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ARTICLE

Drug–drug interactions between pemafibrate and statins on pharmacokinetics in healthy male volunteers: Open-label, randomized, 6-sequence, 3-period crossover studies

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Abstract

Elevated triglyceride levels are associated with an increased risk of cardiovascular events despite guideline-based statin treatment of low-density lipoprotein cholesterol. Peroxisome proliferator-activated receptor α (PPARα) agonists exert a significant triglyceride-lowering effect. However, combination therapy of PPARα agonists with statins poses an increased risk of rhabdomyolysis, which is rare but a major concern of the combination therapy. Pharmacokinetic interaction is suspected to be a contributing factor to the risk. To examine the potential for combination therapy with the selective PPARα modulator (SPPARMα) pemafibrate and statins, drug–drug interaction studies were conducted with open-label, randomized, 6-sequence, 3-period crossover designs for the combination of pemafibrate 0.2 mg twice daily and each of 6 statins once daily: pitavastatin 4 mg/day ($n = 18$), atorvastatin 20 mg/day ($n = 18$), rosuvastatin 20 mg/day ($n = 29$), pravastatin 20 mg/day ($n = 18$), simvastatin 20 mg/day ($n = 20$), and fluvastatin 60 mg/day ($n = 19$), involving healthy male volunteers. The pharmacokinetic parameters of pemafibrate and each of the statins were similar regardless of coadministration. There was neither an effect on the systemic exposure of pemafibrate nor a clinically important increase in the systemic exposure of any of the statins on the coadministration although the systemic exposure of simvastatin was reduced by about 15% and its open acid form by about 60%. The HMG-CoA reductase inhibitory activity in plasma samples from the simvastatin and pemafibrate combination group was about 70% of that in the simvastatin alone group. In conclusion, pemafibrate did not increase the systemic exposure of statins, and vice versa, in healthy male volunteers.

Previous presentation: This work has been previously presented as poster abstract in the International Symposium on Atherosclerosis (ISA) 2018, Toronto, Canada. 9–12 June 2018 by N. Hounslow, H. Suganami, and M. Nakamura. Poster No. P5.052 Pemafibrate Minimally Affected the Systemic Exposure of Statins, and Vice Versa, in Healthy Male Volunteers. *Atheroscler Suppl* **32**, 156 (2018).

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

For the treatment of hypertriglyceridemia persisting despite statin treatment, combination therapy with a PPARα agonist is a frequently selected option. Since both statins and PPARα agonists are considered associated with the risk of myopathy, potential drug–drug interactions are a concern when considering the combination therapy.

WHAT QUESTION DID THIS STUDY ADDRESS?

Are the systemic exposures of pemafibrate and statins increased when coadministered?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Maximum therapeutic doses of pemafibrate did not increase the exposure to coadministered statins. None of the statins had any effect on the pharmacokinetics of pemafibrate.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Pemafibrate may be safely used in combination with statins. Large-scale studies confirm that pemafibrate effectively reduces triglyceride concentration above target in patients taking statins without increasing the risk of myopathy.

INTRODUCTION

Elevated levels of triglycerides, triglyceride-rich lipoproteins, and their remnants are causally associated with atherosclerotic cardiovascular diseases in epidemiologic and genetic studies.[1] The associations persist even in patients taking statins who are at the goal of low-density lipoprotein cholesterol but with elevated triglycerides.[1] In fact, in such patients with triglycerides >200 mg/dL fenofibrate or bezafibrate may be considered according to 2021 European Society of Cardiology guidelines.[2] Among oral agents, peroxisome proliferator-activated receptor α (PPARα) agonists are the most efficacious drug class for lowering triglyceride levels[3]; however, there has been concern that their use in combination with statins may increase the risk of myopathy and rhabdomyolysis, especially in patients with chronic kidney disease.[4–6] The mechanisms leading to musculoskeletal adverse events (AEs) are not well understood, but drug–drug interactions which increase the blood concentration of the statin and/or the PPARα agonist are associated with a higher risk.[5]

Pemafibrate, a selective PPARα modulator (SPPARMα), has been approved in Japan since 2017, followed by Thailand, Singapore, and Malaysia. It is highly selective for the PPARα receptor and effectively reduces triglyceride, triglyceride-rich lipoproteins, and remnant cholesterol levels both as monotherapy or in combination with statins, in patients with or without type 2 diabetes.[7–12] Unlike the other PPARα agonists, pemafibrate is mainly eliminated via the liver, and its blood concentration is not significantly increased in patients with reduced renal function.[4,13] In recent real-world studies of patients receiving pemafibrate in Japan, 51%[14] and 58%[15] of patients were also treated with statins indicating a medical need for the combination. Pemafibrate is currently under investigation for the treatment of non-alcoholic steatohepatitis with positive results in a recent phase II trial in patients with non-alcoholic fatty liver disease.[16] This article presents the results of pharmacokinetic drug–drug interaction studies with pemafibrate and 6 statins.

METHODS

Study design

This article reports four open-label, randomized, 3-treatment, 3-period, 6-sequence crossover studies to examine pharmacokinetic drug–drug interactions between pemafibrate 0.2 mg twice daily and each of the following 6 statins once daily: pitavastatin 4 mg (K-877-05 study); atorvastatin 20 mg (K-877-06 study); rosuvastatin 20 mg (K-877-08 study); and pravastatin 20 mg, simvastatin 20 mg, and fluvastatin 60 mg (K-877-18 study) using the products shown in Data S1. These studies were conducted from September 9th to November 30th, 2010; from September 16th to December 6th, 2010; from May 31st to September 16th, 2011; and from May 21st to October 12th, 2012, respectively. The study with rosuvastatin was conducted in the United Kingdom while

the others were in Japan. The doses of study drugs chosen were the highest doses approved in Japan, except in the case of atorvastatin.[17–22] The highest dose of atorvastatin approved in Japan is 40 mg/day, but this dose is restricted to patients with severe familial hypercholesterolemia.[18] In Europe the highest dose of rosuvastatin is 40 mg/day but this dose is contraindicated in combination with fibrates, and also in Japanese and Chinese patients.[19] Therefore, a dose of 20 mg/day was selected for both drugs.

Study participants

Each study enrolled healthy male volunteers with a body mass index (BMI) ranging from 18.5 to <30 who were aged 18–65 years in the study with rosuvastatin, or 20–35 years in the other studies. Participants were randomly assigned to one of six treatment-sequence groups to receive three different treatments during each of three treatment periods in a different order, that is, pemafibrate alone (Treatment P), statin alone (Treatment S), or the combination of the two (Treatment C) in the order of P-S-C, P-C-S, S-P-C, S-C-P, C-P-S, or C-S-P in Treatment Period 1-2-3, respectively. In Treatment P, pemafibrate was administered at the dose of 0.2 mg twice daily in the morning and evening for 7 days (Days 1–7) without the evening dose on Day 7. In Treatment S, an assigned statin was administered at the indicated dose once daily in the morning for 7 days. Treatment C was the combination of Treatments P and S with the exception for the study with rosuvastatin where pemafibrate was administered in the evening on Day 7 as well.

At least 7-day washout period was required between each treatment administration. Participants attended for screening between Days −21 and −2 of Treatment Period 1 in the study with rosuvastatin or between Days −20 and −2 of Treatment Period 1 in the other studies. They were hospitalized in the morning of the day before drug administration (Day −1) of each treatment period. They were discharged on Day 8 of each treatment period in the studies with pitavastatin and atorvastatin; Day 8 for Treatment S and Day 9 for Treatments P and C in the studies with pravastatin, simvastatin, and fluvastatin; and Day 8 for Treatment P and Day 10 in Treatments S and C in the study with rosuvastatin (Figure 1).

Sample collection and measurement of drug concentrations

Blood samples were collected before the morning dose on Days 1–7 and after the morning dose on Day 7 as shown in Figure 2a–n. Urine samples were collected before the morning dose on Day 1 as control samples, and pooled urine was collected until 24, 48, or 72 h after the morning dose on Day 7 (Table S1). The plasma and urine concentrations of drugs were determined by high-performance liquid chromatography–tandem mass spectrometry (Data S1).

The examined metabolites of pemafibrate included K-15823 (hydroxylated 4-methoxyphenyl group of pemafibrate [position 3]), K-15827 (methoxyphenyl-removed form of pemafibrate), K-15828 (desmethylated 4-methoxyphenyl group of pemafibrate), K-15834 (hydroxylated benzoxazole group of pemafibrate [position 6]), K-23467 (N-dealkylated pemafibrate), K-23469 (dicarboxylated pemafibrate), and K-23605 (oxidized benzyl position of pemafibrate), the latter three of which were only measured in the studies with pravastatin, simvastatin, and fluvastatin. The metabolites of statins included pitavastatin lactone form, pitavastatin glucuronide, *o*-hydroxy atorvastatin, *p*-hydroxy atorvastatin, rosuvastatin lactone form, N-desmethyl

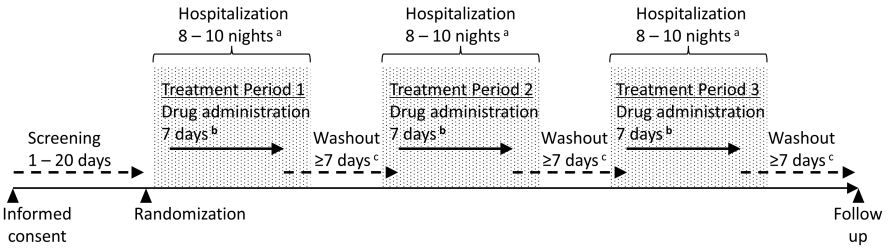
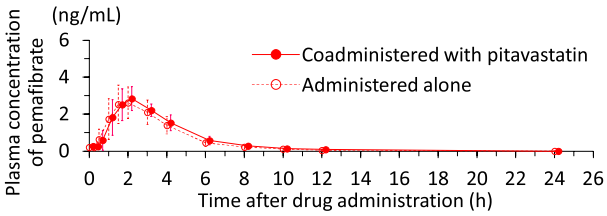
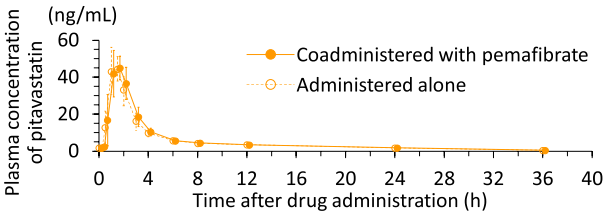


FIGURE 1 Study design. [a]Participants were discharged after the final blood sampling, depending on what study drugs they received. The timing of blood sampling after the final morning dose of 7-day repeated administration was 24 h for pravastatin, simvastatin, and fluvastatin; 24 and 36 h for pitavastatin and atorvastatin; and 24, 36, 48, and 72 h for rosuvastatin. That for pemafibrate was 24 h in the studies with pitavastatin, atorvastatin, and rosuvastatin and 24, 36, and 48 h in the studies with pravastatin, simvastatin, and fluvastatin. [b]Participants received study drugs for 7 days from the morning to the second day of hospitalization. They received one of three treatments, pemafibrate alone, statin alone, and the combination of the two, during each of three hospitalization periods in the order of allocated one of the six sequence groups. [c]Washout period was the same within the same individual.

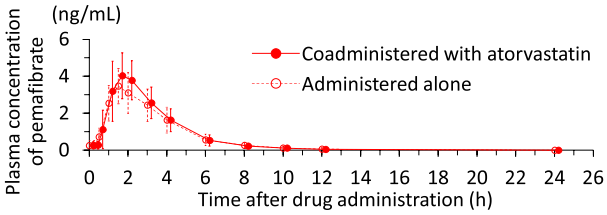
(a) Pemafibrate with or without pitavastatin



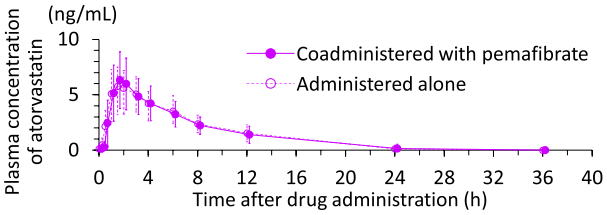
(b) Pitavastatin with or without pemafibrate



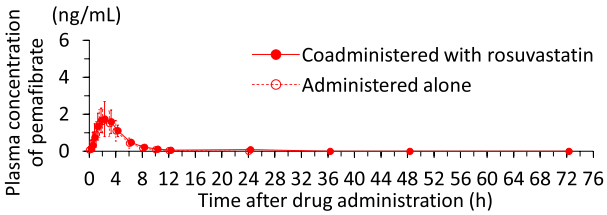
(c) Pemafibrate with or without atorvastatin



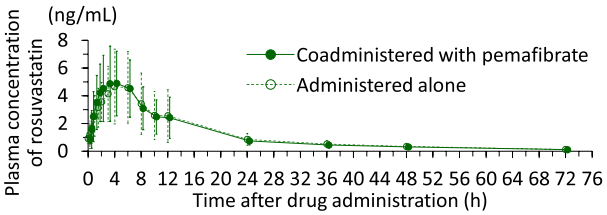
(d) Atorvastatin with or without pemafibrate



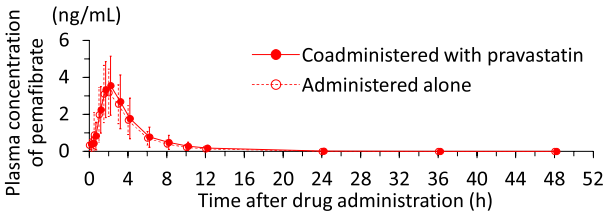
(e) Pemafibrate with or without rosuvastatin



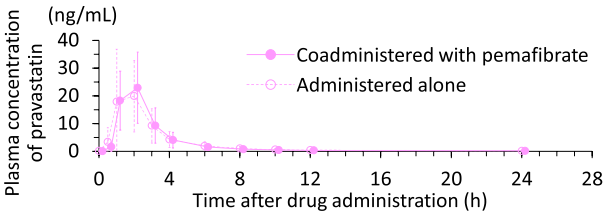
(f) Rosuvastatin with or without pemafibrate



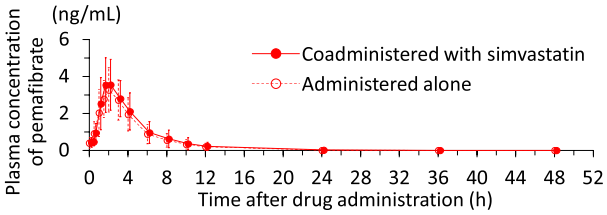
(g) Pemafibrate with or without pravastatin



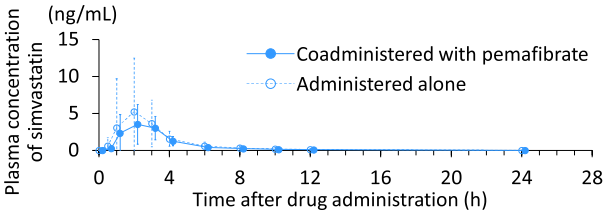
(h) Pravastatin with or without pemafibrate



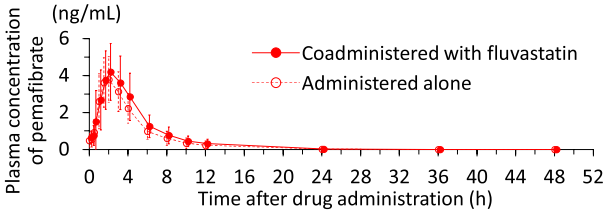
(i) Pemafibrate with or without simvastatin



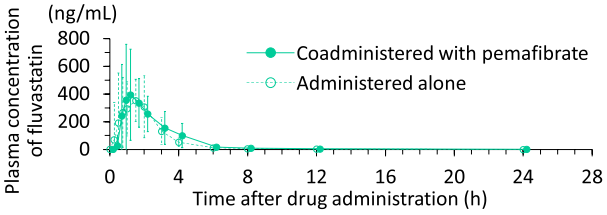
(j) Simvastatin with or without pemafibrate



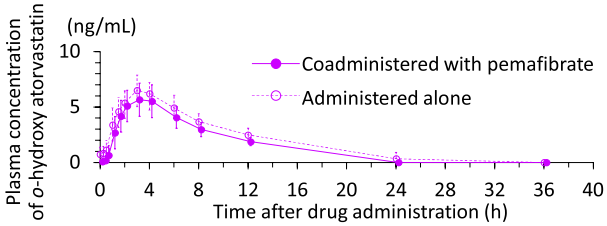
(k) Pemafibrate with or without fluvastatin



(l) Fluvastatin with or without pemafibrate



(m) *o*-hydroxy atorvastatin with or without pemafibrate



(n) Simvastatin open acid with or without pemafibrate

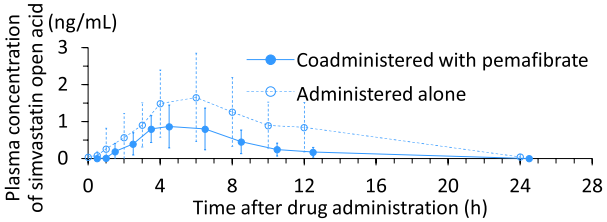


FIGURE 2 Plasma concentration–time curves for pemafibrate and statins in the studies with pitavastatin (a, b; $n = 18$), atorvastatin (c, d; $n = 18$), rosuvastatin (e, f; $n = 24$), pravastatin (g, h; $n = 18$), simvastatin (i, j; $n = 19^{\dagger}$), and fluvastatin (k, l; $n = 19^{\ddagger}$), and those for *o*-hydroxy atorvastatin (m; $n = 18$) and simvastatin open acid form (n; $n = 19$) in the studies with atorvastatin and simvastatin, respectively. Data are presented as mean ± SD. Solid circles and lines indicate data with coadministration, and open circles and dashed lines indicate those without coadministration. $^{\dagger}n = 18$ for pemafibrate administered alone. $^{\ddagger}n = 18$ except for pemafibrate administered alone.

rosuvastatin, 3α-iso-pravastatin, and simvastatin open acid form, which is an active form of simvastatin. Unchanged simvastatin is a lactone form without 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitory activity, and the active and inactive forms are present in equilibrium in the systemic circulation, including the other simvastatin metabolites.[23] In the study with simvastatin, an additional in vitro examination was performed to measure the HMG-CoA reductase inhibitory activity of plasma samples derived from the active forms only and both the active and inactive forms as previously reported (Data S1).[24]

Pharmacokinetic end points

Plasma pharmacokinetic end points included plasma concentrations at each sampling time, maximum observed concentration (C_{max}), elapsed time from dosing at which C_{max} was apparent (t_{max}), pre-dose plasma concentration observed at steady state (C_{trough}), area under the concentration–time curve within the dosing interval (τ) at steady state ($AUC_{0\text{-}\tau}$), mean residence time at steady state (MRT_{ss}), apparent terminal elimination rate constant (Kel), apparent terminal elimination half-life ($t_{1/2}$), apparent volume of plasma cleared of the analyte per unit time following oral dosing at steady state (CL_{ss}/F), and apparent volume of distribution of the analyte following oral dosing at steady state (Vd_{ss}/F) of unchanged pemafibrate, unchanged statins, and the specified metabolites of them.

Urinary pharmacokinetic end points included the total amount of unchanged parent drug or metabolites excreted in the urine at steady state (Ae) and that expressed as a fraction (%) of the dose of the relevant parent drug (%Ae).

Evaluation of pharmacokinetic drug–drug interactions

To evaluate pharmacokinetic drug–drug interactions, C_{max} and $AUC_{0\text{-}\tau}$ were compared between Treatments P and C for pemafibrate and its metabolites or Treatments S and C for statins and their metabolites. The compared treatments were considered similar if the 90% confidence intervals (CIs) of geometric mean ratios (GMRs) for C_{max} and $AUC_{0\text{-}\tau}$ fell within the boundary of 0.80–1.25.[25–27]

To calculate GMRs, natural logarithmically transformed C_{max} and $AUC_{0\text{-}\tau}$ were analyzed using a linear model with group, participant (within group), period, treatment, and period×treatment (i.e., carry-over term) as fixed effects to estimate the difference in the least squares means between the treatments, which was then back-transformed by exponential transformation. The 90% CI for the difference in the least squares means of natural logarithmically transformed values was calculated based on the least squares mean and intraindividual variation and then back-transformed.

If the carry-over effect was not significant with $p \geq 0.15$, the carry-over term was removed from the model. If it was statistically significant with $p < 0.15$, the data from the model with carry-over term were analyzed; however, if the significance level was $p < 0.05$, the calculated CIs were used for reference purposes only.

Safety

Safety end points included the incidence of AEs and the changes in physiological and laboratory tests.

Sample size

No formal sample size calculation was performed because the present studies were exploratory phase I studies. The goal was to determine whether any clinically significant increase or decrease in the systemic exposure of the study drugs would be observed when administered in combination, and the sample sizes were determined from previous experience. The 0.8–1.25 boundaries of 90% CI of GMRs for C_{max} and $AUC_{0\text{-}\tau}$ used in the present studies to examine the effects of drug–drug interaction was conservative, considering that the boundaries were designed for drugs with narrow therapeutic index or unknown safety and all the drugs examined in the present studies have a fairly broad therapeutic index. Thus, minimum three participants per arm were considered appropriate to describe pharmacokinetic parameters, and 18 were randomized with a few more participants reserved for replacement in case that randomized participants were withdrawn from the studies except for those with rosuvastatin. In the study with rosuvastatin, 24 were randomized to ensure the data from at least 18 participants.

FIGURE 3 Geometric means for C_{max} and $AUC_{0\text{-}\tau}$ of pemafibrate, when administered alone or coadministered with statins, and the ratio of that when administered alone to that when coadministered with statins (a) and the same for plasma concentrations of statins (b). The dose of pemafibrate was 0.2 mg twice daily, and those of statins were once daily at the dose of 4 mg for pitavastatin; 20 mg for atorvastatin, rosuvastatin, pravastatin, and simvastatin; and 60 mg for fluvastatin. Data are presented as geometric mean (coefficient of variation) for C_{max} and $AUC_{0\text{-}\tau}$ and as the ratio of geometric means [90% confidence interval]. The units of C_{max} and $AUC_{0\text{-}\tau}$ are ng/mL and ng·h/mL, respectively. [†]$n = 18$; [‡]Calculated for reference purposes only because of statistically significant carry-over effect ($p = 0.0225$). C_{max}, maximum plasma concentration; $AUC_{0\text{-}\tau}$, area under the curve within the dosing interval (τ) at steady state.

Software

Pharmacokinetic parameters were estimated using WinNonlin (Pharsight, CA, USA) version 6.1 in K-877-05, K-877-06, and K-877-08 studies and version 6.3 in K-877-18 study. Statistical analyses were performed using SAS (SAS institute, NC, USA) version 9.1.3 in the K-877-05 and K-877-06 studies, version 8.2 or more recent version in the K-877-08 study, and version 9.2 in K-877-18 study.

Ethics statement

The studies were conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice. Prior to conducting each study, the protocols, the volunteer information and consent forms, and other relevant study documents were approved by the appropriate Ethics Committee and the Medicines and Healthcare Products Regulatory Agency in the United Kingdom or the Investigational Review Board in Japan. These were phase I exploratory pharmacokinetic studies and were not registered in a clinical trial registry because phase I studies were considered exempt from the requirement for registration at the time that they were conducted.

RESULTS

Study population

In total, 28, 27, 29, and 96 participants were enrolled in K-877-05 (pitavastatin), K-877-06 (atorvastatin), K-877-08 (rosuvastatin), and K-877-18 (pravastatin, simvastatin, and fluvastatin) studies, respectively (Figures S1–S4). Among those, 18, 18, 29, 18, 18, and 18 were randomly allocated to either of six groups in the studies with pitavastatin, atorvastatin, rosuvastatin, pravastatin, simvastatin, and fluvastatin, respectively. In the study with rosuvastatin, five out of the 29 participants were additionally recruited and randomly assigned to replace five discontinuations after drug administration. In the studies with pitavastatin, simvastatin, and fluvastatin, discontinuations after drug administration ($n = 1$, 2, and 1, respectively) were replaced by reserved or additionally enrolled participants. Therefore, 19, 18, 29, 18, 20, and 19 participants received study drugs, and 18, 18, 24, 18, 18, and 18 completed the studies with pitavastatin, atorvastatin, rosuvastatin, pravastatin, simvastatin, and fluvastatin, respectively. Participants who received at least one dose of study drugs were included in the safety analysis set, excluding one consent withdrawal in the study with pitavastatin ($n = 18$, 18, 29, 18, 20, and 19, respectively). One of two discontinuations in the study with simvastatin occurred after completing Treatment S and C in the S-C-P group, lacking the data for pemafibrate administered alone. One discontinuation in the study with fluvastatin occurred after completing Treatment P in the P-C-S group, providing only the data for pemafibrate administered alone. These two participants were included to calculate pharmacokinetic parameters, with the former included to evaluate drug–drug interactions, in addition to those who completed the study.

In the safety analysis set, 29 in the study with rosuvastatin were Caucasians aged 20–60 years with BMI of 19.5–29.2, and 93 in total in the other studies were Japanese aged 20–34 years with BMI of 18.4–27.5. (Table S2).

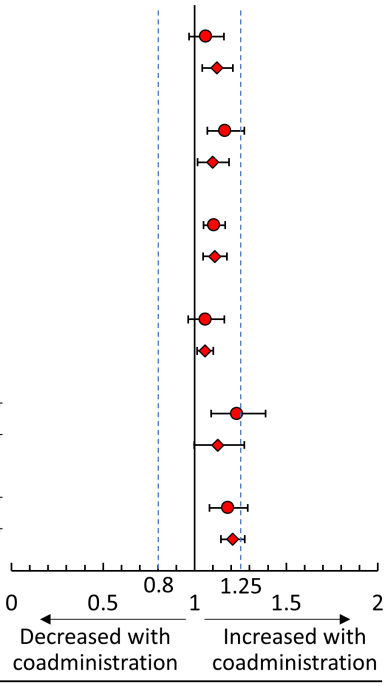
Pharmacokinetic parameters

Plasma concentrations of metabolites of pemafibrate were not fully quantifiable. Those of K-15823 and K-15827 were under the limit of quantification (0.05 ng/mL) except for two participants with K-15823 concentrations quantifiable at only one point of 12 h after coadministration with simvastatin. Those of K-15828 and K-15834 were quantifiable in most participants but at limited points with 10- to 100-times lower C_{max} and $AUC_{0\text{-}\tau}$ than that of pemafibrate. Those of unchanged pemafibrate and statins with and without coadministration were similar (Figure 2a–l). Those of *o*-hydroxy atorvastatin and simvastatin open acid form were lower in the treatment period with coadministration than without coadministration (Figure 2m,n).

All the geometric means of C_{max} and $AUC_{0\text{-}\tau}$ were estimated using the model without a carry-over term except for C_{max} of atorvastatin, for which the carry-over term was statistically significant ($p = 0.0225$) and included in the model to provide with the estimation of reference purpose. As shown in Figure 3 and Table S3, C_{max} and $AUC_{0\text{-}\tau}$ of pemafibrate and statins were overall similar across the

(a)

Pharmacokinetic parameter of pemafibrate	Without statin	With statin	Ratio [90% CI] of geometric mean C_{max} or $AUC_{0-\tau}$ when administered with to without statin
Study with pitavastatin (n=18)			
C_{max}	2.8 (32.6)	3.0 (22.8)	1.061 [0.970–1.160]
$AUC_{0-\tau}$	9.8 (30.4)	11.0 (19.2)	1.122 [1.041–1.209]
Study with atorvastatin (n=18)			
C_{max}	3.6 (28.4)	4.2 (26.9)	1.166 [1.069–1.272]
$AUC_{0-\tau}$	12.0 (32.0)	13.1 (31.8)	1.098 [1.016–1.187]
Study with rosuvastatin (n=24)			
C_{max}	1.8 (38.7)	1.9 (43.2)	1.106 [1.048–1.167]
$AUC_{0-\tau}$	6.7 (43.2)	7.4 (45.5)	1.110 [1.046–1.177]
Study with pravastatin (n=18)			
C_{max}	3.4 (38.4)	3.6 (40.3)	1.058 [0.964–1.162]
$AUC_{0-\tau}$	12.4(39.7)	13.1 (52.1)	1.057 [1.013–1.102]
Study with simvastatin (n=19)			
C_{max}	3.4 (32.9) †	4.1 (24.5)	1.230 [1.090–1.388] †
$AUC_{0-\tau}$	13.8 (38.5) †	15.4 (38.5)	1.125 [0.997–1.270] †
Study with fluvastatin (n=19)			
C_{max}	4.0 (29.6)	4.7 (29.9) †	1.181 [1.080–1.290] †
$AUC_{0-\tau}$	16.1 (35.5)	19.4 (32.6) †	1.207 [1.144–1.274] †



(b)

Pharmacokinetic parameter of statin	Without pemafibrate	With pemafibrate	Ratio [90% CI] of geometric mean C_{max} or $AUC_{0-\tau}$ when administered with to without pemafibrate
Study with pitavastatin (n=18)			
C_{max} of pitavastatin	49.0 (18.6)	49.6 (14.2)	1.011 [0.973–1.050]
$AUC_{0-\tau}$ of pitavastatin	167.3 (13.6)	173.4 (14.4)	1.036 [1.007–1.066]
Study with atorvastatin (n=18)			
C_{max} of atorvastatin	6.3 (28.3)	6.5 (36.4)	1.032 [0.960–1.109] ‡
$AUC_{0-\tau}$ of atorvastatin	46.9 (32.9)	43.8 (39.3)	0.934 [0.851–1.024]
C_{max} of *o*-hydroxyl form	6.8 (17.9)	5.9 (21.8)	0.875 [0.826–0.927]
$AUC_{0-\tau}$ of *o*-hydroxyl form	66.4 (18.4)	52.1 (18.7)	0.784 [0.736–0.836]
Study with rosuvastatin (n=24)			
C_{max} of rosuvastatin	4.6 (51.2)	5.0 (48.0)	1.092 [1.016–1.174]
$AUC_{0-\tau}$ of rosuvastatin	54.9 (56.9)	56.2 (49.1)	1.025 [0.964–1.091]
Study with pravastatin (n=18)			
C_{max} of pravastatin	21.7 (66.4)	24.1 (46.0)	1.107 [0.908–1.351]
$AUC_{0-\tau}$ of pravastatin	52.3 (62.1)	55.7 (49.2)	1.065 [0.922–1.231]
Study with simvastatin (n=19)			
C_{max} of simvastatin	4.5 (122.7)	3.9 (52.8)	0.858 [0.660–1.114]
$AUC_{0-\tau}$ of simvastatin	13.3 (91.7)	11.3 (47.0)	0.846 [0.722–0.992]
C_{max} of open acid form	1.5 (65.8)	0.9 (49.0)	0.626 [0.541–0.725]
$AUC_{0-\tau}$ of open acid form	15.3 (65.9)	6.2 (58.8)	0.405 [0.345–0.475]
Study with fluvastatin (n=18)			
C_{max} of fluvastatin	469.0 (60.5)	464.0 (61.3)	0.989 [0.790–1.239]
$AUC_{0-\tau}$ of fluvastatin	907.7 (29.8)	1044.5 (31.5)	1.151 [1.057–1.253]

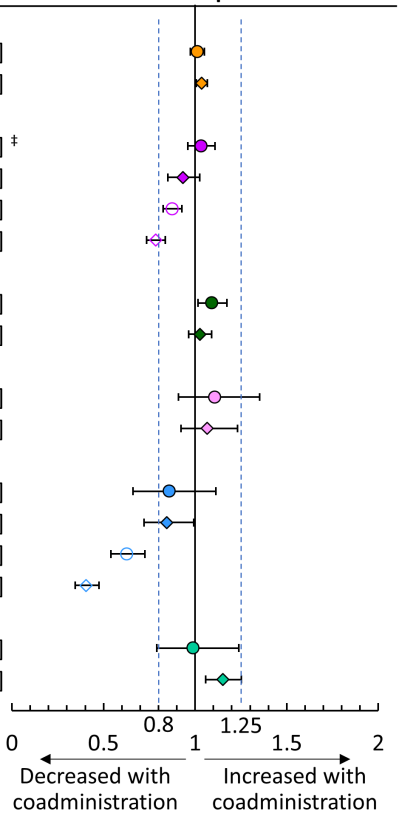


TABLE 1 The effects of coadministration of pemafibrate on the HMG-CoA reductase inhibitory activity of plasma samples in participants treated with simvastatin.

Parameter	Treatment at the time of blood sampling	*n*	Active HMG-CoA reductase inhibitors in plasma samples before base hydrolysis[a]	Total HMG-CoA reductase inhibitors in plasma samples after base hydrolysis[a]
C_{max} (ng-Eq/mL)	Simvastatin alone	18	26.2 (60.7); 25.8 [18.3–35.5]	118 (73.3); 129 [81–157]
	With pemafibrate	18	28.0 (41.8); 31.1 [22.4–42.4]	123 (41.7); 138 [96–149]
$AUC_{0\text{-}\tau}$ (ng-Eq·h/mL)	Simvastatin alone	18	180 (63.9); 188 [115–211]	441 (42.9); 451 [335–595]
	With pemafibrate	18	131 (43.7); 133 [106–185]	413 (28.8); 443 [385–486]

Note: Data are presented as geometric mean (coefficient of variation); median [interquartile range].

[a]The concentration of active and total HMG-CoA reductase inhibitors were expressed as simvastatin acid equivalents by measuring the inhibitory activity of plasma samples before and after base hydrolysis.[24]

treatment conditions, with coefficients of variations less than 50% in 80% of the cases. The coefficients of variations were relatively large for simvastatin and pravastatin administered alone. The other plasma pharmacokinetic parameters such as t_{max}, $t_{1/2}$, Kel, MRT_{ss}, CL_{ss}/F, and Vd_{ss}/F were also similar across the conditions (Table S3).

No urine concentrations of pemafibrate or its metabolites were above the limit of quantification (1 ng/mL) except for K-23467, K-23469, and K-23605. Coadministration of pemafibrate and statins had no effect on the urinary excretion of pemafibrate, statins, or their metabolites.

Pharmacokinetic drug–drug interactions

The GMRs for C_{max} and $AUC_{0\text{-}\tau}$ of each drug with and without coadministration are summarized in Figure 3.

In the studies with pitavastatin, rosuvastatin, and pravastatin, the 90% CIs of GMRs for C_{max} and $AUC_{0\text{-}\tau}$ of pemafibrate with or without coadministration of pitavastatin, rosuvastatin, and pravastatin were well within the 0.80–1.25 boundary. That was similar for pitavastatin, rosuvastatin, and pravastatin except for C_{max} of pravastatin with the upper limit of 90% CI slightly above 1.25 (1.107 [0.908–1.351]).

In the studies with atorvastatin and fluvastatin, C_{max} of pemafibrate slightly increased with coadministration of atorvastatin and fluvastatin with the GMRs of 1.166 [1.069–1.272] and 1.181 [1.080–1.290], respectively. That was similar for $AUC_{0\text{-}\tau}$ of pemafibrate with coadministration of fluvastatin with the GMR of 1.207 [1.144–1.274]. For atorvastatin, while the 90% CIs of GMRs for C_{max} and $AUC_{0\text{-}\tau}$ were well within the 0.80–1.25 boundary, $AUC_{0\text{-}\tau}$ of *o*-hydroxy atorvastatin slightly decreased with the lower limit of 90% CI below 0.8 (0.784 [0.736–0.836]). For fluvastatin, the lower limit of 90% CI for C_{max} was slightly lower than 0.8 (0.989 [0.790–1.239]) but $AUC_{0\text{-}\tau}$ slightly increased (1.151 [1.057–1.253]) with coadministration of pemafibrate.

In the study with simvastatin, C_{max} and $AUC_{0\text{-}\tau}$ of pemafibrate slightly increased with the GMRs of 1.230 [1.090–1.388] and 1.125 [0.997–1.270], respectively. On the other hand, C_{max} and $AUC_{0\text{-}\tau}$ of unchanged simvastatin decreased with the GMRs of 0.858 [0.660–1.114] and 0.846 [0.722–0.992], respectively. Those of simvastatin open acid form also decreased with the GMRs of 0.626 [0.541–0.725] and 0.405 [0.345–0.475], respectively. The additional in vitro examination on the HMG-CoA reductase inhibitory activity of plasma samples revealed that $AUC_{0\text{-}\tau}$ for active HMG-CoA reductase inhibitors was 180 and 131 ng-Eq·h/mL when simvastatin was administered alone and with pemafibrate, respectively, while that for total HMG-CoA reductase inhibitors was 441 and 413 ng-Eq·h/mL, respectively (Table 1). Therefore, the HMG-CoA reductase inhibitory activity of simvastatin when coadministered with pemafibrate was ~70% of that when simvastatin was administered alone.

Safety

As shown in Table 2, AEs were observed in 53 out of 122 participants in total without any death or serious AE. The following three AEs in the study with rosuvastatin led to discontinuation: one severe sciatica during coadministration of pemafibrate and rosuvastatin, one moderate musculoskeletal chest pain with rosuvastatin alone, and one blood creatine phosphokinase increased observed a day before the first administration of the last treatment period. For all the three, the causal relationship with study drugs was ruled out. All the other AEs were mild except for one moderate gastroenteritis or one moderate viral upper respiratory tract infection. Overall, there was no notable safety finding.

DISCUSSION

None of the statins had any clinically meaningful effect on the pharmacokinetics of pemafibrate when administered

TABLE 2 Summary of adverse events.

Study	Pitavastatin ($n=18$)	Atorvastatin ($n=18$)	Rosuvastatin ($n=29$)	Pravastatin ($n=18$)	Simvastatin ($n=20$)	Fluvastatin ($n=19$)	Total ($n=122$)
Any adverse event	4 [3]	15 [11]	18 [14]	7 [5]	16 [10]	17 [10]	77 [53]
Pemafibrate alone	2 [1]	6 [4]	3 [3]	2 [2]	2 [2]	3 [2]	18 [14]
Statin alone	1 [1]	6 [6]	6 [6]	2 [2]	6 [4]	7 [6]	28 [25]
Combination	1 [1]	3 [3]	9 [7]	3 [3]	8 [6]	7 [6]	31 [26]
Adverse event leading to discontinuation	0	0	3 [3]	0	0	0	3 [3]
Pemafibrate alone	0	0	0	0	0	0	0
Statin alone	0	0	1 [1][a]	0	0	0	1 [1]
Combination	0	0	2 [2][b,c]	0	0	0	2 [2]
Death or serious adverse event	0	0	0	0	0	0	0
Severe adverse event	0	0	1 [1][b]	0	0	0	1 [1]
Moderate adverse event	1 [1][d]	0	2 [2][a,e]	0	0	0	3 [3]
Mild adverse event	1 [1]	5 [4]	14 [11]	1 [1]	7 [5]	9 [7]	37 [29]
Laboratory test abnormal	2 [2]	10 [9]	1 [1][c]	6 [4]	9 [6]	8 [5]	36 [27]
Adverse event for which a causal relationship with study drugs could not be ruled out	1 [1]	8 [6]	0	3 [2]	10 [7]	12 [9]	34 [25]

Data are presented as the number of events [the number of participants who had at least one event].

[a]Musculoskeletal chest pain.

[b]Sciatica.

[c]Blood creatine phosphokinase increased.

[d]Gastroenteritis.

[e]Viral upper respiratory tract infection.

in combination. There were no clinically significant increases in the systemic exposure of pemafibrate despite slight increases in the GMRs for C_{max} of pemafibrate when administered in combination with atorvastatin, simvastatin, and fluvastatin and those for $AUC_{0\text{-}\tau}$ of pemafibrate in combination with simvastatin and fluvastatin.

On the other hand, the maximum therapeutic dose of pemafibrate did not increase the systemic exposure to co-administered statins. Although the exposure of *o*-hydroxy atorvastatin, which is an active metabolite of atorvastatin, was slightly decreased, the consequence on the efficacy of atorvastatin was considered small. On the other hand, co-administration of pemafibrate led to the largest changes observed among the present studies, that is, the decreases in the systemic exposure of simvastatin and its open acid form by ~15% and 60%, respectively; however, the HMG-CoA reductase inhibitory activity of plasma samples remained ~70%. This may be partially because simvastatin open acid form accounts for only ~25% of all active HMG-CoA reductase inhibition in plasma.[28] The detailed mechanism of the decreases is not clear. The major cytochrome P450 (CYP) isoform that metabolizes atorvastatin and simvastatin is CYP3A4.[5,18,21] The major uridine-diphospho glucuronosyl transferases (UGT) isoforms that mediate the glucuronidation of atorvastatin and simvastatin leading to their lactone forms include UGT1A1.[29,30] According to the prescribing information, pemafibrate is mainly metabolized by CYP2C8, CYP2C9, and CYP3A and is a substrate for UGT1A1.[31] However, a similar decrease in the exposure of simvastatin was observed when coadministered with fenofibrate with no marked decrease in the HMG-CoA reductase inhibitory activity[28] although fenofibrate is not an inhibitor of CYP3A4[5] and its glucuronidation is mediated by UGT1A9 and UGT2B7.[32] The overall metabolic pathways of these drugs involve not only CYP and UGT isoforms but also drug transporters, which make the pathways complex. Nevertheless, the reduction in simvastatin concentrations and activity are not likely to importantly decrease the efficacy of the drug or increase the risk of AEs.

The urinary excretion of pemafibrate is extremely low; the plasma concentration of pemafibrate did not increase in individuals with renal dysfunction; and pemafibrate is not contraindicated in patients with severe renal dysfunction, even though caution is recommended when using pemafibrate in these patients.[31] These pharmacokinetic properties of pemafibrate compare favorably to the commonly used PPARα agonists which are mainly eliminated in urine.[5] Gemfibrozil and fenofibrate are contraindicated in patients with severe renal dysfunction, and there are concerns about the use of these drugs in combination with statins, with some combinations being contraindicated.[33–39] In fact, the risk of musculoskeletal AEs including myopathy and rhabdomyolysis was not increased with pemafibrate on top of statin-based treatment compared to placebo in the PROMINENT trial in 10,497 patients with a median follow-up period of 3.4 years. Overall, 96% of patients were taking a statin in the trial and 69% were taking a high intensity statin. The hazard ratio for risk of myopathy was 0.94 [95% CI, 0.88–1.01].[40]

There are limitations to interpret the present results. Firstly, these were studies in a small number of healthy male volunteers without a formal sample size calculation. However, the observed CIs for the pharmacokinetic parameters were narrow and for the most part fitted within the pre-specified limits, which were themselves conservative. Secondly, volunteers in the rosuvastatin study in the United Kingdom were older with a greater BMI than those in the studies conducted in Japan. Therefore, the results may not be generalized to a broader spectrum of patients. Finally, the statin doses are more typical of those used in Japan; therefore, it will require further studies to know if higher doses have greater effects. However, the safety of the combination of pemafibrate and statins was confirmed in the large-scale outcomes trial as mentioned above.

In conclusion, pemafibrate did not increase the systemic exposure of statins, and vice versa, in healthy male volunteers especially in combination with pitavastatin and rosuvastatin.

AUTHOR CONTRIBUTIONS

T.K., N.H., H.S., and R.T. wrote the manuscript; N.H., H.S., and R.T. designed and performed the research; H.S. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

T.K., H.S., and R.T. are employees of Kowa Company, Ltd. N.H. was an employee of Kowa Pharmaceutical Europe Co., Ltd and is a part-time consultant after retirement.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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