Summary Report of Benefit-Risk Assessment

PARMODIA FILM-COATED TABLETS 0.1MG

NEW DRUG APPLICATION

Active Ingredient(s)	Pemafibrate
Product Registrant	DKSH Singapore Pte Ltd
Product Registration Number	SIN16492P
Application Route	Abridged evaluation
Date of Approval	18 May 2022

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A INTRODUCTION

Parmodia is indicated as adjunctive therapy to diet or other non-pharmacological treatment (e.g., exercise) to reduce triglyceride (TG) and to increase high density lipoprotein-cholesterol (HDL-C) in patients with dyslipidaemia characterised by high TG ≥150mg/dl, particularly when there is evidence of associated risk such as hypertension and smoking.

The active substance, pemafibrate, modulates peroxisome proliferator activated receptor alpha which is involved in the expression of genes involved in fatty acid beta-oxidation, leading to decreased plasma TG concentration, decreased TG-rich lipoprotein, decreased apolipoprotein (Apo) C-3, and increased HDL-C.

Parmodia is available as film-coated tablets containing 0.1mg of pemafibrate. Other ingredients in the tablet core are lactose monohydrate, croscarmellose sodium, microcrystalline cellulose, hydroxypropyl cellulose and magnesium stearate. Ingredients in the film coating include hypromellose, triethyl citrate, light anhydrous silicic acid, titanium oxide and carnauba wax.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, pemafibrate, is manufactured at API Corporation Yoshitomi Plant, Fukuoka, Japan. The drug product, Parmodia, is manufactured at Kowa Company Ltd., Aichi, Japan.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates, and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6A, and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods are validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented was adequate to support storage at 25°C with a re-test period of 60 months. The drug substance is packaged in polyethylene bags in a fibre drum.

Drug product:

The tablet is manufactured using a wet granulation approach, followed by film-coating. The process is considered a standard process.

The manufacturing site involved is compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A, and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods were validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and dissolution testing is presented.

The stability data submitted was adequate to support the approved shelf-life of 36 months when stored at or below 30 ºC. The container closure system is a polyvinyl chloride/aluminium blister in an aluminium-laminated bag.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of Parmodia as adjunctive therapy to diet or other non-pharmacological treatment (e.g., exercise) to reduce TG and to increase HDL-C in patients with dyslipidaemia characterised by high TG ≥150mg/dl, was based on six pivotal studies (K-877-09, K-877-17, K-877-16, K-877-14, K-877-13, and K-877-15). Four of the studies investigated Parmodia as monotherapy while two studies investigated the drug in combination with other anti-hyperlipidaemic drugs.

Monotherapy studies

Study K-877-09
Study K-877-09 was a Phase III, multi-centre, placebo- and active-controlled, randomised, double-blind, parallel-group study in patients with dyslipidaemia (high TG and low HDL-C levels) to demonstrate the superiority of the fasting serum TG reduction with the administration of pemafibrate at 0.1, 0.2, and 0.4 mg/day for 12 weeks compared with placebo. The study also assessed non-inferiority of the fasting serum TG reduction with the administration of pemafibrate at 0.2 and 0.4 mg/day compared with fenofibrate (FF) capsule 200 mg/day.

Patients were randomly allocated to the placebo, pemafibrate 0.1, 0.2, and 0.4 mg/day, and FF 100 and 200 mg/day groups at a ratio of 1:1:3:2:2:3.

The primary efficacy endpoint was the percentage changes in the fasting serum TG at Weeks 8, 10, and 12 from baseline. The key secondary efficacy endpoints were changes in the HDL-C and non-HDL-C levels from baseline. The number of subjects required was 29 in the placebo group, 29 in the pemafibrate 0.1 mg/day group, 97 in the pemafibrate 0.2 mg/day group, 68 in the pemafibrate 0.4 mg/day group, 97 in the FF 200 mg/day group and 68 in the FF 100 mg/day group to obtain a power of 90% or higher for the primary endpoint analysis.

A total of 526 patients were randomised: 43 patients in the placebo group, 45, 128 and 85 patients in the pemafibrate 0.1mg, 0.2mg and 0.4mg groups, respectively as well as 85 and 140 patients in the FF 100mg and 200mg groups, respectively. The mean age was 50.3 ± 10.2 years (mean ± standard deviation [SD]), body weight was 76.77 ± 13.21 kg, BMI was 26.73 ± 3.68 kg/m^2, TG was 355.6 ± 138.3 mg/dL, HDL-C was 39.2 ± 5.5 mg/dL. The percentage of patients aged 65 years and above was 9.3%, and the percentage of males was 91.2%. In terms of patients with risk factors, 29.3% of the patients had hypertension and 63% of the patients were current or previous smokers.

When compared to placebo, pemafibrate demonstrated a statistically significantly greater reduction of TG from baseline across the dose groups. The difference in the percentage change in TG from baseline versus placebo were -43.567% (95%CI: -54.011, -33.124, p≤0.01) in the pemafibrate 0.1mg/day group, -43.991% (95%CI: -55.455, -32.528, p≤0.01) in the 0.2mg/day group and -49.127% (95%CI: -60.922, -37.333, p≤0.01) in the 0.4mg/day group.

Pemafibrate also demonstrated non-inferiority to FF 200mg/day in terms of percentage change in TG from baseline based on the pre-specified non-inferiority margin of 10%. The difference in the percentage change in TG from baseline versus FF 200mg/day were 4.844% (95%CI: 0.388, 9.299) in the pemafibrate 0.2mg/day group and -0.302% (95%CI: -5.300, 4.696) in the 0.4mg/day group.

For the secondary endpoints, pemafibrate resulted in numerically higher HDL-C levels compared to placebo. The HDL-C levels were 48.6±9.0 mg/dL in the 0.1mg/day group, 49.6±9.4 mg/dL in the 0.2mg/day group and 47.0±9.7 mg/dL in the 0.4mg/day group, and 39.9±5.7 mg/dL in the placebo group. Pemafibrate also resulted in numerically lower non-HDL-C compared to placebo. The non-HDL-C levels were 162.3±33.3 mg/dL in the 0.1mg/day group, 174.8±38.1 mg/dL in the 0.2mg/day group and 169.4±35.7 mg/dL in the 0.4mg/dL group, and 181.0±29.8 mg/dL in the placebo group.

When compared with FF, the HDL-C levels in the pemafibrate groups (range: 47.0 to 49.6 mg/dL) were similar to that in the FF groups (range: 47.0 to 52.0 mg/dL). The non-HDL-C levels in the pemafibrate groups (range: 162.3 to 174.8 mg/dL) were also similar to that in the FF groups (range: 159.9 to 179.6 mg/dL).

Summary of key efficacy results of pemafibrate versus placebo (Study K-877-09)

Treatment group (N)	**Baseline fasting serum TG) (mg/dL)**	**Percent change in fasting serum TG**	
		Percent change from baseline) (%) (95%CI)	**Difference from placebo in percent change) (%) (95%CI)**
Placebo (N=43)	346.1±130.9	-2.775 [-11.783, 6.233]	-
PARMODIA 0.1mg/day (N=45)	332.4 ± 106.1	–46.342 [-51.785,-40.899]	-43.567 [-54.011,-33.124]
PARMODIA 0.2 mg/day (N=128)	367.2±153.6	-46.766 [-49.985, -43.547]	-43.991** [-55.455, -32.528]
PARMODIA 0.4 mg/day (N=84)	362.6±158.5	-51.902 [-55.841, -47.963]	-49.127** [-60.922, -37.333]

***: p ≤0.01*

Summary of key efficacy results of pemafibrate versus FF (Study K877-09)

Treatment group (N)	**Baseline fasting serum TG) (mg/dL)**	**Percent change in fasting serum TG**	
		Percent change from	**Difference from**

		baseline) (%) (95%CI)	FF 200 mg/day in percent change (%) (95%CI)
PARMODIA 0.2 mg/day (N=128)	367.2±153.6	-46.690 [-49.904, -43.477]	4.844 [0.388, 9.299]
PARMODIA 0.4 mg/day (N=84)	362.6±158.5	-51.836 [-55.768, -47.903]	-0.302 [-5.300, 4.696]
Micronized FF 100 mg/day (N=85)	362.0±135.1	-38.261 [-42.230, -34.291]	-
Micronized FF 200mg/day (N=140)	347.3±123.8	-51.534 [-54.616, -48.452]	-

Study K-877-17
Study K-877-17 was a Phase III, double-blind, FF-controlled, randomised, parallel-group study conducted at 10 sites in Japan to investigate the efficacy and safety of pemafibrate in Japanese patients with dyslipidaemia characterized by high TG and low HDL-C levels at baseline. Patients were randomised equally (1:1:1) to receive pemafibrate at 0.2 mg/day or 0.4 mg/day or FF tablet 106.6 mg/day (correspond to FF capsule 134mg/day) during the 24-week treatment period.

The primary efficacy endpoint was the percentage change in TG from baseline to Weeks 8, 12, 16, 20 and 24. The key secondary efficacy endpoints were changes in the HDL-C and non-HDL-C levels from baseline. 66 patients per group were required to provide 94.4% power to evaluate the superiority of pemafibrate 0.4mg/day over FF, assuming that the TG lowering rates of pemafibrate 0.2 mg/day, and 0.4 mg/day were -42% and -50%, respectively, and the TG lowering rate of FF 106.6 mg/day was -39%.

A total of 225 patients were randomised: 75 in the pemafibrate 0.2 mg/day group, 74 in the pemafibrate 0.4 mg/day group, and 76 in the FF 106.6 mg/day group. The mean age was 53.2 ± 10.9 years, body weight was 74.88 ± 14.98 kg, and BMI was 26.33 ± 3.79 kg/m^2. The mean baseline levels of fasting serum TG were 237.1 ± 62.4 mg/dL and 41.7 ± 5.0 mg/dL for HDL-C. The proportion of patients aged 65 years or older was 17.5% and the proportion of male patients was 81.2%. In terms of patients with risk factors, 27.4% of patients had hypertension and 69.1% of patients were current or previous smokers.

When compared with FF, pemafibrate demonstrated a statistically significantly greater reduction of TG from baseline across the dose groups. The difference in the percentage change in TG from baseline versus FF 106.6 mg/day were -6.541% (95%CI: -12.004, -1.078, $p<0.05$) in the 0.2mg/day group and -6.166% (95%CI: -11.576, -0.755, $p<0.05$) in the 0.4mg/day group.

For the secondary endpoints, numerically, similar HDL-C levels were observed between pemafibrate and FF. The HDL-C levels were 50.6±9.3 mg/dL in the 0.2mg/day group, 49.4±8.6 mg/dL in the 0.4mg/day group and 48.8±7.9 mg/dL in the FF 106.6mg/day group. Similar non-HDL-C levels were also observed between pemafibrate and FF. The non-HDL-C levels were 167.7±27.6 mg/dL in the 0.2mg/day group, 170.2±36.0 mg/dL in the 0.4mg/day group, and 163.3±33.6 mg/dL in the FF 106.6mg/day group.

Summary of key efficacy results (Study K-877-17)

Treatment group (N)	Baseline fasting serum TG) (mg/dL)	Percent change in fasting serum TG	
		Percent change from baseline) (%) (95%CI)	Difference from FF 106.6mg/day in percent change (%) (95%CI)
PARMODIA 0.2 mg/day (N=73)	242.4 ± 55.3	-46.226 [-50.122,-42.329]	-6.541* [-12.004, -1.078]
PARMODIA 0.4 mg/day (N=74)	233.3 ± 60.8	-45.850 [-49.678,-42.023]	–6.166* [–11.576, –0.755]
FF 106.6mg/day (N=76)	235.6 ± 71.7	-39.685 [-43.511,-35.858]	-

**: p <0.05*

Study K-877-16

Study K-877-16 was a Phase III randomised, double-blind, parallel, placebo-controlled study conducted at 34 sites in Japan to investigate the efficacy and safety of pemafibrate in Japanese patients with hypertriglyceridemia and type 2 diabetes mellitus.

Pemafibrate was administered for a total of 52 weeks after a screening period of up to 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, patients were randomised equally (1:1:1) to receive placebo or pemafibrate 0.2 mg/day or 0.4 mg/day. During Period 2, patients who had received pemafibrate 0.2 mg/day or 0.4 mg/day in Period 1 continued on pemafibrate at the same dose as that in Period 1, and patients assigned to the placebo group in Period 1 received pemafibrate 0.2 mg/day.

The primary efficacy endpoint was the percent change from baseline in fasting serum TG at the final visit in Period 1. The key secondary efficacy endpoints were changes from baseline in lipid-related and glucose-related variables at the last visit in Period 1 and fasting serum TG in treatment period (Period 1 and 2 combined). For statistical testing, 21 patients per group were required to provide at least 90% power, assuming that the difference of pemafibrate from placebo in terms of the percent change from baseline in fasting serum TG at the last visit of Period 1, would be -46%.

In Period 1, a total of 167 patients were randomised: 57 in the placebo group, 54 in the pemafibrate 0.2 mg/day group and 56 in the pemafibrate 0.4 mg/day group. There were 160 patients completed Period 1 and entered Period 2: 55 in the placebo group, 54 in the pemafibrate 0.2 mg/day group, 51 in the pemafibrate 0.4 mg/day group. The mean age was 60.5 ± 10.5 years, body weight was 70.61 ± 13.29 kg and BMI was 25.91 ± 3.50 kg/m^2. The baseline values were 262.1 ± 104.1 mg/dL for TG and 48.0 ± 18.0 mg/dL for HDL-C. The proportion of patients aged 65 years or older was 34.9%, and the proportion of male patients was 72.9%. The mean HbA1c was 6.96 ± 0.44%. 92 patients (55.4%) were naive for anti-diabetic drugs and 120 patients (72.3%) had metabolic syndrome. In terms of patients with risk factors, 61.4% of patients had hypertension and 62% of patients were current or previous smokers.

In Period 1, pemafibrate demonstrated a statistically significantly greater reduction in TG from baseline compared to placebo. The difference in the percentage change in TG from baseline versus placebo were -33.534% (95%CI: -45.154, -21.914, p≤0.01) in the 0.2mg/day group and -34.280% (95%CI: -45.723, -22.836, p≤0.01) in the 0.4mg/day group. In Period 2, the effect of reduction of TG from baseline was maintained in patients who remained on pemafibrate at the

end of 52 weeks. In addition, patients who were previously on placebo and placed on pemafibrate 0.2 mg/day demonstrated a similar magnitude of reduction in TG from baseline (-46.835%), indicating that the drug is efficacious.

For the secondary endpoints, pemafibrate resulted in a statistically significantly greater increase in HDL-C from baseline compared to placebo. The difference in the percentage change in HDL-C from baseline versus placebo ranged between 5.850% ($p \leq 0.05$) and 12.238% ($p \leq 0.01$). Pemafibrate 0.2mg/day also resulted in a statistically significantly greater reduction in non-HDL-C from baseline compared to placebo. The difference in the percentage change in non-HCL-C from baseline versus placebo ranged between -4.855% ($p = 0.106$) and -10.654% ($p \leq 0.01$). However, pemafibrate did not cause significant changes serum glucose and insulin levels.

Summary of key efficacy results (Study K-877-16)

Treatment group (N)	**Baseline fasting serum TG (mg/dL)**	**Percent change in fasting serum TG**		
		Timepoint	**Percent change from baseline (%) (95%CI)**	**Difference from placebo in percent change (%) (95%CI)**
Placebo (N=57)	284.3 ± 117.6	Week 24	-10.814 [-17.933, -3.694]	-
		Week 52	-46.835 [-52.967, -40.704]	-
PARMODIA 0.2mg/day (N=54)	240.3 ± 93.5	Week 24	-44.347 [-51.656, -37.038]	-33.534** [-45.154,-21.914]
		Week 52	-43.629 [-49.924, -37.334]	-
PARMODIA 0.4mg/day (N=55)	260.4 ± 95.9	Week 24	-45.093 [-52.283, -37.904]	-34.280** [-45.723,-22.836]
		Week 52	-46.552 [-52.744, -40.360]	-

***: p ≤0.01*

Study K-877-14

Study K-877-14 was an open-label, uncontrolled study conducted at 32 sites in Japan to evaluate the long-term safety and efficacy of pemafibrate in Japanese patients with hypertriglyceridemia.

The study drug was administered for 52 weeks. During the treatment period over 24 weeks, patients received pemafibrate at 0.2 mg/day and a dose increase to pemafibrate 0.4 mg/day was allowed in patients with inadequate response to the initial treatment (TG ≥150 mg/dL) at Week ≥12. Treatment was continued till Week 52.

The primary efficacy endpoint was the percent change from baseline in fasting serum TG at Week 52. The key secondary efficacy endpoints were percent change from baseline in other lipid related variables.

A total of 189 patients were included in the analysis. The mean age was 57.8 ± 10.5 years, body weight was 71.76 ± 13.86 kg, and BMI was 26.02 ± 3.45 kg/m^2 in all patients treated with

pemafibrate. The mean TG was 249.7 ± 77.5 mg/dL, and the mean HDL-C was 45.7 ± 10.6 mg/dL. The proportion of patients aged 65 years or older was 30.2% and the proportion of males was 77.8%. In terms of patients with risk factors, 53.4% of patients had hypertension and 63.5% of patients were current or previous smokers.

The percentage change from baseline in fasting serum TG at Week 24 was -48.77% ± 20.47 with a statistically significant decrease from baseline ($p < 0.001$). The percentage change from baseline in fasting serum TG at Week 52 was -45.93% ± 21.84 with a statistically significant decrease from baseline ($p < 0.001$), demonstrating that the TG lowering effect of pemafibrate was sustained. There were 16 out of 189 patients (8.5%) who required dose escalation to 0.4 mg/day during the first 24 weeks and 29 out of 189 patients (15.3%) who required dose escalation to 0.4mg/day over 52 weeks. While the proportion of patients who required a dose increase was small, the data was considered reasonable to support dose escalation to 0.4mg/day in patients with inadequate response to the lower dose at Week ≥12. For the secondary endpoints, pemafibrate resulted in numerical increase in HDL-C (22.28%) and reduction of non-HDL-C (-7.22%) from baseline at Week 24 and the effects were maintained at Week 52.

Combination studies

Study K-877-13
Study K-877-13 was a Phase III randomised, double-blind, parallel-group study conducted at 26 sites in Japan to investigate the efficacy and safety of pemafibrate in combination with pitavastatin in patients with dyslipidaemia characterized by high TG and high non-HDL-C levels.

Patients received pitavastatin 2 mg/day during the run-in and screening periods of ≤16 weeks, followed by placebo or twice daily pemafibrate as an add-on therapy at 0.1, 0.2, or 0.4 mg/day in 1:1:1:1 ratio during the 12-week treatment period. The regimen of pitavastatin remained the same as that during the screening period.

The primary efficacy endpoint was the percent change in the fasting serum TG level at Week 12 of the treatment period from the baseline of the treatment period. The key secondary efficacy endpoints were percentage change in the HDL-C and non-HDL-C levels from the baseline at Week 12 of the treatment period. As the percent change in the TG level was expected to be half under concomitant administration of pitavastatin and pemafibrate compared with that under the administration of pitavastatin alone, the percent change in the TG level was assumed to be 0 for the placebo group, -22% for the pemafibrate 0.1 mg/day group, -24% for the pemafibrate 0.2 mg/day group, and -26% for the pemafibrate 0.4 mg/day group, and the SD was assumed to be 30% in all groups. The superiority of pemafibrate was evaluated at a significance level of 5% on a two-tailed test, and the number of subjects per group to obtain a power of 80% or higher was determined to be 38. The planned number of subjects per group was set at 42 after incorporating a termination rate of 10%.

A total of 188 patients were randomised: 46 in the placebo group, 45 in the pemafibrate 0.1 mg/day group, 49 in the pemafibrate 0.2 mg/day group and 48 in the pemafibrate 0.4 mg/day group. The mean age was 53.4 ± 10.1 years, weight was 75.98 ± 13.47 kg, BMI was 27.27 ± 3.81 kg/m^2, TG was 362.5 ± 145.3 mg/dL, HDL-C was 46.2 ± 10.2 mg/dL. In terms of patients with risk factors, 54.1% of patients had hypertension and 63.5% of patients were current or previous smokers.

Compared to pitavastatin alone, pemafibrate plus pitavastatin resulted in a statistically significantly greater reduction in TG from baseline ($p \leq 0.01$). The difference in the percentage change in TG from baseline ranged between -46.062% and -53.353% in the pemafibrate plus pitavastatin groups compared to -6.898% in the pitavastatin alone group.

For the secondary endpoints, pemafibrate plus pitavastatin resulted in numerically greater increase from baseline in HDL-C compared to pitavastain alone. The percentage increase in HDL-C levels from baseline ranged between 15.15% and 22.71% in the pemafibrate plus pitavastatin groups compared to 2.06% in the pitavastatin alone group. In addition, pemafibrate plus pitavasatin resulted in numerically greater reduction from baseline in non-HDL-C compared to pitavastatin alone. The percentage reduction from baseline in non-HDL-C levels ranged between 11.66% and 13.99% compared to 5.38% in the pitavasatin alone group.

Summary of key efficacy results (Study K-877-13)

Fasting serum TG	**Placebo (N=41)**	**Pemafibrate**		
		0.1 mg/day (N=42)	**0.2 mg/day (N=45)**	**0.4 mg/day (N=42)**
Baseline (mg/dl)	382.0 ± 176.0	347.1 ± 122.9	353.3 ± 160.0	368.6 ± 116.1
Week 12 (mg/dl)	339.9 ± 180.1	189.5 ± 111.3	154.5 ± 76.1	168.2 ± 89.6
% change (95%CI)	-6.898 [-14.725,0.928]	-46.062 [-53.789,-38.336]**	-53.353 [-60.811,-45.895]**	-52.003 [-59.720,-44.286]**

***: p ≤0.01*

Study K-877-15

Study K-877-15 was a Phase III randomised, double-blind, parallel-group study conducted at 53 sites in Japan to investigate the efficacy and safety of pemafibrate in combination with statins (atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin) in Japanese patients with hypertriglyceridemia.

The study drug was administered as an add-on therapy to baseline statin treatments for a total of 24 weeks, over two periods of 12 weeks each. The patients were randomised in 2:3:3 ratio to the placebo group, pemafibrate 0.2 mg group and pemafibrate 0.2/0.4 mg group. Patients assigned to the placebo group and pemafibrate 0.2 mg group were to receive placebo and pemafibrate 0.2 mg/day, respectively, throughout the treatment period (Periods 1 and 2). Patients assigned to the pemafibrate 0.2/0.4 mg (dose-increase) group received pemafibrate 0.2 mg/day in Period 1 (12 weeks), and patients with TG ≥150 mg/dL at Week 8 of Period 1 received an increased dose of pemafibrate 0.4 mg/day in Period 2 (12 weeks). The increased dose was continued in Period 2, irrespective of TG levels at the subsequent visits.

The primary efficacy endpoint was the percent change in TG from baseline to end of treatment. The key secondary efficacy endpoints were percent change in the fasting serum HDL-C and non-HDL-C levels from the baseline at the end of the treatment period. The sample size was planned to be 400 based on considerations for adequate safety evaluation.

A total of 423 patients were randomised: 108 in the placebo group, 150 in the pemafibrate 0.2 mg/day group, 165 in the pemafibrate 0.2/0.4 mg group). The mean age was 57.2 ± 11.3 years, body weight was 74.60 ± 14.22 kg, BMI was 27.23 ± 3.97 kg/m^2, TG was 328.8 ± 133.1 mg/dL, HDL-C was 45.6 ± 10.0 mg/dL. In terms of patients with risk factors, 64.5% of patients had hypertension and 71.4% of patients were current or previous smokers.

Compared to statin alone, pemafibrate plus statin resulted in a statistically significantly greater reduction in TG from baseline (p≤0.01). The percentage reduction in TG from baseline ranged between 46.821% and 50.848% in the pemafibrate plus statin groups compared to 0.841% in the placebo group.

For the secondary endpoints, pemafibrate plus statin resulted in numerically higher HDL-C levels compared to statin alone. The HDL-C levels ranged between 52.0 and 54.8 mg/dL in the pemafibrate plus statin groups compared to 46.8 mg/dL in the statin alone group. In addition, pemafibrate plus statin resulted in numerically lower non-HDL-C levels compared to statin alone. The levels of non-HDL-C ranged between 137.7 and 139.3 mg/dL in the pemafibrate plus statin group compared to 150.5 mg/dL in the statin alone group.

Summary of key efficacy results (K-877-15)

Fasting serum TG	**Placebo N=108**	**Pemafibrate 0.2 mg/day N=150**	**Pemafibrate 0.2/0.4 mg/day N=165**
Baseline (mg/dL)	329.0 ± 135.0	333.3 ± 132.2	324.5 ± 133.4
End of treatment (mg/dL)	307.7 ± 154.1	176.6 ± 124.9	156.8 ± 108.5
% change (95%CI)	-0.841 [-6.810,5.128]	-46.821 [-51.888,-41.755]**	-50.848 [-55.678,-46.018]**

***: p ≤0.01*

Overall, the studies demonstrated that pemafibrate when used as a monotherapy or in combination with statins resulted in statistically significantly greater decrease in fasting TG from baseline compared to placebo or statin alone. Pemafibrate also resulted in numerically greater increase in HDL-C and reduction of non-HDL-C from baseline compared to placebo or statin alone. The magnitude of change in the lipid levels was similar between pemafibrate and FF. While the incremental benefit was modest with increasing doses, pemafibrate 0.4 mg/day showed numerically greater reduction in TG from baseline compared to the lower doses. In addition, Study K-877-14 showed that a small of proportion of patients with inadequate response to the initial treatment of pemafibrate 0.2mg/day at Week ≥12 (i.e., TG remained ≥150 mg/dL) could benefit from an increase in dosage to pemafibrate 0.4 mg/day.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of Parmodia was based on safety data in 3,079 patients with dyslipidaemia pooled from the pivotal and Phase II and III studies.

Overview of safety profile

AE	**Placebo (N=298)**	**All pemafibrate groups (24 weeks) (N=1,363)**	**All pemafibrate groups (52 weeks) (N=1,418)**
Any AE	164 (55.0%)	704 (51.7%)	795 (56.1%)
Severity			
Mild	135 (45.3%)	540 (39.6%)	604 (42.6%)
Moderate	16 (5.4%)	79 (5.8%)	107(7.5%)
Severe	1 (0.3%)	11 (0.8%)	14 (1.0%)
SAE	5 (1.7%)	38 (2.8%)	51 (3.6%)
Discontinuations due to AE	2 (0.7%)	41 (3.0%)	51 (3.6%)
Deaths due to AE	0	1 (0.1%)	2 (0.1%)

More than 50% of the patients in the pemafibrate and the placebo groups experienced an adverse event (AE). Common AEs included nasopharyngitis, diabetes mellitus, upper respiratory tract inflammation and increased blood creatine phosphokinase levels. The majority of the AEs were mild in severity and the incidence of AEs was similar between pemafibrate 0.2mg/day and 0.4mg/day groups and comparable to the FF groups. The incidence of AEs was also similar when pemafibrate was administered as monotherapy or in combination with statins.

The most reported treatment-related AEs included cholelithiasis (1.4%) and blood creatine phosphokinase increased (0.8%) which are known AEs for the fibrate class of drugs. The incidences of SAE (including acute myocardial infarct and gastroesophageal reflux disease) and discontinuations due to AEs were low and comparable to that observed with FF. All the SAEs were also considered unrelated to the study drugs except for one case each of abdominal wall haematoma, bile duct stone, diabetes mellitus, cerebral infarction and calculus ureteric. In terms of AE of special interest, there were no significant differences in the incidence of rhabdomyolysis standardised MedDRA query (SMQ) AEs between the pemafibrate (up to 3.2%) and placebo group (4.4%) at Week 12. In addition, no dose relationship was observed for the AEs in the pemafibrate group. With regard to hepatotoxicity, the incidence of drug related hepatic disorders (SMQ) abnormal liver function test values were lower in the pemafibrate groups (range: 0.4% to 2.2%) compared to the FF groups (range: 6.6% to 15.7%). There was one death in the pemafibrate 0.2 mg/day group in Study K-877-14 due to acute myocardial infarction and one death in the pemafibrate 0.4 mg/day group in Study K-877-09 due to pulmonary embolism but the causal relationship of the deaths with the study drug was excluded by the investigator.

Overall, pemafibrate was generally well tolerated and the incidence of AEs was comparable to FF. The incidence of SAEs, discontinuations due to AEs were also low and there was no dose relationship for the AEs.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Fibrates are a class of drugs with established TG-lowering effects, and they are used first line to treat dyslipidaemia characterized by high TG level and normal LDL-C level. Pemafibrate is a selective PPAR alpha modulator which could be an alternative to the currently available fibrates.

In the monotherapy studies, pemafibrate 0.1, 0.2 and 0.4 mg/day were superior to placebo as well as fenofibrate capsule 100mg/day and tablet 106.6mg/day; and pemafibrate 0.2 and 0.4 mg/day were non-inferior to fenofibrate capsule 200mg/day in terms of TG reductions. In the combination studies, pemafibrate 0.1, 0.2 or 0.4 mg/day added on to statins resulted in statistically significantly greater decrease from baseline in fasting TG compared to statins alone. In terms of secondary endpoints, pemafibrate resulted in numerically greater increase in HDL-C and reduction of non-HDL-C from baseline compared to placebo. The magnitude of change in the lipid levels was similar between pemafibrate and fenofibrate.

There was no statistically significant dose-response between pemafibrate 0.2mg/day and 0.4mg/day groups in terms of reduction in TG from baseline. Nonetheless, it was demonstrated

that a small proportion of patients could benefit from an increase in dosage to pemafibrate 0.4 mg/day if they had inadequate response to the lower dose at Week ≥12. In addition, the safety profile of the higher dose group was comparable to the lower dose group. Hence, the maximum proposed dose of 0.4mg/day was considered acceptable.

In terms of safety, pemafibrate was generally well tolerated with lower or similar AE incidence compared to fenofibrate. In addition, no dose relationship was observed for the AEs in the pemafibrate groups. With regard to SAEs and discontinuations due to AEs, the incidences were also low with pemafibrate.

Overall, the benefit risk profile of Parmoidia for use as adjunctive therapy to diet or other non-pharmacological treatment to reduce TG and to increase HDL-C in patients with dyslipidaemia was considered favourable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Parmoidia as adjunctive therapy to diet or other non-pharmacological treatment (e.g. exercise) to reduce TG and to increase HDL-C in patients with dyslipidaemia characterised by high TG ≥150mg/dl, was favourable and approval of the product registration was granted on 18 May 2022.

APPROVED PACKAGE INSERT AT REGISTRATION

1. NAME OF THE MEDICINAL PRODUCT

PARMODIA film-coated tablets 0.1 mg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 0.1 mg of pemafibrate.
For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
White round film-coated tablets debossed 'Kowa 217' on one face and a score line on the reverse.
The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PARMODIA is indicated as adjunctive therapy to diet or other nonpharmacological treatment (e.g. exercise) to reduce TG and to increase HDL-C in patients with dyslipidemia characterised by high TG ≥150 mg/dL, particularly when there is evidence of associated risk such as hypertension and smoking.

4.2 Posology and method of administration

Patients should be on a lipid-lowering diet before the initiation of PARMODIA, and should continue dietary control during treatment. Serum lipid levels should be monitored periodically. If an adequate response has not been achieved, complementary or different therapeutic measures should be considered.

Posology
Adult
The usual adult dose is 0.1 mg twice daily. The dose may be individualized according to the patient's age and symptoms. The maximum dose is 0.2 mg twice daily.

Elderly
No dose adjustment is necessary.

Since elderly patients often have reduced physiological function, PARMODIA should be carefully administered with close monitoring for signs of adverse reactions and clinical status of the patient.

Pediatric population
The safety of PARMODIA in low birth weight infants, newborns, infants, and children has not been established. No data are available.

Patients with renal impairment
PARMODIA should be used with caution in patients with renal impairment defined as estimated glomerular filtration rate (eGFR) 30 to 59 mL/min/1.73 m^2 or creatinine clearance 30 to 59 mL/min. A lower starting dose or prolonged dosing intervals should be considered (see section 4.8).

PARMODIA is contraindicated in patients with renal impairment defined as eGFR <30 mL/min/1.73 m^2 or creatinine clearance <30 mL/min (see section 4.3 and section 4.8).

Patients with hepatic impairment
PARMODIA should be used with caution in patients with hepatic disorder (Child-Pugh grade A cirrhosis, etc.) or a history of hepatic disorder. Dose reduction should be considered as necessary (see section 5.2).

PARMODIA is contraindicated in patients with severe hepatic disorder, Child-Pugh grade B or C cirrhosis, or biliary obstruction (see section 4.3 and section 5.2).

Method of administration
PARMODIA should be taken orally twice daily in the morning and evening. PARMODIA can be taken without regard to meals.

4.3 Contraindications

PARMODIA is contraindicated:

- in patients with known hypersensitivity to pemafibrate or to any of the excipients
- in patients with severe hepatic disorder, Child-Pugh grade B or C cirrhosis, or biliary obstruction
- in patients with renal impairment defined as eGFR <30 mL/min/1.73 m^2 or creatinine clearance <30 mL/min
- in patients with cholelithiasis
- in pregnant or possibly pregnant women
- in patients receiving concomitant cyclosporine or rifampicin

4.4 Special warnings and precautions for use

Muscle effects
Muscle toxicity, including very rare cases of rhabdomyolysis (with and without acute renal failure), has been reported with other lipid-lowering agents.

Muscle toxicity should be suspected in patients presenting diffuse myalgia, myositis, muscle cramps and weakness and/or marked increases in CK (>5 times the upper limit of normal range [ULN]). In such cases, treatment with PARMODIA should be stopped.

An increased risk of rhabdomyolysis has been reported with other fibrates when co-administered with an HMG-CoA reductase inhibitor (statin), especially in cases of pre-existing muscular disease. PARMODIA should be used with caution in patients receiving statins.

Liver effects
In common with other lipid-lowering agents, PARMODIA should be used with caution in patients with hepatic disorder or those with a history of hepatic disorder. Abnormal liver function tests may occur. The plasma concentration of PARMODIA may increase in patients with hepatic disorder (Child-Pugh grade A cirrhosis, etc.) (see section 5.2). Liver function should be monitored periodically during treatment.

Renal effects
In patients with renal impairment, renal function should be monitored periodically during treatment with PARMODIA. If eGFR is <30 mL/min/1.73 m^2 or creatinine clearance is <30 mL/min, PARMODIA should be discontinued. If eGFR is 30 to 59 mL/min/1.73 m^2 or creatinine clearance is 30 to 59 mL/min, dose reduction or prolonged dosing intervals should be considered.

Cholelithiasis
Since cholelithiasis has been reported, PARMODIA should be used with caution in patients with a history of cholelithiasis.

Pediatric population
The safety of PARMODIA in low birth weight infants, newborns, infants, and children has not been established. No data are available.

4.5 Interaction with other medicinal products and other forms of interaction

PARMODIA is metabolized mainly by cytochrome P450 (CYP) 2C8, CYP2C9, and CYP3A. PARMODIA is a substrate of organic anion transporting polypeptide (OATP) 1B1 and OATP1B3.

Contraindications for co-administration (Do not co-administer with the following drugs.)

Drug	Clinical symptoms/Treatment	Mechanism/Risk factors
Cyclosporine	Concomitant administration of cyclosporine or rifampicin with PARMODIA resulted in an increase in the plasma concentration of pemafibrate (see section 5.2).	Presumably due to inhibition of OATP1B1, OATP1B3, CYP2C8, CYP2C9, and CYP3A by cyclosporine.
Rifampicin		Presumably due to inhibition of OATP1B1 and OATP1B3 by rifampicin.

Precautions for co-administration (PARMODIA should be administered with caution when co-administered with the following drugs.)

Drug	Clinical symptoms/Treatment	Mechanism/Risk factors
HMG-CoA reductase inhibitors Pravastatin sodium Simvastatin Fluvastatin sodium, etc.	Muscle toxicity should be suspected in patients presenting diffuse myalgia, myositis, muscle cramps and weakness and/or marked increases in CK (>5 times ULN). In such cases, treatment with PARMODIA should be stopped.	Risk factor: patients with pre-existing muscular disease
Clopidogrel sulfate	Concomitant administration of clopidogrel sulfate or clarithromycin with PARMODIA resulted in an increase in the plasma concentration of pemafibrate (see section 5.2). Dose reduction of PARMODIA should be considered as necessary when used concomitantly with PARMODIA.	Presumably due to inhibition of CYP2C8 and OATP1B1 by clopidogrel sulfate.
Clarithromycin HIV protease inhibitors Ritonavir, etc.		Presumably due to inhibition of CYP3A, OATP1B1 and OATP1B3 by clarithromycin (or HIV protease inhibitors).
Fluconazole	Concomitant administration of fluconazole with PARMODIA resulted in an increase in the plasma concentration of pemafibrate (see section 5.2).	Presumably due to inhibition of CYP2C9 and CYP3A by fluconazole.
Anion exchange resins Cholestyramine Colestimide	PARMODIA should be administered with the longest interval possible after the intake of anion exchange resins because the plasma concentration of pemafibrate may be decreased.	PARMODIA may be absorbed onto anion exchange resins, and the absorption of pemafibrate may be reduced.

Drug	Clinical symptoms/Treatment	Mechanism/Risk factors
Strong CYP3A inducers Carbamazepine Phenobarbital Phenytoin Foods containing hypericum perforatum (St. John's wort), etc.	The plasma concentration of pemafibrate may be decreased, which may reduce the efficacy of PARMODIA.	The strong induction of CYP3A by these drugs may accelerate the metabolism of pemafibrate.

4.6 Fertility, pregnancy and lactation

Pregnancy
PARMODIA is contraindicated in pregnant or possibly pregnant women (see section 4.3). The safety of PARMODIA has not been established for use during pregnancy.

Breast-feeding
The use of PARMODIA should be avoided in breast-feeding women. If the administration of PARMODIA is unavoidable, breast-feeding should be discontinued. An animal study (rat) has shown that PARMODIA is excreted in rat milk.

Fertility
No current data.

4.7 Effects on ability to drive and use machines

No studies of the effects of PARMODIA on a patient's ability to drive, or to measure a reduced capacity to safely use machines have been performed.

4.8 Undesirable effects

Summary of the safety profile
In clinical studies conducted by the time of approval in Japan, adverse reactions were observed in 206 of 1,418 patients (14.5%). The most commonly reported adverse reactions included cholelithiasis observed in 20 patients (1.4%), diabetes mellitus in 20 patients (1.4%), and blood creatine phosphokinase increased in 12 patients (0.8%).

Summary of adverse reactions
Adverse reactions and frequencies observed in clinical studies conducted by the time of approval in Japan are listed below. If any of the following adverse reactions or similar is observed, the patients should be treated appropriately according to the symptoms.

	≥1%	≥0.1% to <1%
Liver	Cholelithiasis	Hepatic function abnormal, Aspartate aminotransferase increased, Alanine aminotransferase increased
Muscle		Blood creatine phosphokinase increased, Myoglobin blood increased, Myalgia
Skin		Rash, Itching
Others	Diabetes mellitus (including Diabetes mellitus aggravated)	Glycosylated haemoglobin increased, Low density lipoprotein increased, Blood uric acid increased

4.9 Overdose

There is no specific treatment in the event of overdose. The patient should be treated symptomatically and supportive measures instituted as required. Since pemafibrate is highly bound to plasma proteins, hemodialysis is unlikely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Not yet assigned
ATC Code: Not yet assigned

Mechanism of action
Pemafibrate activates PPARα by binding to this receptor and regulates the target gene expression, leading to decreased plasma triglyceride (TG) concentration, decreased triglyceride-rich lipoprotein, decreased apolipoprotein (Apo) C-3, and increased HDL-cholesterol.
(1) The activation of PPARα by pemafibrate was more potent than the activation of PPARγ or PPARδ, indicating the selectivity of pemafibrate to PPARα (*in vitro*).
(2) Pemafibrate inhibited TG synthesis in the liver (rats).
(3) Pemafibrate significantly reduced TG secretory rate (rats).
(4) Pemafibrate increased LPL activity (rats).
(5) Pemafibrate significantly reduced plasma concentrations of ApoC-3 and Angiopoietin-like Protein 3, which negatively regulate LPL activity; moreover, pemafibrate inhibited the gene expression (*Apoc3, Angptl3*) in the liver. In addition, pemafibrate upregulated the expression of genes (*Aco, Cpt1a*) involved in β-oxidation of free fatty acids that inhibits LPL activity (rats).
(6) Pemafibrate facilitated plasma TG clearance (rats).
(7) Pemafibrate increased plasma concentration of fibroblast growth factor 21 (FGF21), a protein that reduces TG concentration and increases HDL-cholesterol concentration (rats).

Pharmacodynamic effects
Pharmacological action
(1) Effect of reducing plasma lipid
When pemafibrate was orally administered to rats with high fructose-induced hypertriglyceridemia, plasma TG concentration was decreased in a dose-dependent manner.
(2) Effect of increasing HDL-cholesterol
When pemafibrate was orally administered to human ApoA-1 transgenic mice, plasma concentration of HDL-cholesterol and concentration of human ApoA-1 were increased.
(3) Anti-arteriosclerotic effect
When pemafibrate was orally administered to LDL-receptor deficient mice under high fat/high cholesterol diet, the area of lipid deposition area in the aortic sinus was decreased.

Clinical efficacy
Phase 2/3 Comparative Confirmatory Study with Fenofibrate
In patients with dyslipidemia who had high TG and low HDL-cholesterol levels, placebo, 0.2 mg/day or 0.4 mg/day of PARMODIA (twice daily after breakfast and dinner), or micronized fenofibrate capsules of 100 mg/day or 200 mg/day (once daily after breakfast) was administered for 12 weeks. The percent change in fasting serum TG was as presented in the following table, which shows the superiority of PARMODIA groups over the placebo group, and non-inferiority of PARMODIA 0.2 mg/day and 0.4 mg/day groups over the micronized fenofibrate capsule 200 mg/day group.

Table 1. Percent change in fasting serum TG in placebo group and PARMODIA groups

Treatment group and Baseline fasting serum TG[a] (mg/dL)	Percent change in fasting serum TG[b]	
	Percent change from baseline[c] (%)	Difference from placebo in percent change[d] (%)
Placebo 346.1±130.9, n=43	-2.775 [-11.783, 6.233]	-
PARMODIA 0.2 mg/day 367.2±153.6, n=128	-46.766 [-49.985, -43.547]	-43.991** [-55.455, -32.528]
PARMODIA 0.4 mg/day 362.6±158.5, n=84	-51.902 [-55.841, -47.963]	-49.127** [-60.922, -37.333]

a) Mean ± SD To convert TG from mg/dL to mmol/L, multiply by 0.0113
b) Repeated measures analysis of covariance for all treatment groups, with Weeks 8, 10, and 12 as repeated time points and baseline value as a covariate (The results of the PARMODIA 0.1 mg/day group are omitted.)
c) Least square mean [95% CI]
d) Least square mean [Adjusted 95% CI] **: p ≤0.01 (Dunnett's test)

Table 2. Percent change in fasting serum TG in PARMODIA groups and micronized fenofibrate capsule groups

Treatment group and Baseline fasting serum TG[a] (mg/dL)	Percent change in fasting serum TG[b]	
	Percent change from baseline (%)	Difference from micronized fenofibrate capsule 200 mg/day group in percent change (%)
PARMODIA 0.2 mg/day 367.2±153.6, n=128	-46.690 [-49.904, -43.477]	4.844 [0.388, 9.299]
PARMODIA 0.4 mg/day 362.6±158.5, n=84	-51.836 [-55.768, -47.903]	-0.302 [-5.300, 4.696]
Micronized fenofibrate capsule 100 mg/day[c] 362.0±135.1, n=85	-38.261 [-42.230, -34.291]	-
Micronized fenofibrate capsule 200 mg/day[c] 347.3±123.8, n=140	-51.534 [-54.616, -48.452]	-

a) Mean ± SD To convert TG from mg/dL to mmol/L, multiply by 0.0113
b) Repeated measures analysis of covariance for all treatment groups, with Weeks 8, 10, and 12 as repeated time points and baseline value as a covariate (The results of the PARMODIA 0.1 mg/day group are omitted.)
Least square mean [95% CI] Non-inferiority margin: 10%

The change over time in LDL-cholesterol was as presented in the following table.

Table 3. Change over time in LDL-cholesterol by group

	Placebo group	PARMODIA group		Micronized fenofibrate capsule group	
		0.2 mg/day	0.4 mg/day	100 mg/day	200 mg/day
Baseline	133.8±33.9 (43)	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)	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)	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)	149.1±33.3 (122)	144.8±32.2 (80)	148.8±32.5 (79)	137.0±32.3 (128)

Mean ± SD (mg/dL) To convert LDL-C from mg/dL to mmol/L, multiply by 0.0259

(number of subjects)

Phase 3 Comparative Confirmatory Study with Fenofibrate

In patients with dyslipidemia who had high TG and low HDL-cholesterol levels, placebo, 0.2 mg/day or 0.4 mg/day of PARMODIA (twice daily after breakfast and dinner), or fenofibrate tablets of 106.6 mg/day (once daily after breakfast) was administered for 24 weeks. The fenofibrate tablets (solid dispersion) of 106.6 mg are equivalent to micronized fenofibrate capsules of 134 mg. The percent change in fasting serum TG was as presented in the following table, which shows the non-inferiority of all PARMODIA groups over the fenofibrate tablet 106.6 mg/day group.

Table 4. Percent change in fasting serum TG in PARMODIA groups and fenofibrate tablet group

Treatment group and Baseline fasting serum TG[a] (mg/dL)	Percent change in fasting serum TG[b]	
	Percent change from baseline (%)	Difference from fenofibrate tablet 106.6 mg/day group[c] in percent change
PARMODIA 0.2 mg/day 242.4±53.3, n=73	-46.226 [-50.122, -42.329]	-6.541 [-12.004, -1.078]
PARMODIA 0.4 mg/day 233.3±60.8, n=74	-45.850 [-49.678, -42.023]	-6.166 [-11.576, -0.755]
Fenofibrate tablet 106.6mg/day 235.6±71.7, n=76	-39.685 [-43.511, -35.858]	-

a) Mean ± SD To convert TG from mg/dL to mmol/L, multiply by 0.0113
b) Repeated measures analysis of covariance with Weeks 8, 12, 16, 20, and 24 as repeated time points and baseline value as a covariate
Least square mean [95% CI] Non-inferiority margin: 10%
c) Fenofibrate tablets (solid dispersion) of 106.6 mg are equivalent to micronized fenofibrate capsules of 134 mg.

The change over time in the LDL-cholesterol was as presented in the following table.

Table 5. Change over time in LDL-cholesterol by group

	PARMODIA group		Fenofibrate tablet 106.6 mg/day group
	0.2 mg/day	0.4 mg/day	
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)

Mean ± SD (mg/dL) To convert LDL-C from mg/dL to mmol/L, multiply by 0.0259
(number of subjects)
LOCF: Last observation carried forward

Phase 3 Long-term Administration Study in Dyslipidemia Patients with High TG Levels

In patients with dyslipidemia who had high TG levels, PARMODIA 0.2 mg/day (a dose increase to PARMODIA 0.4 mg/day was allowed as necessary in subjects with inadequate response to PARMODIA 0.2 mg/day at Week 12 and after) was administered twice daily before or after breakfast and dinner for 52 weeks. The percent change from the baseline fasting serum TG of 249.7±77.5 mg/dL (2.82±0.88 mmol/L) (Mean ± SD [the same applies hereinafter], n=189) at Week 24 and Week 52 were -48.77±20.47% and -45.93±21.84%, respectively (Last observation carried forward [LOCF] method was used). LDL-cholesterol value was 119.3±31.7 mg/dL (3.09±0.82 mmol/L) at baseline, and 116.6±29.1 mg/dL (3.02±0.75 mmol/L) at Week 52 (n=189).

Phase 3 Long-term Administration Study in Patients with Dyslipidemia and Type 2 Diabetes Mellitus

In patients with dyslipidemia and type 2 diabetes mellitus, placebo/PARMODIA 0.2 mg/day (starting from Week 24, the treatment was switched from placebo to PARMODIA 0.2 mg/day), PARMODIA 0.2 mg/day, or PARMODIA 0.4 mg/day was administered twice daily before or after breakfast and dinner for 52 weeks. The percent change in fasting serum TG at Week 24 and Week 52 (LOCF) was as presented in the following table.

Table 6. Percent change in fasting serum TG in Placebo/PARMODIA 0.2 mg/day group and PARMODIA groups (at Weeks 24 and 52)

Treatment group and Baseline fasting serum TG[a] (mg/dL)	Percent change in fasting serum TG[b]		
	Time point	Percent change from baseline[c] (%)	Difference from placebo in percent change[d] (%)
Placebo (up to Week 24) PARMODIA 0.2 mg/day (from Week 24) 284.3±117.6, n=57	Week 24	-10.814 [-17.933, -3.694]	-
	Week 52	-46.835 [-52.967, -40.704]	-
PARMODIA 0.2 mg/day 240.3±93.5, n=54	Week 24	-44.347 [-51.656, -37.038]	-33.534 [-45.154,-21.914]
	Week 52	-43.629 [-49.924, -37.334]	-
PARMODIA 0.4 mg/day 260.4±95.9, n=55	Week 24	-45.093 [-52.283, -37.904]	-34.280 [-45.723,-22.836]
	Week 52	-46.552 [-52.744, -40.360]	-

a) Mean ± SD To convert TG from mg/dL to mmol/L, multiply by 0.0113
b) Analysis of covariance with baseline value as a covariate
Last observation carried forward (LOCF) method was used.
c) Least square mean [95% CI]
d) Least square mean [Adjusted 95% CI]

5.2 Pharmacokinetic properties

Plasma pemafibrate concentration

(1) Single dose administration

When a single dose of PARMODIA 0.1 mg was orally administered under fasted conditions to healthy Japanese adult males (16 subjects), the plasma concentration versus time and pharmacokinetic parameters are as presented in the following figure.

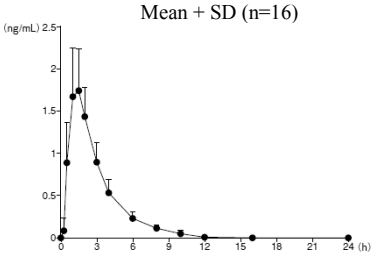

Figure. The plasma concentration versus time after a single oral dose in fasted healthy adult males.

Table 7. Pharmacokinetic parameters after a single oral dose in fasted healthy adult males.

C_{max} (ng/mL)	$AUC_{0\text{-}inf}$ (ng·h/mL)	t_{max} (h)	$t_{1/2}$ (h)
1.82±0.54	5.75±1.50	1.50 (1.00, 2.00)	1.88±0.31

C_{max}, $AUC_{0\text{-}inf}$, $t_{1/2}$: Mean ± SD
t_{max}: Median (Minimum, Maximum)
n=16

(2) Repeated dose administration

When PARMODIA 0.2 mg/day or 0.4 mg/day was orally administered twice daily after breakfast and dinner for 7 days to healthy Japanese adult males (8 subjects), the pharmacokinetic parameters on Day 1 and Day 7 are as presented in the following table. The plasma concentration reached a steady state on Day 2. The accumulation ratio based on $AUC_{0\text{-}\tau}$ (repeated dosing/initial dosing, Mean ± SD) were 1.0997±0.0688 and 1.1169±0.1814, respectively.

Table 8. Pharmacokinetic parameters after repeated oral doses in healthy adult males

Dose of PARMODIA	Time point	C_{max} (ng/mL)	$AUC_{0\text{-}\tau}$ (ng·h/mL)	t_{max} (h)	$t_{1/2}$ (h)
0.2 mg/day Twice daily	Day 1	1.401±0.249	4.884±1.201	2.000 (1.00, 3.00)	-
	Day 7	1.593±0.366	5.404±1.515	2.000 (1.00, 3.00)	1.528±0.402
0.4 mg/day Twice daily	Day 1	2.968±0.905	10.975±2.335	2.000 (1.00, 3.00)	-
	Day 7	3.572±1.021	12.207±2.900	2.000 (1.00, 3.00)	1.708±0.158

C_{max}, $AUC_{0\text{-}\tau}$, $t_{1/2}$: Mean ± SD, -: Not calculated
t_{max}: Median (Minimum, Maximum)
n=8

(3) Food effect

When a single dose of PARMODIA 0.1 mg was orally administered to healthy Japanese adult males (16 subjects), the ratio [90% CI] of geometric means of fasted state to fed state for C_{max} and $AUC_{0\text{-}t}$ were 0.873 [0.803, 0.950] and 0.911 [0.863, 0.961].

Absorption

The absolute bioavailability of pemafibrate was 61.5% (Data for non-Japanese subjects).

Plasma protein binding ratio

The human plasma protein binding ratio of pemafibrate was ≥99%.

Metabolism

(1) When a single dose of ^{14}C-pemafibrate was orally administered to healthy adult subjects, the main metabolites in plasma were an oxidized form at the benzyl position, and a mixture of glucuronide conjugate of dicarboxylated form and *N*-dealkylated form (Data for non-Japanese subjects).

(2) Pemafibrate is a substrate of CYP2C8, CYP2C9, CYP3A4, CYP3A7, UGT1A1, UGT1A3, and UGT1A8 (*in vitro*).

Excretion

(1) When a single dose of ^{14}C-pemafibrate was administered to healthy adult subjects, excretion of radioactivity in urine and feces up to 216 hours after administration was 14.53% and 73.29%, respectively (Data for non-Japanese subjects). Pemafibrate is excreted mainly in the feces.

(2) Pemafibrate is a substrate of P-gp, BCRP, OATP1A2, OATP1B1, OATP1B3, OCT2, and NTCP (*in vitro*).

Drug interactions

(1) Co-administration with cyclosporin, rifampicin, clopidogrel, clarithromycin, fluconazole, digoxin, or warfarin

When PARMODIA was co-administered with each drug in healthy adult subjects (non-Japanese), the effect on the pharmacokinetic parameters was as presented in the following table.

Table 9. Effect of co-administration of PARMODIA and each drug on pharmacokinetic parameters (data for non-Japanese subjects)

Co-administrated drug	Dose of Co-administrated drug	Dose of PARMODIA	Analyte	Ratio of geometric means [90% CI] (Combination therapy/monotherapy)	
				C_{max}	$AUC_{0\text{-}inf}$
Cyclosporine	600 mg Single-dose	0.4 mg Single-dose	PARMODIA	8.9644 [7.5151, 10.6931] n=14	13.9947 [12.6175,15.5223] n=12
Rifampicin	600 mg Single-dose	0.4 mg Single-dose	PARMODIA	9.4336 [8.3626, 10.6419] n=20	10.9009 [9.9154, 11.9844] n=17
	600 mg/day Once daily 10 days Monotherapy	0.4 mg Monotherapy	PARMODIA	0.3792[a)] [0.3378, 0.4257] n=20	0.2221[a)] [0.2065, 0.2389] n=16
Clopidogrel	300 mg Single dose Day 4	0.4 mg Single dose Day 4	PARMODIA	1.4855 [1.3915, 1.5858] n=20	2.3728 [2.2473, 2.5052] n=20
	75 mg/day Once daily 5 days Days 5 to 9	0.4 mg Single-dose Day 7	PARMODIA	1.3415 [1.2583, 1.4302] n=20	2.0876 [1.9811, 2.1998] n=20
Clarithromycin	1,000 mg/day Twice daily 8 days	0.4 mg Single-dose	PARMODIA	2.4246 [2.1632, 2.7174] n=18	2.0975 [1.9158, 2.2964] n=17
Fluconazole	400 mg/day Once daily 11 days	0.4 mg Single-dose	PARMODIA	1.4409 [1.2899, 1.6096] n=19	1.7891 [1.6638, 1.9239] n=17
Digoxin	0.5 mg/day Twice daily (Day 1), 0.25 mg/day Once daily 16 days	0.8 mg/day Twice daily 6 days Days 11 to 16	Digoxin	1.0325 [0.9511, 1.1210] n=19	0.9463[b)] [0.9090, 0.9850] n=19
Warfarin*	5 mg/day Once daily (Day 1 and Day 2), Maintenance dose[c)] Once daily 21 days	0.4 mg/day Twice daily 8 days Days 14 to 21	R-warfarin	1.004 [0.972, 1.037] n=19	1.029[b)] [1.004, 1.055] n=19
			S-warfarin	0.929 [0.889, 0.970] n=19	0.951[b)] [0.926, 0.976] n=19

a) Geometric mean ratios [90% CI] of PARMODIA monotherapy after repeated administration of rifampicin to PARMODIA monotherapy before repeated administration of rifampicin for C_{max} and $AUC_{0\text{-}inf}$.

b) $AUC_{0\text{-}\tau}$

c) On Day 3 through Day 9, the dosage was adjusted to achieve an international normalized ratio of prothrombin time (PT-INR) of 1.2 to 2.2. On Day 10 and thereafter, the maintenance dose that achieved PT-INR of 1.2 to 2.2 was administered.

* Least square mean ratios [90% CI] of repeated co-administration of warfarin with PARMODIA to repeated warfarin monotherapy for PT-INR and PT were 1.0196 [0.9878, 1.0514] (n=19) and 1.0191 [0.9869, 1.0512] (n=19).

Note: The approved dosage and administration of PARMODIA is an oral dose of 0.1 mg twice daily, and the maximum dosage is an oral dose of 0.2 mg twice daily (see section 4.2).

(2) Co-administration with HMG-CoA reductase inhibitors

When PARMODIA and HMG-CoA reductase inhibitors were co-administered to healthy adult males (Japanese and non-Japanese), the effect of co-administration on the pharmacokinetic parameters was as presented in the following table.

Table 10. Effect of co-administration of PARMODIA and each drug on pharmacokinetic parameters (data for Japanese and non-Japanese subjects)

Co-administrated drug	Dose of co-administrated drug	Dose of PARMODIA	Analyte	Ratio of geometric means [90% CI] (Combination therapy/monotherapy)		
					C_{max}	$AUC_{0\text{-}\tau}$
Atorvastatin	20 mg/day Once daily 7 days	0.4 mg/day Twice daily 7 days	PARMODIA (n=18)		1.166 [1.069, 1.272]	1.098 [1.016, 1.187]
			Atorvastatin (n=18)		1.032 [0.960, 1.109]	0.934 [0.851, 1.024]
			o-hydroxyatorvastatin (n=18)		0.875 [0.826, 0.927]	0.784 [0.736, 0.836]
Simvastatin	20 mg/day Once daily 7 days	0.4 mg/day Twice daily 7 days	PARMODIA (n=18)		1.230 [1.090, 1.388]	1.125 [0.997, 1.270]
			Simvastatin (n=19)		0.858 [0.660, 1.114]	0.846 [0.722, 0.992]
			Open acid form of simvastatin (n=19)		0.626 [0.541, 0.725]	0.405 [0.345, 0.475]
Pitavastatin	4 mg/day Once daily 7 days	0.4 mg/day Twice daily 7 days	PARMODIA (n=18)		1.061 [0.970, 1.160]	1.122 [1.041, 1.209]
			Pitavastatin (n=18)		1.011 [0.973, 1.050]	1.036 [1.007, 1.066]
Pravastatin	20 mg/day Once daily 7 days	0.4 mg/day Twice daily 7 days	PARMODIA (n=18)		1.058 [0.964, 1.162]	1.057 [1.013, 1.102]
			Pravastatin (n=18)		1.107 [0.908, 1.351]	1.065 [0.922, 1.231]
Fluvastatin	60 mg/day Once daily 7 days	0.4 mg/day Twice daily 7 days	PARMODIA (n=18)		1.181 [1.080, 1.290]	1.207 [1.144, 1.274]
			Fluvastatin (n=18)		0.989 [0.790, 1.239]	1.151 [1.057, 1.253]
Rosuvastatin	20 mg/day Once daily 7 days	0.4 mg/day Twice daily 7 days	PARMODIA (non-Japanese subjects, n=24)		1.106 [1.048, 1.167]	1.110 [1.046, 1.177]
			Rosuvastatin (non-Japanese subjects, n=24)		1.092 [1.016, 1.174]	1.025 [0.964, 1.091]

Special populations

Pharmacokinetics in Patients with Fatty Liver and Patients with Hepatic Cirrhosis

When a single dose of PARMODIA 0.2 mg was orally administered to Japanese patients with fatty liver and patients with hepatic cirrhosis, the ratios of pharmacokinetic parameters (patients with fatty liver or with hepatic cirrhosis to subjects with normal hepatic function) were as presented in the following table. Compared with subjects with normal hepatic function, the exposure was higher in patients with fatty liver and patients with hepatic cirrhosis.

Table 11. Ratios [90% CI] of geometric means of patients with fatty liver or hepatic cirrhosis to subjects with normal hepatic function (n=8) for C_{max} and $AUC_{0\text{-}t}$.

	C_{max}	$AUC_{0\text{-}t}$
Fatty liver group (n=10)	1.198 [0.819, 1.750]	1.194 [0.836, 1.707]
Mild hepatic cirrhosis Child-Pugh grade A group (n=8)	2.329 [1.561, 3.475]	2.076 [1.425, 3.026]
Moderate hepatic cirrhosis Child-Pugh grade B group (n=6)	3.882 [2.520, 5.980]	4.191 [2.790, 6.294]

Pharmacokinetics in Patients with Renal Impairment

When a single dose of PARMODIA 0.2 mg was orally administered to Japanese patients with renal impairment (mild, moderate, severe, or end-stage renal failure), the ratios of pharmacokinetic parameters (patients with renal impairment to subjects with normal renal function) were as presented in the following table. Compared with subjects with normal renal function, the exposure was higher in patients with renal impairment; however, the exposure did not increase as the renal function reduced.

Table 12. Ratios [90% CI] of geometric means of patients with renal impairment to subjects with normal renal function (n=8) for C_{max} and $AUC_{0\text{-}t}$

	C_{max}	$AUC_{0\text{-}t}$
Mild renal impairment group [50 ≤ Ccr < 80 mL/min] (n=8)	1.644 [1.155, 2.342]	1.629 [1.161, 2.287]
Moderate renal impairment group [30 ≤ Ccr < 50 mL/min] (n=8)	1.093 [0.767, 1.556]	1.154 [0.822, 1.620]
Severe renal impairment group [Ccr < 30 mL/min] (n=7)	1.545 [1.072, 2.228]	1.296 [0.913, 1.841]
End-stage renal failure group [Undergoing hemodialysis] (n=7)	1.258 [0.872, 1.813]	1.607 [1.131, 2.282]

5.3 Preclinical safety data

In a carcinogenicity study in mice (≥0.075 mg/kg/day), an increase in the incidence of hepatocellular carcinomas and hepatocellular adenomas was observed. In a carcinogenicity study in rats (≥0.3 mg/kg/day in male rats and ≥1 mg/kg/day in female rats), an increase in the incidence of hepatocellular carcinomas, hepatocellular adenomas, pancreatic acinar cell carcinomas, pancreatic acinar cell adenomas, testicular Leydig cell adenomas, and thyroidal follicular epithelial cell adenomas was observed. All of these findings are considered to be specific to rodents.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose hydrate, Croscarmellose sodium, Microcrystalline cellulose, Hydroxypropylcellulose, Magnesium stearate

Film coating
Hypromellose, Triethyl citrate, Light anhydrous silicic acid, Titanium oxide, Carnauba wax

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30ºC.

After the tablet is divided, store away from humidity, and use within 4 months.

6.5 Nature and contents of container

PVC/Aluminium blisters in an aluminium-laminated bag, in a carton of 100 tablets (10 blisters x 10 tablets).

6.6 Special precautions for disposal

To protect the environment, do not dispose of via waste water or household waste.

7. PRODUCT OWNER

Kowa Company, Ltd.
6-29, Nishiki 3-chome, Naka-ku, Nagoya, Aichi, JAPAN

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION

10. DATE OF REVISION OF THE TEXT