)

Characteristic	Discontinued treatment (n=689)
Observation period, weeks, mean ± SD	94.1 ± 27.9
Treatment period, weeks, mean ± SD	93.0 ± 28.9
Reason for discontinuation of observation*	
Loss to follow-up, n (%)	306 (44.4)
AEs, n (%)	105 (15.2)
Patient requested discontinuation of treatment (unrelated to AEs), n (%)	97 (14.1)
Insufficient therapeutic effect, n (%)	31 (4.5)
Other, n (%)	152 (22.1)

*Duplications were possible.

AE adverse event, *SD* standard deviation

Supplementary Table S3. Types of adverse drug reactions (ADRs) in the safety analysis set (N=3610)

Occurrence of ADRs	**n (%)**
Number of patients with ADRs	147 (4.07)
Number of patients with serious ADRs	8 (0.22)
Types of ADRs, n (%)	
Laboratory tests	60 (1.66)
Blood CPK increased	14 (0.39)
Glycosylated hemoglobin increased	14 (0.39)
Low-density lipoprotein increased	10 (0.28)
Blood uric acid increased	6 (0.17)
GFR decreased	4 (0.11)
BP increased	4 (0.11)
Blood creatinine increased	3 (0.08)
Blood urea increased	3 (0.08)
AST increased	2 (0.06)
Blood glucose increased	2 (0.06)
Urinary albumin-to-creatinine ratio increased	2 (0.06)
Blood alkaline phosphatase increased	2 (0.06)
ALT increased	1 (0.03)
γ-GT increased	1 (0.03)
Urine output increased	1 (0.03)
Hepatic enzymes increased	1 (0.03)
Hepatobiliary disorders	24 (0.66)
Cholelithiasis†	11 (0.30)
Hepatic function abnormal	9 (0.25)
Cholecystitis†	2 (0.06)
Liver disorder	2 (0.06)
Bile duct stone††	1 (0.03)
Biliary colic††	1 (0.03)
Cholangitis††	1 (0.03)
Cholecystitis acute††	1 (0.03)
Gallbladder polyp	1 (0.03)
Musculoskeletal and connective tissue disorders	14 (0.39)
Myalgia	8 (0.22)
Muscle spasms	1 (0.03)
Muscle weakness	1 (0.03)
Myositis	1 (0.03)
Pain in jaw	1 (0.03)
Spinal osteoarthritis††	1 (0.03)
Joint range of motion decreased	1 (0.03)
Metabolic and nutritional disorders	14 (0.39)
Diabetes mellitus	5 (0.14)
Dyslipidemia	3 (0.08)

Diabetes mellitus inadequate control	2 (0.06)
Hypokalemia††	2 (0.06)
Gout	2 (0.06)
Hypercholesterolemia	1 (0.03)
Hyperuricemia	1 (0.03)
Gastrointestinal disorders	13 (0.36)
Constipation	3 (0.08)
Dyspepsia	2 (0.06)
Gastrointestinal disorder	2 (0.06)
Abdominal distension	1 (0.03)
Abdominal pain	1 (0.03)
Chronic gastritis	1 (0.03)
Diarrhea	1 (0.03)
Feces discolored	1 (0.03)
Gastric polyp	1 (0.03)
Gastritis erosive	1 (0.03)
Nausea	1 (0.03)
Skin and subcutaneous tissue disorders	11 (0.30)
Pruritus	6 (0.17)
Cutaneous amyloidosis	1 (0.03)
Dermatitis allergic	1 (0.03)
Drug eruption	1 (0.03)
Eczema	1 (0.03)
Rash	1 (0.03)
Renal and urinary tract disorders	8 (0.22)
Renal impairment	6 (0.17)
Hematuria	1 (0.03)
Pollakiuria	1 (0.03)
General and systemic disorders and administration site conditions	7 (0.19)
Abnormal feeling	2 (0.06)
Edema peripheral	2 (0.06)
Chest pain	1 (0.03)
Drug interaction	1 (0.03)
Malaise	1 (0.03)
Therapeutic response decreased	1 (0.03)
Nervous system disorder	4 (0.11)
Hypoesthesia	2 (0.06)
Dizziness	1 (0.03)
Hemiparesis	1 (0.03)
Vascular disorder	3 (0.08)
Hypertension	2 (0.06)
Hot flashes	1 (0.03)
Blood and lymphatic system disorders	3 (0.08)
Anemia	1 (0.03)
Folate deficiency anemia	1 (0.03)
Iron deficiency anemia††	1 (0.03)

Respiratory, thoracic, and mediastinal disorders	1 (0.03)
Combined pulmonary fibrosis and emphysema††	1 (0.03)
Reproductive system and breast disorders	1 (0.03)
Prostatitis	1 (0.03)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	1 (0.03)
Gastrointestinal submucosal tumor	1 (0.03)
Colorectal adenocarcinoma††	1 (0.03)
Surgical and medical procedures	1 (0.03)
Cholecystectomy††	1 (0.03)
Mental disorder	1 (0.03)
Anxiety	1 (0.03)

Values are expressed as n (%).

ADRs were classified based on MedDRA/J Version 25.1.

†2 cases of serious ADRs; ††1 case of a serious ADR.

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *BP* blood pressure, *CPK* creatine phosphokinase, *GFR* glomerular filtration rate, *γ-GT* gamma-glutamyl transferase

Supplementary Table S4. Changes in safety parameters in the safety analysis set

	Baseline	24 months	LOCF
CPK, U/L			
N	2056	1425	2056
Measured value, mean ± SD	120.8 ± 96.1	120.7 ± 100.6	122.8 ± 108.0
Change, mean ± SD		2.4 ± 103.3	2.0 ± 108.0
sCr, mg/dL			
N	3213	2379	3213
Measured value, mean ± SD	0.85 ± 0.25	0.86 ± 0.33	0.87 ± 0.35
Change, mean ± SD		0.02 ± 0.21***	0.02 ± 0.22***
eGFR, mL/min/1.73m^2			
N	3213	2379	3213
Measured value, mean ± SD	71.5 ± 20.5	70.1 ± 21.5	70.4 ± 21.2
Change, mean ± SD		−1.2 ± 13.3***	−1.1 ± 12.9***
BUN, mg/dL			
N	2785	2002	2785
Measured value, mean ± SD	16.1 ± 5.2	16.7 ± 5.5	16.8 ± 7.0
Change, mean ± SD		0.7 ± 4.8***	0.7 ± 6.1***
AST, U/L			
N	3257	2402	3257
Measured value, mean ± SD	30.3 ± 17.4	26.3 ± 12.8	26.7 ± 14.5
Change, mean ± SD		−4.0 ± 14.5***	−3.6 ± 15.3***
ALT, U/L			
N	3283	2415	3283
Measured value, mean ± SD	34.4 ± 26.5	24.0 ± 16.0	24.9 ± 17.7
Change, mean ± SD		−10.0 ± 20.4***	−9.4 ± 21.6***
γ-GT, U/L			
N	3035	2205	3035
Measured value, mean ± SD	72.7 ± 92.5	47.1 ± 74.0	48.9 ± 75.9
Change, mean ± SD		−24.1 ± 62.0***	−23.8 ± 64.6***
Total bilirubin, mg/dL			
N	1861	1259	1861
Measured value, mean ± SD	0.64 ± 0.31	0.59 ± 0.24	0.59 ± 0.25
Change, mean ± SD		−0.05 ± 0.29***	−0.05 ± 0.27***
HbA1c, NGSP %			
N	2638	1939	2638
Measured value, mean ± SD	6.8 ± 1.3	6.8 ± 1.2	6.8 ± 1.2
Change, mean ± SD		0.0 ± 0.8***	0.0 ± 0.9***
SBP, mmHg			
N	3231	2525	3231
Measured value, mean ± SD	131.6 ± 15.1	131.9 ± 13.8	132.2 ± 14.3
Change, mean ± SD		0.6 ± 15.1**	0.6 ± 15.6**
DBP, mmHg			
N	3230	2523	3230
Measured value, mean ± SD	77.5 ± 11.5	76.7 ± 10.1	77.0 ± 10.5

Change, mean ± SD	−0.6 ± 10.7**	−0.5 ± 10.9*

Wilcoxon signed-rank test was performed for changes. ***P<0.001, **P<0.01, *P<0.05

ALT alanine transaminase, *AST* aspartate aminotransferase, *BUN* blood urea nitrogen, *CPK* creatine phosphokinase, *DBP* diastolic blood pressure, *eGFR* estimated glomerular filtration rate, *γ-GT* gamma-glutamyl transferase, *HbA1c* glycated hemoglobin, *LOCF* last observation carried forward, *NGSP* National Glycohemoglobin Standardization Program, *SBP* systolic blood pressure, *sCr* serum creatinine, *SD* standard deviation

Supplementary Table S5. Changes in lipid parameters in the efficacy analysis set

	Baseline	24 months	LOCF
Mixed TG, mg/dL			
N	3462	2591	3462
Measured value, mean ± SD	380.5 ± 302.7	200.4 ± 184.2	207.3 ± 187.7
% change, mean ± SD	–	−36.1 ± 44.1	−35.2 ± 44.5
HDL-C, mg/dL			
N	3259	2411	3259
Measured value, mean ± SD	47.2 ± 12.9	51.5 ± 13.9	51.6 ± 14.1
% change, mean ± SD	–	10.9 ± 25.7	11.4 ± 25.2
TC, mg/dL			
N	2117	1465	2117
Measured value, mean ± SD	209.5 ± 48.0	192.3 ± 37.5	195.0 ± 38.4
% change, mean ± SD	–	−4.8 ± 17.7	−4.9 ± 17.7
LDL-C, mg/dL			
N	3023	2212	3023
Measured value, mean ± SD	109.2 ± 34.3	109.9 ± 30.4	111.1 ± 31.1
% change, mean ± SD	–	9.4 ± 48.3	9.3 ± 45.3
Non-HDL-C, mg/dL			
N	1734	1197	1734
Measured value, mean ± SD	154.5 ± 39.5	137.3 ± 35.9	139.4 ± 35.8
% change, mean ± SD	–	−6.9 ± 24.5	−7.0 ± 23.8

One-sample t-tests were performed for the percent changes before administration and at each measurement period. P<0.001 in all cases

HDL-C high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *LOCF* last observation carried forward, *SD* standard deviation, *TC* total cholesterol, *TG* triglyceride

Supplementary Table S6. Changes in serum triglycerides (TGs) according to use of prior medications for dyslipidemia (switched/add-on group), concomitant use of statins, and baseline TG in the efficacy analysis set

	Mixed TG (N=3462)		Fasting TG (N=1407)		Non-fasting TG (N=1907)	
	Baseline	**LOCF**	**Baseline**	**LOCF**	**Baseline**	**LOCF**
Switched group						
n	1316		481		779	
Measured value, mg/dL	349.4 ± 310.7	236.5 ± 237.9	315.2 ± 252.0	216.3 ± 270.1	368.5 ± 344.2	248.6 ± 224.0
% change	–	−20.8 ± 51.2***	–	−22.9 ± 48.4***	–	−20.7 ± 50.9***
Add-on group						
n	2146		926		1128	
Measured value, mg/dL	399.6 ± 296.1	189.4 ± 146.0	371.5 ± 282.0	173.3 ± 137.4	416.8 ± 291.3	203.8 ± 199.8
% change	–	−44.1 ± 37.1***	–	−44.5 ± 38.9***	–	−43.7 ± 37.3***
Patients with statins						
n	1099		449		612	
Measured value, mg/dL	339.4 ± 233.8	187.1 ± 200.9	323.8 ± 234.0	182.7 ± 258.3	350.4 ± 236.4	196.8 ± 161.1
% change	–	−37.3 ± 39.9***	–	−37.4 ± 42.8***	–	−35.9 ± 39.5***
Patients without statins						
n	2363		958		1295	
Measured value, mg/dL	399.7 ± 328.2	216.7 ± 180.6	365.6 ± 289.1	190.5 ± 155.5	419.1 ± 343.6	234.1 ± 230.1
% change	–	−34.3 ± 46.4***	–	−37.0 ± 43.9***	–	−33.5 ± 47.1***
Baseline TG ≥150, <400						
n	2133		898		1146	
Measured value, mg/dL	264.3 ± 66.0	173.9 ± 103.4	259.8 ± 66.6	159.1 ± 88.0	267.2 ± 65.3	183.1 ± 110.1
% change	–	−32.3 ± 38.5***	–	−37.1 ± 32.7***	–	−29.3 ± 41.9***
Baseline TG ≥400, <600						

n		654		235		396
Measured value, mg/dL	480.5 ± 56.7	237.4 ± 155.0	481.2 ± 57.1	224.0 ± 159.4	480.6 ± 57.1	244.2 ± 153.3
% change	–	−50.3 ± 31.9***	–	−53.3 ± 33.2***	–	−48.7 ± 32.4***
Baseline TG ≥600, <1000						
n		290		85		185
Measured value, mg/dL	750.4 ± 106.4	353.0 ± 386.3	755.8 ± 104.1	373.0 ± 551.8	746.7 ± 104.4	363.3 ± 305.9
% change	–	−52.7 ± 47.9***	–	−50.4 ± 65.9***	–	−51.0 ± 40.5***
Baseline TG ≥1000						
n		130		49		72
Measured value, mg/dL	1490.2 ± 613.0	438.7 ± 403.0	1422.8 ± 442.7	426.7 ± 363.9	1534.7 ± 691.4	499.4 ± 667.4
% change	–	−69.4 ± 25.8***	–	−69.4 ± 26.0***	–	−65.9 ± 38.4***

Mean ± SD are given for measured value and percent change.

Switched group; patients switched from a prior dyslipidemia medication to pemafibrate.

Add-on group; patients who received pemafibrate in addition to existing dyslipidemia medication.

Mixed TG; TG under fasting or non-fasting conditions.

***P<0.001, One-sample t-test for percent changes vs baseline.

LOCF last observation carried forward, *SD* standard deviation

Supplementary Table S7. Changes in serum low-density lipoprotein cholesterol (LDL-C) according to baseline LDL-C in the efficacy analysis set

	Baseline	LOCF
Baseline LDL-C <140		
n	2490	
Measured value, mg/dL	98.3 ± 25.8	107.1 ± 29.7
% change	–	15.2 ± 47.0***
Baseline LDL-C ≥140, <180		
n	464	
Measured value, mg/dL	154.2 ± 10.5	128.5 ± 30.2
% change	–	−16.4 ± 19.8***
Baseline LDL-C ≥180, <200		
n	45	
Measured value, mg/dL	188.2 ± 5.9	139.7 ± 31.9
% change	–	−25.7 ± 16.9***
Baseline LDL-C ≥200		
n	24	
Measured value, mg/dL	223.5 ± 25.5	135.6 ± 35.4
% change	–	−38.1 ± 18.1***

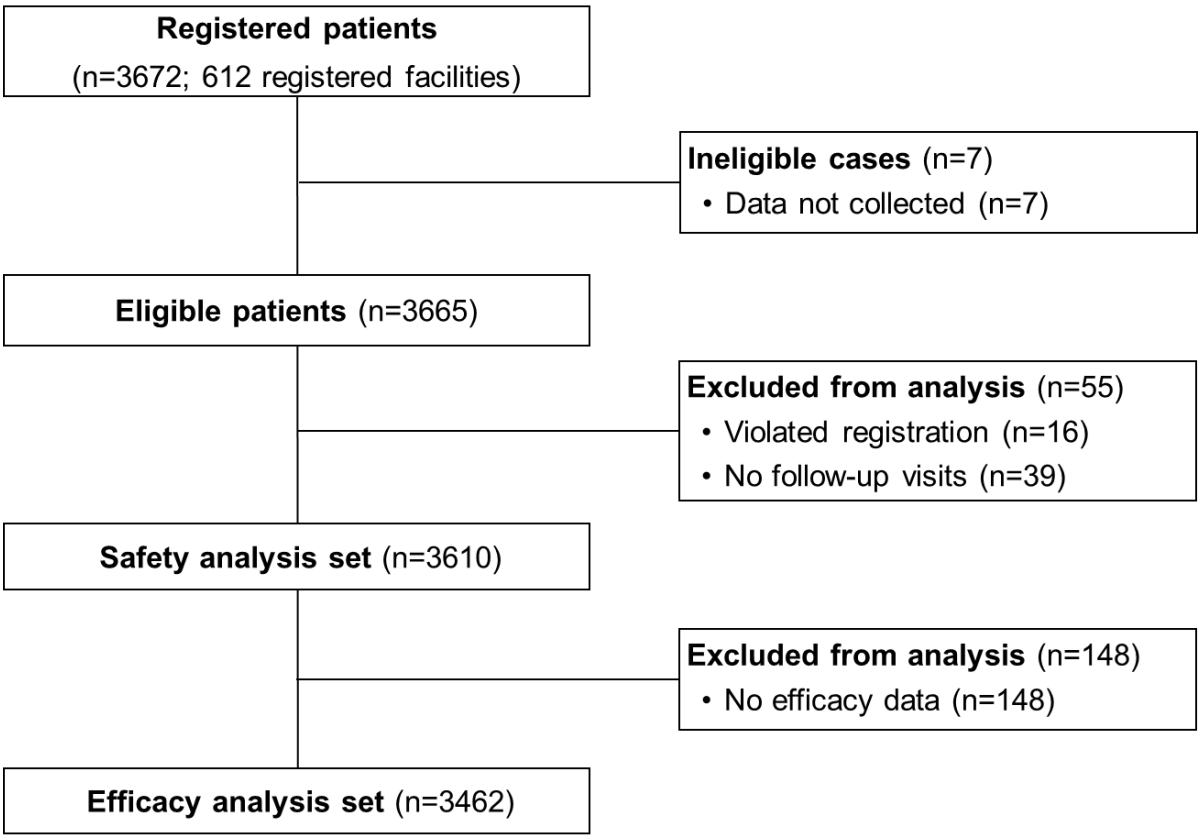
Mean ± SD are given for measured value and percent change.

*** P<0.001, one-sample t-tests were performed for percent changes vs baseline.

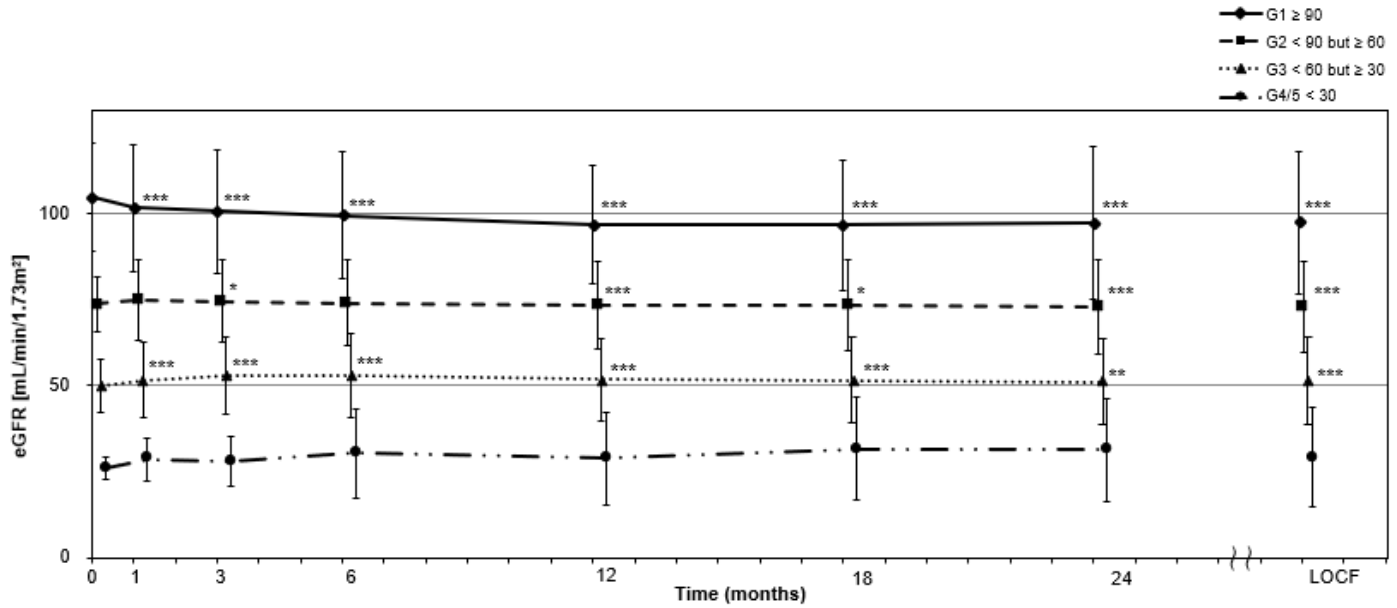
LOCF last observation carried forward, *SD* standard deviation

Supplementary figures

Supplementary Fig. S1 Patient disposition.



Supplementary Fig. S2 Estimated glomerular filtration rate (eGFR) transition according to baseline eGFR. Wilcoxon signed-rank tests were performed for the percent changes before administration and at each measurement period. *LOCF* last observation carried forward.



Observation period, month	Baseline	1	3	6	12	18	24	LOCF
G1, Mean (n)	105 (502)	102 (290)	101 (374)	100 (404)	97 (410)	97 (370)	97 (373)	97 (502)
G2, Mean (n)	74 (1787)	75 (997)	75 (1253)	74 (1455)	73 (1483)	73 (1307)	73 (1310)	73 (1787)
G3, Mean (n)	50 (888)	52 (515)	53 (637)	53 (759)	52 (732)	52 (663)	51 (672)	52 (888)
G4/5, Mean (n)	26 (36)	29 (22)	28 (26)	30 (33)	29 (29)	32 (25)	31 (24)	29 (36)

*** P<0.001, ** P<0.01, * P<0.05