Supplementary Materials

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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Study drugs

The study drugs used in the present studies were pemafibrate 0.2 mg tablets (Investigational product, Kowa Company, Ltd., Tokyo, Japan), pitavastatin 2 mg tablets (Livalo®, Kowa Company, Ltd., Tokyo, Japan), atorvastatin 10 mg tablets (Lipitor®, Astellas Pharma Inc., Tokyo, Japan), rosuvastatin 20 mg tablets (Crestor®, AstraZeneca UK Ltd., London, United Kingdom), pravastatin 10 mg tablets (Mevalotin®, Daiichi Sankyo Company, Ltd., Tokyo, Japan), simvastatin 20 mg tablets (Lipovas®, MSD K.K., Tokyo, Japan), and fluvastatin 30 mg tablets (Lochol®, Novartis Pharma K.K., Tokyo, Japan).

Analytical methods to determine plasma and urine concentrations of the drugs

The plasma and urine concentrations of pemafibrate and its metabolites were determined centrally at Shin Nippon Biomedical Laboratories, Ltd. (Tokyo, Japan) by validated methods using high-performance liquid chromatography (HPLC)-tandem mass spectrometry (MS/MS). The range of quantification was 0.05–50 ng/mL in plasma and 1–1000 ng/mL (0.05–50 ng/mL for K-23467, K-23469, and K-23605) in urine.

Concentrations of pemafibrate and its metabolites were determined using analytical methods similar to previously reported ones [1,2] as briefly described as follows. As calibration samples for plasma concentrations, each of methanol solutions containing different amounts of standard substances was mixed with 250 μL of ethanol solution containing 2% propylene glycol. The mixed solutions were dried with evaporation under nitrogen at 40°C. To the dried residue, 100 μL of blank plasma was added. Then, 100 μL of the calibration samples or study plasma samples was mixed with 900 μL of 0.1% aqueous acetic acid. Each sample was extracted with 5 mL of tert-butylmethyl ether for 10 min. After 10 min of centrifugation, the organic layer was transferred and mixed with 250 μL of ethanol solution containing 2% propylene glycol. The solution was dried with evaporation under nitrogen at 40°C and the dried residue was dissolved in aqueous methanol. Urine samples were similarly prepared.

The obtained samples were analyzed using HPLC from Shimadzu Corporation (Kyoto Japan) with Symmetry C18 column (2.1 × 50 mm id, 5 μm) from Waters Corporation (MA USA) or similar one, and then using API4000 triple-quadrupole mass spectrometer or similar one (AB SCIEX, CA, USA) equipped with electrospray ionization operated in the positive ion mode with quantification in multiple reaction monitoring mode.

Sample preparations for statins were basically similar to the methods for pemafibrate and several conditions previously described [3-8] but performed as quickly as possible under ice cold conditions. Briefly, for the case of simvastatin, samples were mixed with acetonitrile solution containing internal standard. Acetonitrile/ammonium acetate was added to the samples and solid phase extraction was applied. After the extraction, the solvent was evaporated under nitrogen at approximately 40°C. The dried residues were dissolved in the reconstitution solution of acetonitrile/ammonium acetate solution before going to measurement.

For other statins, the samples were similarly mixed with acetonitrile solutions containing each internal standard, where methanol was also added in for atorvastatin, pravastatin, and fluvastatin. Solid phase extraction was applied for rosuvastatin. Extraction methods were not applied to other statins, for which analytes were separated by centrifugation. The solid phase extraction for rosuvastatin and centrifugation for other statins were followed by evaporation under nitrogen at approximately 40°C except for pitavastatin. The reconstitution solution used to dissolve the dried residues were formic acid-methanol solution for atorvastatin, ammonium formate and methanol solution containing formic acid for rosuvastatin, methanol solution for pravastatin, and formic acid for fluvastatin. For pitavastatin, the samples were mixed with ammonium formate after the centrifugation.

The HPLC-MS/MS methods were performed with similar system equipped with electrospray ionization operated in the positive ion mode with quantification in multiple reaction monitoring mode for most cases. The negative ion mode was used for pravastatin and simvastatin open acid.

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chromatography-tandem mass spectrometry for pharmaceutical study. Biomed Chromatogr. 2008 Feb;22(2):131-5. doi: 10.1002/bmc.905. PMID: 17703482.

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In vitro assessment of HMG-CoA reductase inhibitory activity of plasma samples in the study with simvastatin

The principle of measuring the HMG-CoA reductase inhibitory activity of plasma samples was to determine the amount of mevalonic acid produced from the reaction of HMG-CoA with HMG-CoA reductase and NADHP in presence of simvastatin and simvastatin-derived HMG-CoA reductase inhibitors present in the plasma samples as previously reported. [9]

Plasma samples were treated with acetonitrile for protein precipitation to prepare protein-deprived solutions. The plasma-derived solution was divided into aliquots. One of the aliquots was mixed with potassium phosphate buffer to be used for the measurement of HMG-CoA reductase inhibitory activity derived from simvastatin-derived metabolites present in the samples as the active forms. The other of the aliquots was treated with base hydrolysis to transform the lactone forms of simvastatin and simvastatin-derived metabolites into the open acid forms, for which measured HMG-CoA reductase inhibitory activity was regarded as derived from both the active and inactive forms. The aliquot treated with the base hydrolysis was then neutralized with potassium phosphate buffer. The samples were further prepared with Triton solution and set at 96-well plate.

Enzyme working solution containing HMG-CoA reductase, Triton, and potassium phosphate buffer was added to the 96-well plate. Then, enzyme substrate solution containing [^{14}C]-HMG-CoA,

NADHP, Triton, and potassium phosphate buffer was added to the samples on the plate. The mixed samples were incubated at 37˚C for 30 min. Hydrochloric acid was added to the samples to stop the reaction to produce [^{14}C]-mevalonic acid. After the reaction was stopped, [^{14}C]-mevalonic acid was lactonized to [^{14}C]-mevalonolactone. The samples were loaded into the anion exchange resin column, and then the pass-through was collected. After transferred to scintillation vials, the collected solutions were mixed with scintillation cocktail, and the radio activity derived from [^{14}C]-mevalonolactone was determined on a scintillation counter.

The determined inhibitory activities from the samples treated without base hydrolysis were regarded as attributed from all simvastatin-derived metabolites that were present in the plasma samples as open acid forms (active HMG-CoA inhibitors). Those with base hydrolysis were regarded as attributed from simvastatin and all the metabolites including those present as lactone forms (total HMG-CoA inhibitors). The inhibitory activity was converted into plasma-concentration equivalent value with a unit of ng-Eq/mL according to a calibration curve of HMG-CoA reductase activity to the concentration of simvastatin open acid form.

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Table S1 Schedule of urine collection to determine urine concentrations of pemafibrate and statins

Study	Day 1		Days 2–6	Days 7–10						
	Pre-dose	Post-dose 0–24h	Post-dose 0–24h	Pre-dose	Post-dose on Day 7					
					0h	12h	24h	36h	48h	60h	72h
Studies with pitavastatin and atorvastatin	X			<---------- ----><---- ---->							
Study with rosuvastatin											
Treatment P	X			X	<---------->						
Treatments S and C	X			X	<----><----><----><----><----><----><----><----><----><----><----><----><----><---->						
Studies with pravastatin, simvastatin, and fluvastatin											
Treatments P and C	X	<----->	<----->		<----><----><----><----><----><----><----><----><----><---->						
Treatment S	X				<----><----><----><---->						

The X marks and double-headed arrows indicate casual and pooled sampling, respectively.

Pre-dose, before morning dose; Post-dose, after morning dose;

Treatment P, treatment with pemafibrate alone; Treatment S, treatment with statin alone; Treatment C, treatment with pemafibrate and statin.

Table S2 Baseline characteristics of safety population

	Study with pitavastatin	Study with atorvastatin	Study with rosuvastatin	Study with pravastatin	Study with simvastatin	Study with fluvastatin
n	18	18	29	18	20	19
Age, years						
Mean±SD	27.1±3.8	25.9±3.9	37.3±12.0	26.2±2.9	24.7±3.2	24.7±3.0
Median [Interquartile range]	27 [24–29.8]	25 [23–29.5]	36 [28–45]	25 [24.3–28.8]	24 [23–26.25]	25 [23–26.5]
Minimum, maximum	21, 34	22, 33	20, 60	22, 31	20, 32	20, 31
Body mass index, kg/m^2						
Mean±SD	20.7±1.4	21.6±2.9	24.7±2.4	20.7±2.3	21.7±2.3	20.6±1.9
Median [Interquartile range]	20.8 [19.7–21.8]	20.5 [19.4–23.1]	24.4 [22.9–26.7]	19.9 [19.2–21.4]	22 [19.5–23.4]	20 [19.3–21.3]
Minimum, maximum	18.5, 23.4	18.4, 27.5	19.5, 29.2	18.6, 26.8	18.8, 25.6	18.6, 25.5

Table S3 Extended results of pharmacokinetic parameters of pemafibrate and statins

Study	Parameter	Pemafibrate		Statin	
		Without statin	With statin	Without pemafibrate	With pemafibrate
With pitavastatin	C_{max} (ng/mL)	2.8 (32.6);	3.0 (22.8);	49.0 (18.6);	49.6 (14.2);
		3.0 [2.0–3.5]	2.8 [2.6–3.6]	47.8 [44.4–55.2]	50.7 [46.3–53.2]
(n=18)	AUC_{0-T} (ng·h/mL)	9.8 (30.4);	11.0 (19.2);	167.3 (13.6);	173.4 (14.4);
		10.3 [7.7–12.3]	10.9 [10.3–12.4]	163.5 [152.6–186.2]	172.4 [156.8–193.8]
	t_{max} (h)	2.0 (1.0, 3.0);	2.0 (1.0, 3.0);	1.5 (1.0,1.5);	1.5 (1.0,2.0);
		[1.5–2.0]	[1.5–2.0]	[1.0–1.5]	[1.0–2.0]
	$t_{1/2}$ (h)	2.0 (27.2);	2.0 (24.5);	11.0 (18.9);	10.7 (14.3);
		2.0 [1.7–2.3]	1.8 [1.7–2.5]	11.3 [9.5–12.5]	10.4 [9.6–11.2]
	Kel (1/h)	0.342 (24.0);	0.352 (22.0);	0.063 (19.5);	0.065 (12.6);
		0.354 [0.305–0.397]	0.381 [0.278–0.412]	0.062 [0.055–0.073]	0.067 [0.062–0.072]
	MRT_{ss} (h)	3.5 (11.8);	3.7 (16.8);	9.7 (10.6);	9.1 (10.3);
		3.6 [3.4–3.7]	3.6 [3.3–4.0]	9.8 [9.0–10.2]	9.1 [8.7–9.6]
	CL_{ss}/F (L/h)	20.4 (32.9);	18.2 (22.1);	22.9 (13.8);	22.1 (15.1);
		19.8 [16.3–25.8]	18.4 [16.2–19.4]	23.4 [20.6–25.1]	22.2 [19.7–24.4]
	Vd_{ss}/F (L)	59.6 (37.6);	51.7 (28.8);	364.2 (27.8);	339.5 (25.8);
		58.6 [44.4–82.6]	48.7 [43.1–60.4]	374.5 [302.7–452.9]	328.4 [277.4–384.6]

With atorvastatin	C_{max} (ng/mL)	3.6 (28.4);	4.2 (26.9);	6.3 (28.3);	6.5 (36.4);
		3.6 [3.2–3.9]	4.3 [3.4–5.0]	6.3 [5.1–7.7]	6.4 [4.8–8.4]
(n=18)	$AUC_{0-\tau}$ (ng·h/mL)	12.0 (32.0);	13.1 (31.8);	46.9 (32.9);	43.8 (39.3);
		11.6 [10.3–14.2]	13.2 [10.7–15.7]	44.2 [40.1–55.7]	43.9 [36.9–54.5]
	t_{max} (h)	1.5 (1.0, 3.0);	1.5 (1.0, 3.0);	1.5 (0.5, 3.0);	1.5 (0.5, 4.0);
		[1.5–1.5]	[1.5–2.0]	[1.0–2.0]	[1.5–2.0]
	$t_{1/2}$ (h)	1.7 (25.5);	1.6 (33.1);	6.2 (51.7);	6.2 (40.1);
		1.8 [1.5–2.0]	1.6 [1.3–2.1]	5.6 [5.0–7.6] [a]	5.5 [4.6–8.1] [b]
	Kel (1/h)	0.398 (25.0);	0.426 (35.1);	0.112 (37.9);	0.112 (32.8);
		0.394 [0.350–0.471]	0.432 [0.330–0.519]	0.124 [0.091–0.139] [a]	0.127 [0.086–0.150] [b]
	MRT_{ss} (h)	3.3 (16.6);	3.0 (13.0);	9.3 (50.6);	9.3 (34.6);
		3.2 [2.8–3.6]	3.0 [2.8–3.2]	8.1 [7.2–11.4] [a]	8.5 [6.7–12.4] [b]
	CL_{ss}/F (L/h)	16.7 (34.0);	15.2 (30.2);	426.8 (31.8);	457.1 (41.1);
		17.2 [14.1–19.4]	15.2 [12.7–18.6]	452.0 [358.9–499.3]	456.2 [367.3–542.8]
	Vd_{ss}/F (L)	42.0 (23.1);	35.7 (20.1);	3760.7 (53.3);	3872.3 (33.1);
		40.6 [36.1–46.0]	34.1 [32.3–40.5]	3705.3 [2975.0–4295.4] [a]	4029.5 [3011.1–5014.3] [b]
With rosuvastatin	C_{max} (ng/mL)	1.8 (38.7);	1.9 (43.2);	4.6 (51.2);	5.0 (48.0);
		1.7 [1.4–2.2]	1.9 [1.6–2.4]	4.3 [3.5–5.5]	4.9 [4.0–6.7]
(n=24)	$AUC_{0-\tau}$ (ng·h/mL)	6.7 (43.2);	7.4 (45.5);	54.9 (56.9);	56.2 (49.1);
		6.5 [4.7–8.6]	7.5 [5.6–9.0]	49.8 [40.5–70.3]	54.3 [42.5–76.7]

	t_{max} (h)	2.0 (1.5, 4.0);	2.0 (0.5, 4.0);	4.0 (0.3, 6.0);	4.0 (0.5, 6.0);
		[1.5–3.0]	[1.5–3.0]	[3.0–6.0]	[2.0–6.0]
	$t_{1/2}$ (h)	1.7 (35.3);	2.0 (31.2);	17.9 (55.7);	18.8 (55.4);
		1.6 [1.4–2.2] [c]	2.0 [1.4–2.5] [c]	16.4 [14.9–21.1] [c]	16.0 [14.3–22.0] [c]
	MRT_{ss} (h)	3.7 (17.8);	3.7 (21.2);	18.0 (24.5);	16.8 (31.3);
		3.7 [3.2–4.1] [c]	3.7 [3.2–4.5] [c]	17.7 [15.8–20.1] [c]	14.7 [13.7–21.7] [c]
	Kel (1/h)	0.397 (29.0);	0.351 (31.0);	0.039 (30.3);	0.037 (36.5);
		0.431 [0.321–0.488] [c]	0.351 [0.276–0.485] [c]	0.042 [0.033–0.047] [c]	0.043 [0.032–0.048] [c]
	CL_{ss}/F (L/h)	29.9 (38.8);	26.9 (43.4);	364.6 (46.8);	355.6 (46.4);
		30.8 [23.3–42.6]	26.9 [22.3–35.8]	402.1 [284.4–494.1]	368.6 [260.8–471.3]
	Vd_{ss}/F (L)	73.2 (29.0);	73.8 (30.1);	9503.7 (93.8);	9440.2 (67.4);
		74.0 [59.4–90.1] [c]	71.4 [62.3–79.3] [c]	10611.0 [6826.2–13182.7] [c]	7942.5 [5592.1–15673.5] [c]
With pravastatin	C_{max} (ng/mL)	3.4 (38.4);	3.6 (40.3);	21.7 (66.4);	24.1 (46.0);
		3.2 [2.8-3.5]	3.4 [2.7-4.3]	21.2 [13.9–40.1]	24.1 [18.3–32.8]
(n=18)	AUC_{0-T} (ng·h/mL)	12.4(39.7);	13.1 (52.1);	52.3 (62.1);	55.7 (49.2);
		11.9 [9.8-15.9]	12.6 [9.5-18.1]	53.5 [31.8–84.1]	53.6 [47.3–76.2]
	t_{max} (h)	1.8 (0.5, 4.0);	1.5 (1.0, 3.0);	2.0 (1.0, 3.0);	2.0 (1.0, 2.0);
		[1.5-2.0]	[1.5-2.0]	[1.0–2.0]	[1.0–2.0]
	$t_{1/2}$ (h)	2.3 (18.5);	2.5 (31.0);	4.4 (71.3);	7.0 (53.2);
		2.3 [2.2-2.5]	2.3 [2.1–2.6]	4.1 [2.4–8.0] [d]	9.7 [5.6–12.3] [e]

	Kel (1/h)	0.298 (19.2);	0.278 (24.5);	0.156 (64.4);	0.099 (97.4);
		0.298 [0.282–0.316]	0.308 [0.264–0.333]	0.170 [0.087–0.293] [d]	0.072 [0.057–0.142] [e]
	MRT_{ss} (h)	3.8 (13.6);	4.0 (22.2);	3.8 (36.3);	3.7 (26.3);
		3.9 [3.5-4.2]	3.8 [3.5–4.6]	3.9 [3.5–4.8] [d]	4.0 [3.4–4.6] [e]
	CL_{ss}/F (L/h)	16.1 (36.0);	15.3 (40.2);	363.9 (59.4);	341.6 (46.9);
		16.9 [12.6-20.5]	15.8 [11.2–21.1]	355.7 [226.4–609.3]	354.7 [249.6–401.8]
	Vd_{ss}/F (L)	54.1 (31.9);	55.0 (28.8);	2493.7 (76.8);	3673.7 (52.3);
		56.4 [43.0-70.5]	57.5 [46.0–68.6]	2628.1 [1870.8–3505.1] [d]	3518.7 [2533.0–6450.5] [e]
With simvastatin	C_{max} (ng/mL)	3.4 (32.9);	4.1 (24.5);	4.5 (122.7);	3.9 (52.8);
		3.5 [2.9–4.2] [f]	4.1 [3.6–4.9]	3.8 [2.5–6.0]	3.6 [2.8–6.5]
(n=19)	$AUC_{0-\tau}$ (ng·h/mL)	13.8 (38.5);	15.4 (38.5);	13.3 (91.7);	11.3 (47.0);
		14.0 [11.9–16.5] [f]	14.4 [13.3–17.3]	12.7 [9.5–16.9]	11.5 [8.8–17.9]
	t_{max} (h)	2.0 (1.0, 3.0);	1.5 (1.0, 4.0);	1.0 (0.5, 2.0);	1.0 (0.5, 2.0);
		[1.5–2.0] [f]	[1.5–2.0]	[1.0–1.5]	[1.0–2.0]
	$t_{1/2}$ (h)	2.5 (31.3);	2.4 (31.1);	2.9 (27.6);	2.4 (27.1);
		2.6 [1.9–3.1] [f]	2.2 [2.0–2.5]	2.8 [2.4–3.4] [f]	2.4 [1.9–2.9]
	Kel (1/h)	0.276 (31.1);	0.290 (23.4);	0.239 (24.0);	0.291 (28.6);
		0.270 [0.221–0.366] [f]	0.316 [0.274–0.348]	0.248 [0.204–0.284] [f]	0.284 [0.238–0.361]
	MRT_{ss} (h)	4.3 (26.9);	4.1 (31.3);	3.2 (21.2);	2.9 (17.3);
		4.5 [3.5–4.8] [f]	3.9 [3.5–4.8]	3.2 [2.9–3.6] [f]	2.9 [2.6–3.4]

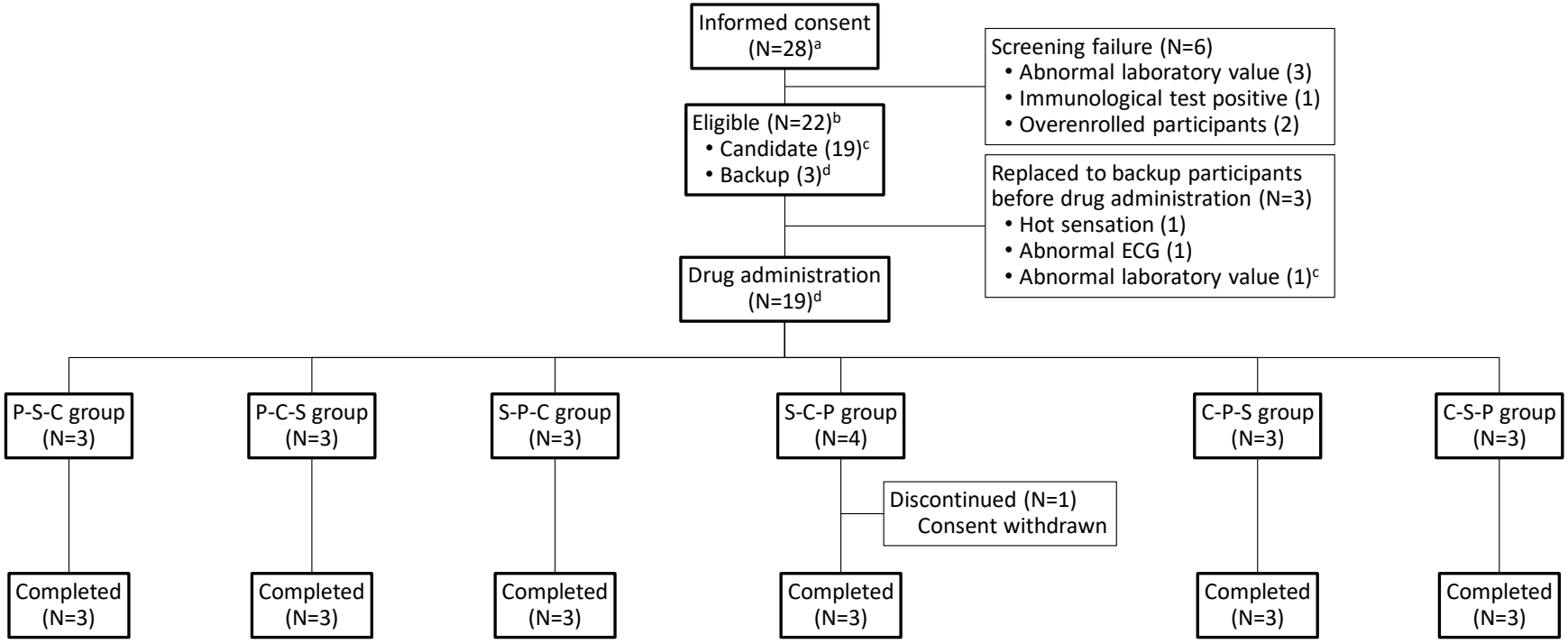
	CL_{ss}/F (L/h)	14.5 (42.3);	13.0 (35.6);	1504.5 (58.7);	1776.7 (72.2);
		14.3 [12.1–16.8] [f]	13.9 [11.6–15.1]	1573.7 [1193.8–2099.0]	1742.6 [1118.9–2273.5]
	Vd_{ss}/F (L)	52.7 (33.4);	44.9 (20.2);	5995.8 (56.0);	6096.7 (55.0);
		51.8 [41.6–62.7] [f]	43.2 [40.7–50.9]	6575.5 [4602.9–8086.3] [f]	5656.3 [4393.9–8664.0]
With fluvastatin	C_{max} (ng/mL)	4.0 (29.6);	4.7 (29.9);	469.0 (60.5);	464.0 (61.3);
		3.8 [3.3–4.6]	4.4 [4.0–6.0] [f]	445.4 [352.8–529.1] [f]	454.5 [338.3–537.9] [f]
(n=19)	AUC_{0-T} (ng·h/mL)	16.1 (35.5);	19.4 (32.6);	907.7 (29.8);	1044.5 (31.5);
		14.9 [12.6–21.6]	19.6 [14.8–24.1] [f]	868.4 [783.9–1052.3] [f]	957.9 [823.0–1168.3] [f]
	t_{max} (h)	2.0 (1.0, 3.0);	2.0 (0.5, 4.0);	1.5 (0.5, 2.0);	1.0 (0.8, 4.0);
		[1.5–2.0]	[1.6–2.8] [f]	[1.0–1.9] [f]	[1.0–2.0] [f]
	$t_{1/2}$ (h)	2.5 (38.6);	2.8 (25.6);	5.8 (25.5);	6.4 (18.6);
		2.2 [2.0–2.5]	2.8 [2.5–3.1] [f]	6.2 [5.5–7.3] [b]	6.5 [5.9–7.3] [a]
	Kel (1/h)	0.281 (26.2);	0.248 (24.3);	0.120 (38.8);	0.108 (28.4);
		0.313 [0.275–0.339]	0.248 [0.222–0.282] [f]	0.112 [0.096–0.127] [b]	0.106 [0.095–0.117] [a]
	MRT_{ss} (h)	4.2 (27.9);	4.5 (29.0);	2.9 (26.9);	3.1 (34.9);
		4.0 [3.8–4.4]	4.4 [3.9–4.8] [f]	3.1 [2.5–3.5] [b]	3.2 [2.3–3.8] [a]
	CL_{ss}/F (L/h)	12.4 (31.7);	10.3 (28.3);	66.1 (25.3);	57.4 (25.4);
		13.5 [9.4–15.9]	10.2 [8.3–13.5] [f]	69.1 [57.1–76.6] [f]	62.8 [51.4–72.9] [f]
	Vd_{ss}/F (L)	44.2 (30.0);	41.6 (26.5);	542.3 (39.8);	533.6 (33.2);
		43.6 [38.6–53.0]	45.0 [32.4–52.4] [f]	611.3 [485.1–694.1] [b]	560.6 [509.0–708.7] [a]

The dose of pemafibrate was 0.2 mg twice daily and the doses of statins were 20 mg for atorvastatin, 4 mg for pitavastatin, 20 mg for rosuvastatin, 20 mg for pravastatin, 20 mg for simvastatin, and 60 mg for fluvastatin once daily.

Data are presented as geometric mean (coefficient of variation); median [interquartile range] except for t_{max}, which is presented as median (minimum, maximum); [interquartile range].

[a] n=17, [b] n=16, [c] n=23, [d] n=11, [e] n=12, [f] n=18.

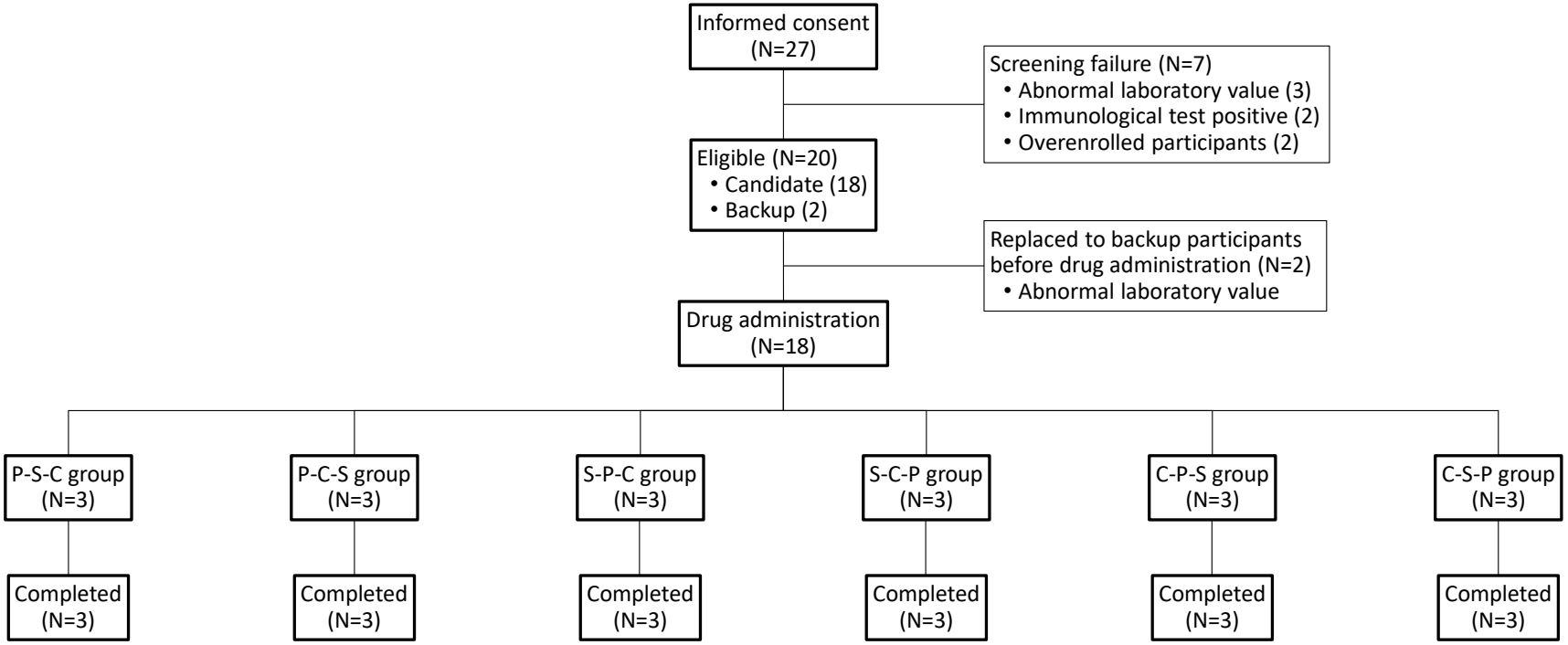
Figure S1 Disposition of participants in the study with pitavastatin (K-877-05 study)



[a] Three participants were additionally recruited because of consent withdrawal of one participant in the S-C-P group during Treatment Period 1.
[b] Including two out of the three additional participants (one for candidate [c] and the other for backup[d]).
[c] The candidate from the additional participants was withdrawn before drug administration due to abnormal laboratory value.
[d] The backup participant among the additional participants was replaced for the candidate from the additional participants.

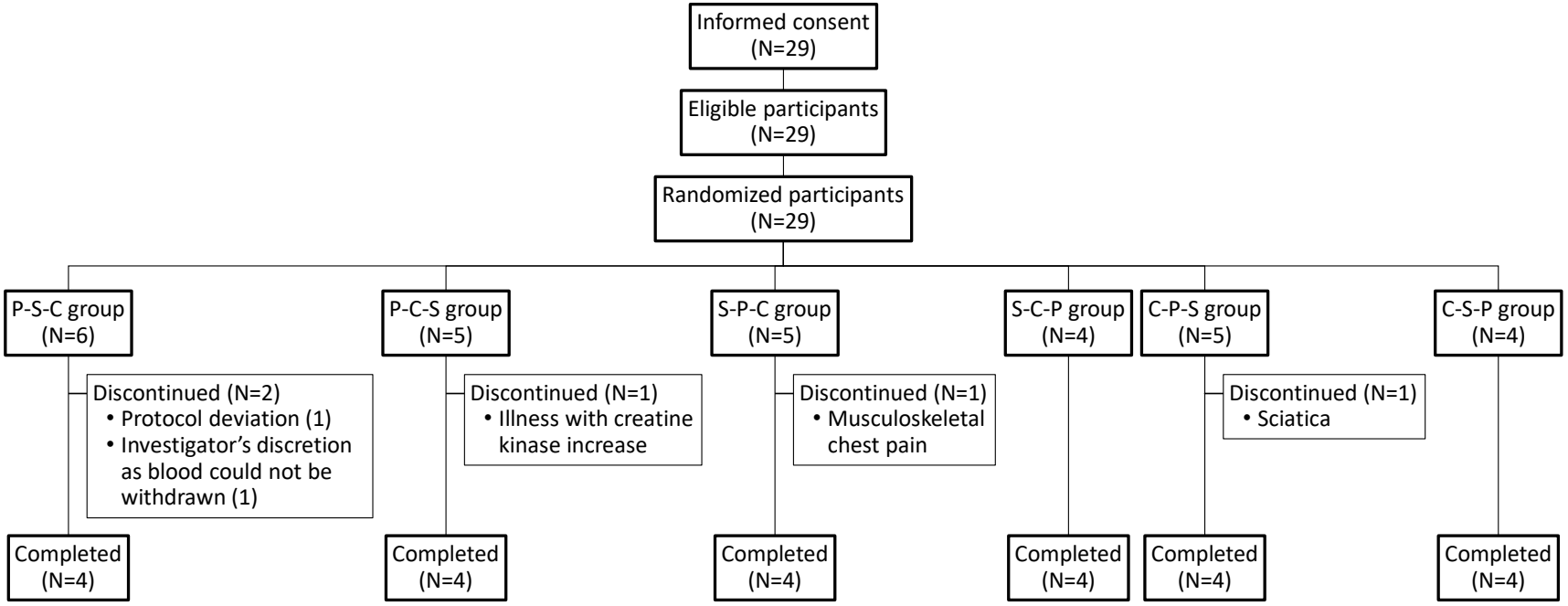
P, S, and C in the group names such as P-S-C and P-C-S indicate the treatment with pemafibrate, statin (pitavastatin), and combination of them, respectively, with its sequence corresponding to the order of the treatment in which participants were to receive.

Figure S2 Disposition of participants in the study with atorvastatin (K-877-06 study)



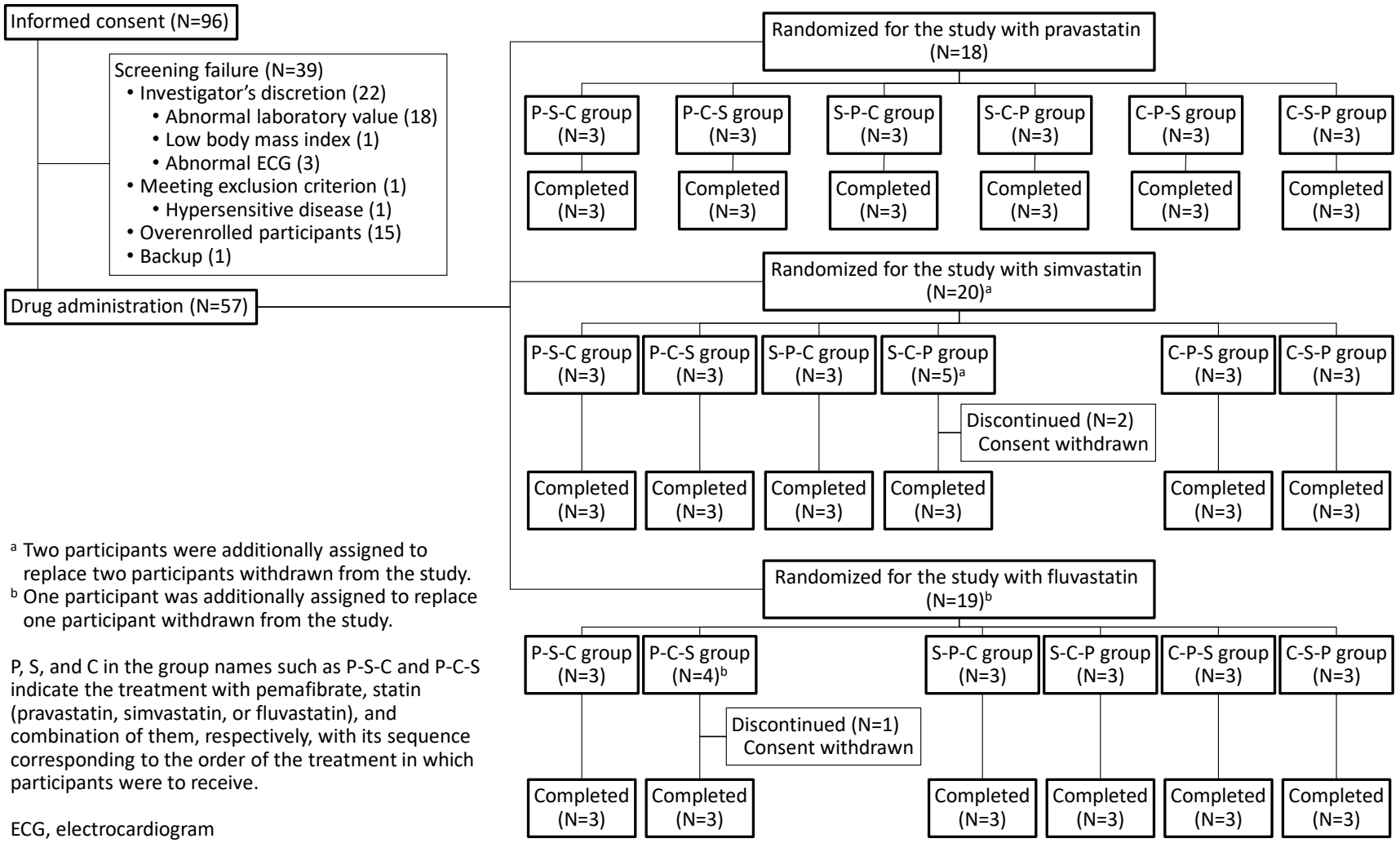
P, S, and C in the group names such as P-S-C and P-C-S indicate the treatment with pemafibrate, statin (atorvastatin), and combination of them, respectively, with its sequence corresponding to the order of the treatment in which participants were to receive.

Figure S3 Disposition of participants in the study with rosuvastatin (K-877-08 study)



P, S, and C in the group names such as P-S-C and P-C-S indicate the treatment with pemafibrate, statin (rosuvastatin), and combination of them, respectively, with its sequence corresponding to the order of the treatment in which participants were to receive.

Figure S4 Disposition of participants in the studies with pravastatin, simvastatin, and fluvastatin (K-877-18 study)



[a] Two participants were additionally assigned to replace two participants withdrawn from the study.
[b] One participant was additionally assigned to replace one participant withdrawn from the study.

P, S, and C in the group names such as P-S-C and P-C-S indicate the treatment with pemafibrate, statin (pravastatin, simvastatin, or fluvastatin), and combination of them, respectively, with its sequence corresponding to the order of the treatment in which participants were to receive.

ECG, electrocardiogram