Table 56. Enalapril PK parameters

Treatment		Enalapril			Enalapril and pitavastatin	
Parameter	**Number of subjects in Day 6**	**Day 6 Geometric Mean**	**Day 6 CV%**	**Number of subjects in Day 11**	**Day 11 Geometric Mean**	**Day 11 CV%**
Tmax (h)	18	1.00*	0.50-1.00	18	1.00*	0.50-2.00
Cmax (ng/mL)	18	134.76	35.91	18	150.64	37.21
AUC0–τ (ng*h/mL)	18	223.86	31.14	18	251.26	31.06
t1/2 (h)	18	1.10	125.26	18	0.86	17.34
CL/F (L/h)	18	89.34	31.06	18	79.60	32.38

* = median

Table 57. Enalaprilat PK parameters

Treatment		Enalapril			Enalapril and pitavastatin	
Parameter	**Number of subjects in Day 6**	**Day 6 Geometric Mean**	**Day 6 CV%**	**Number of subjects in Day 11**	**Day 11 Geometric Mean**	**Day 11 CV%**
Tmax (h)	18	3.00*	2.50-4.00	18	3.00*	2.00-4.00
Cmax (ng/mL)	18	90.74	34.83	18	89.81	32.17
AUC0–τ (ng*h/mL)	18	691.74	24.54	18	682.98	24.35
t1/2 (h)	18	5.97	17.33	18	5.54	19.14

* = median

Table 58. Enalapril PK parameter analyses

Treatment	Enalapril	Enalapril and pitavastatin		
Parameter	Geometric mean		Ratio of geometric means	90% CI
C_{max} (ng/mL)	134.76	150.64	1.12	1.03–1.21
$AUC_{0-\tau}$ (ng*h/mL)	223.86	251.26	1.12	1.06–1.19

Table 59. Enalaprilat PK parameter analyses

Treatment	Enalapril	Enalapril and pitavastatin		
Variable	Geometric mean		Ratio of geometric means	90% CI
Cmax (ng/mL)	90.74	89.81	0.99	0.93–1.05
AUC0–τ (ng*h/mL)	691.74	682.98	0.99	0.95–1.03

The enalapril C_{max} geometric mean ratio in the presence and absence of pitavastatin as well as that of $AUC_{0-\tau}$ are both 1.12. The presence of pitavastatin did significantly affect the enalapril exposure since the 90% CI of their geometric mean ratios are within the 0.8 and 1.25 bioequivalence goalpost.

Enalapril is a prodrug and is converted to the active drug, enalaprilat via hydrolysis. The enalaprilat C_{max} geometric mean ratio in the presence and absence of pitavastatin as well as that of $AUC_{0-\tau}$ are both 0.99. The presence of pitavastatin did significantly affect the enalaprilat exposure since the 90% CI of their geometric mean ratios are within the 0.8 and 1.25 bioequivalence goalpost.

	Study 1.28	Reviewer's Comments
Population	Healthy men	OK
Choice of interacting drug	Enalapril	OATP1B1 substrate *JPET* **318**:395-402 (2006)
Route of administration	Oral	Relevant to pitavastatin tablet
Number of participants	18	Relative bioavailability, OK.
Washout	7 days	Enalapril is a prodrug, enalaprilat $t_{½}$ is ~ 11 hours. Pitavastatin $t_{½}$ is ~10 hours.
Dose selection	4 mg pitavastatin daily for 5 days 20 mg enalapril	Usual oral pitavastatin dose. Usual dose is 20 mg enalapril/d PO for hypertension.
Administration	Enalapril	May be taken without regard to meals.

2.4.2.12 Rifampin

Study 1.27 examined the effect of multiple-dose rifampin and multiple-dose pitavastatin in 18 healthy Caucasian men. Each participant completed 2 treatments (A then B). A minimum of 7 days separated these 2 treatments. In Treatment A, each fasted participant orally received a 4 mg pitavastatin tablet **daily on Days 1 – 5. In Treatment B, each fasted** participant orally received a 600 mg rifampin capsule **daily on Days 1 – 15 and a 4 mg pitavastatin tablet daily on Days 11 – 15. Participants received all** drugs in the fasted state. Serial plasma samples were collected at predose (Day 4 of Treatment A and Day 14 of Treatment B) and 24 hours postdose (Day 5 of Treatment A and Day 15 of Treatment B) to determine pitavastatin and its lactone via validated HPLC/MS/MS assay. Other serial plasma samples were collected at predose (Days 9 and 14 of Treatment B) and 24 hours postdose (Days 10 and 14 of Treatment B) to determine rifampin via validated LC/MS/MS assay.

Figure 52 (left). Plasma pitavastatin concentration – time profile. Figure 53 (right). Plasma pitavastatin lactone concentration – time profile.

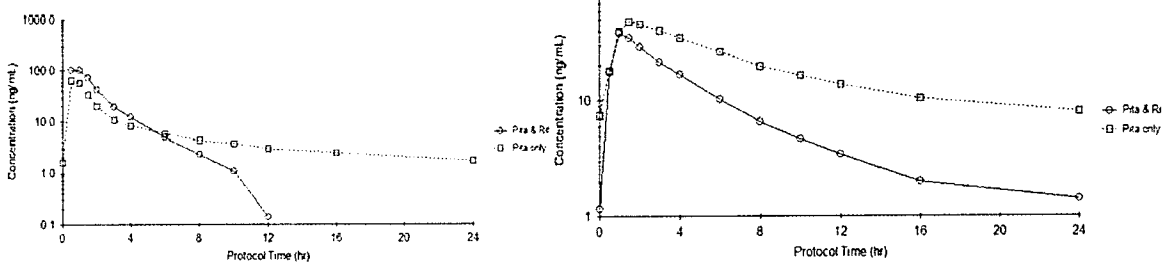


Table 60. Pitavastatin PK parameters

Treatment	Pitavastatin			Pitavastatin and rifampin		
Parameter	**Number of subjects in Day 5**	**Day 5 Geometric Mean**	**Day 5 CV%**	**Number of subjects in Day 15**	**Day 15 Geometric Mean**	**Day 15 CV%**
Tmax (h)	18	0.50*	0.50-1.50	16	0.52*	0.50-1.50
Cmax (ng/mL)	18	65.49	35.78	16	138.47	40.44
AUC0–τ (ng*h/mL)	18	158.79	31.74	16	215.07	29.68
t1/2 (h)	14	15.53	41.80	16	1.92	19.36
CL/F (L/h)	18	25.19	43.79	16	18.60	30.81

* = median

Table 61. Pitavastatin lactone PK parameters

Treatment	Pitavastatin			Pitavastatin and rifampin		
Parameter	Number of subjects in Day 5	Day 5 Geometric Mean	Day 5 CV%	Number of subjects in Day 15	Day 15 Geometric Mean	Day 15 CV%
Tmax (h)	18	1.50*	1.00-3.02	16	1.00*	1.00-2.00
Cmax (ng/mL)	18	46.90	27.03	16	39.53	29.49
AUC0–τ (ng*h/mL)	18	409.19	34.79	16	177.41	28.39
t1/2 (h)	125	12.06	21.66	9	6.38	53.26

* = median

Table 62. Pitavastatin PK parameter analyses

Treatment	Pitavastatin	Pitavastatin and rifampin		
Parameter	Geometric mean		Ratio of geometric means	90% CI
Cmax (ng/mL)	69.16	138.47	2.00	1.57–2.56
AUC0–τ (ng*h/mL)	166.85	215.07	1.29	1.10–1.51

Table 63. Pitavastatin lactone PK parameter analyses

Treatment	Pitavastatin	Pitavastatin and rifampin		
Variable	Geometric mean		Ratio of geometric means	90% CI
Cmax (ng/mL)	47.87	39.53	0.83	0.75–0.90
AUC0–τ (ng*h/mL)	419.45	177.41	0.42	0.40–0.45

The pitavastatin C_{max} geometric mean ratio in the presence and absence of rifampin as well as that of $AUC_{0-\tau}$ is 2.00 and 1.29, respectively. The presence of rifampin significantly affected the pitavastatin C_{max} and $AUC_{0-\tau}$ since the 90% CI of their geometric mean ratios are outside of the 0.8 and 1.25 bioequivalence goalpost.

The pitavastatin lactone C_{max} geometric mean ratio in the presence and absence of rifampin as well as that of $AUC_{0-\tau}$ is 0.83 and 0.42, respectively. The presence of rifampin significantly affected the pitavastatin lactone exposure since the 90% CI of their geometric mean ratios are outside the 0.8 and 1.25 bioequivalence goalpost.

Figure 54. Plasma rifampin concentration – time profile.

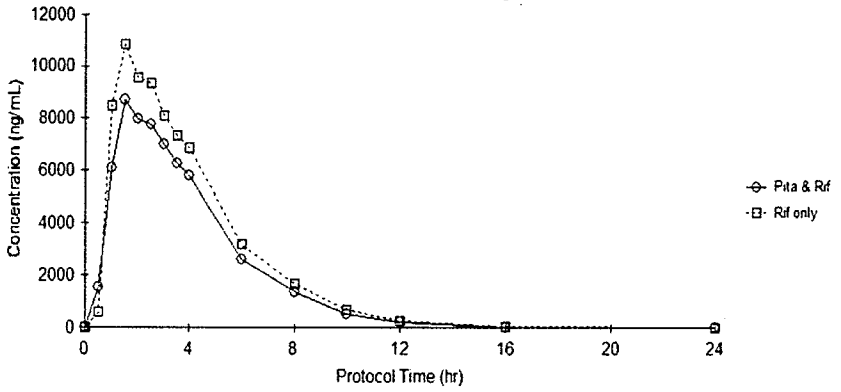


Table 64. Rifampin PK parameters.

Treatment Variable	Rifampin Geometric mean	Rifampin and pitavastatin Geometric mean	Ratio of geometric means	90% CI
Cmax (ng/mL)	10847.46	8941.29	0.82	0.69 – 0.98
AUC0–τ (ng*h/mL)	44957.78	38080.37	0.85	0.75 – 0.95

Parameter	Number of subjects in Day 10	Day 10 Geometric Mean	Day 10 CV%	Number of subjects in Day 15	Day 15 Geometric Mean	Day 15 CV%
Tmax (h)	17	1.50[2]	1.00-3.50	16	1.50[2]	1.00-3.50
Cmax (ng/mL)	17	10961.67	35.90	16	8941.29	31.95
AUC0–τ (ng*h/mL)	17	44490.94	34.37	16	38080.37	26.57
t1/2 (h)	17	1.40	17.75	16	1.43	15.70
CL/F (L/h)	17	13.49	34.67	16	15.76	32.09

[2] = median

Table 65. Rifampin PK parameter analyses

The rifampin C_{max} geometric mean ratio in the presence and absence of pitavastatin as well as that of $AUC_{0-\tau}$ is 0.82 and 0.85, respectively. The presence of pitavastatin significantly affected the rifampin exposure since the 90% CI of their geometric mean ratios are outside the 0.8 and 1.25 bioequivalence goalpost.

	Study 1.27	Reviewer's Comments
Population	Healthy men	OK
Choice of interacting drug	Rifampin	Per the draft Drug Interaction Guidance, rifampin is an in vivo strong CYP3A4/5 inducer. Rifampin is also an OATP1B1 inhibitor.
Route of administration	Oral	Relevant to pitavastatin tablet
Number of participants	18	Relative bioavailability, OK.
Washout	≥ 7 days	Rifampin $t_{½}$ is ~ 3 – 5 hours. Pitavastatin $t_{½}$ is ~10 hours.
Dose selection	4 mg pitavastatin daily for 5 days 60 mg rifampin daily	Usual oral pitavastatin dose. Usual dose is 600 mg rifampin/d is the maximum anti-tuberculosis dose.
Administration	Rifampin	Take ≥ 1 hour prior or 2 hours after a meal.

Pitavastatin calcium's effect on coadministered drugs' PK:

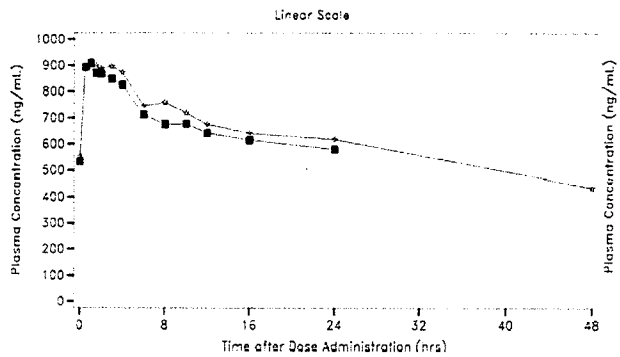
2.4.2.13 Warfarin

Study 1.25US examined the mutual interaction of multiple-dose warfarin and multiple-dose pitavastatin in 24 healthy men (20 Caucasian, 3 African American, and 1 American Indian or Alaska Native).

This was a 2-sequential dosing study. Each participant orally received two 2.5 mg warfarin tablets daily on Days 1 – 3, then individualized warfarin dose per INR 1.2 – 2.2 on Days 4 – 9. On Days 10 –

13, each participant orally received the steady-state maintenance warfarin dose once daily and dose was further adjusted. On Days 14 – 21, each participant orally received the individualized maintenance warfarin dose once daily and a 4 mg pitavastatin tablet once daily. On Day 22, each participant orally received a 4 mg pitavastatin tablet. Each participant received all drugs under fasting state. Serial plasma samples were collected predose and for 24 hours postdose on Day 13 as well as predose and 48 hours postdose on Day 21 for the determination of R- and S- warfarin via a validated LC/MS/MS bioanalytical assay. Serial plasma samples were collected on Days 1 – 23 to determine PT and INR.

Figure 55. Mean plasma R-warfarin concentration-time profiles. Figure 56. Mean plasma S-warfarin concentration-time profiles.



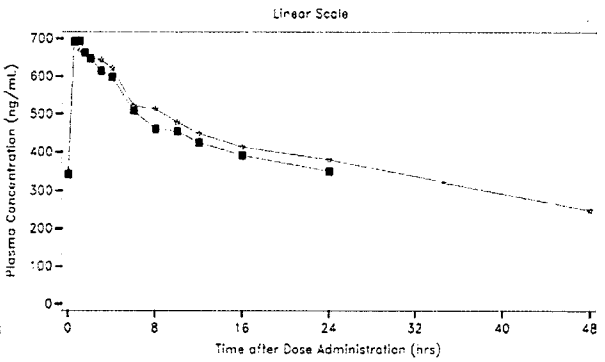


Table 66. Geometric mean (CV%) R-warfarin PK parameters

Parameter	n	Treatment: Warfarin	n	Warfarin with Pitavastatin
$AUC_{0-\tau}$ (ng·h/mL)	23	15505.62 (28.06)	23	16535.39 (27.14)
C_{min} (ng/mL)	24	499.78 (27.86)	23	536.29 (26.71)
C_{max} (ng/mL)	24	935.56 (26.83)	23	956.32 (27.44)
C_{avg} (ng/mL)	23	646.07 (28.06)	23	688.97 (27.14)
K_{el} (L/h)	7	0.016 (33.843)	18	0.014 (18.264)
CL/F (mL/h)	23	148.99 (20.73)	23	139.71 (20.26)
Vd/F (mL)	7	8511.26 (49.86)	18	10890.01 (23.20)
$t_{1/2}$ (h)	7	42.10 (41.10)	18	49.97 (24.41)
T_{max} (h)	24	1.25 (0.50, 4.07)	23	1.50 (0.50, 4.00)

Table 67. Geometric mean (CV%) S-warfarin PK parameters

Parameter	n	Treatment: Warfarin	n	Warfarin with Pitavastatin
$AUC_{0-\tau}$ (ng·h/mL)	23	10579.24 (20.53)	23	11194.23 (24.0485)
C_{min} (ng/mL)	24	315.18 (29.49)	23	329.13 (27.8342)
C_{max} (ng/mL)	24	722.73 (23.58)	23	734.35 (20.7874)
C_{avg} (ng/mL)	23	440.80 (20.53)	23	466.43 (24.0486)
K_{el} (L/h)	12	0.024 (28.856)	20	0.0178 (27.890)
CL/F (mL/h)	23	218.37 (33.41)	23	206.37 (36.39)
Vd/F (mL)	12	11200.72 (52.02)	20	12253.77 (21.14)
$t_{1/2}$ (h)	12	28.95 (35.21)	20	39.02 (32.03)
T_{max} (h)[1]	24	1.00 (0.50, 4.00)	23	1.00 (0.50, 4.00)

Table 68. R- and S-warfarin PK parameters analyses.

	Parameter	Test Warfarin w/ Pitavastatin	Reference Warfarin	Ratio	90% CI Lower–Upper
R-warfarin	$AUC_{0-\tau}$	16535.39	15505.62	1.066	(1.035–1.099)
	C_{max}	956.32	925.25	1.034	(0.994–1.075)
S-warfarin	$AUC_{0-\tau}$	11194.23	10579.24	1.058	(1.026–1.092)
	C_{max}	734.35	710.73	1.033	(0.995–1.073)

The R-warfarin C_{max} geometric mean ratio in the presence and absence of pitavastatin as well as that of $AUC_{0-\tau}$ is 1.03 and 1.07, respectively. The S-warfarin C_{max} geometric mean ratio in the presence and absence of pitavastatin as well as that of $AUC_{0-\tau}$ is 1.03 and 1.06, respectively. The presence of **pitavastatin did not significantly affect the R- and S-warfarin's C_{max} and $AUC_{0-\tau}$** since the 90% CI of all of their geometric mean ratios are within the 0.8 and 1.25 bioequivalence goalpost.

Table 69. Plasma prothrombin time (PT) and international normalized ratio (INR) analyses.

Parameter	Days	Test LSM Warfarin w/ Pitavastatin	Reference LSM Warfarin	Difference	90% CI of the Difference	Ratio	90%CI of the Ratio
PT (sec)	22 vs. 14	17.791	17.987	–0.196	(–0.804, 0.412)	0.989	(0.95, 1.023)
INR	22 vs. 14	1.761	1.774	–0.013	(–0.078, 0.052)	0.993	(0.95, 1.029)

The presence of pitavastatin did not significantly affect the warfarin's PD (PT and INR) since the 90% CIs for the PT and INR differences include zero.

	Study -1.25US	Reviewer's Comments
Population	Healthy men	OK
Choice of interacting drug	Warfarin	Per the draft Drug Interaction Guidance, warfarin (S-) is a recommended CYP2C9 substrate.
Route of administration	Oral	Relevant to pitavastatin tablet
Number of participants	24	Relative bioavailability, OK.
Dose selection	Both 4 mg pitavastatin daily and 5 mg warfarin then per PT and INR	Usual oral pitavastatin dose. Individualized warfarin dose, OK.
Plasma sample collection time for warfarin	24 hours for warfarin alone period; 48 hours for warfarin + pitavastatin period	R-warfarin $t_{½}$ = 37 – 89 h. S-warfarin $t_{½}$ = 21 – 43 h. Time difference is unknown.

2.4.2.14 Digoxin

Study 1.26 examined the mutual interaction between multiple-dose digoxin and multiple-dose pitavastatin in 19 healthy men (18 Caucasian and 1 Black). This was a 3-sequential dosing study. Each participant orally received a 0.25 mg digoxin tablet 12-hourly on Day 1 and then once daily on **Days 2 – 10. On Days 11 – 17, each participant orally received a 0.25 mg digoxin tablet once daily and a 4 mg pitavastatin tablet once daily. On days 18 – 27, each participant orally received a 4 mg** pitavastatin once daily. Each participant received all drugs under fasting state. Serial plasma samples were collected predose and for 24 hours postdose on Days 17 and 27 for the determination of pitavastatin and its lactone via a validated HPLC/MS/MS bioanalytical assay. Serial plasma samples were collected predose and for 24 hours postdose on Days 10 and 17 for the determination of digoxin via a validated LC/MS/MS bioanalytical assay. Serial urine samples were collected for 24 hours

postdose on Days 10 and 17 for the determination of digoxin via a validated LC/MS/MS bioanalytical assay.

Figure 57. Mean plasma digoxin concentration-time profiles.

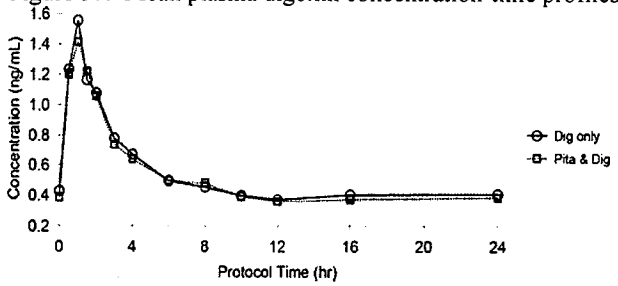


Table 70. Digoxin PK parameters

Parameter	Number of subjects in Day 17	Day 17 (digoxin and pitavastatin) Geometric Mean	Day 17 CV%	Number of subjects in Day 10	Day 10 (digoxin) Geometric Mean	Day 10 CV%
t_{max} (h)	18	1.00	0.50-2.00	18	1.00	0.50-2.00
Cmax (ng/mL)	18	1.52	26.62	18	1.58	27.66
$AUC_{0-\tau}$ (ng*h/mL)	18	11.85	17.79	18	12.27	18.21
$t_{1/2}$ (h)	2	38.57	14.19	1	12.89	NC
V_d/F (L)	2	1105.8	7.01	1	535.01	NC
CL/F (L/h)	18	21.09	19.57	18	20.37	18.79
A_e (ng)	17	108649.40	15.18	13	113003.80	20.32
CL_r (mL/h)	17	8924.87	16.70	13	8887.82	27.62

Table 71. Digoxin PK parameters analyses

Parameter	LS mean Day 10 (digoxin)	LS mean Day 17 (digoxin and pitavastatin)	Ratio of geometric means	90% CI
C_{max} (ng/mL)	1.58	1.52	0.96	0.87-1.06
$AUC_{0-\tau}$ (ng*h/mL)	12.27	11.85	0.97	0.92-1.02

The digoxin C_{max} geometric mean ratio in the presence and absence of pitavastatin as well as that of $AUC_{0-\tau}$ is 0.96 and 0.97, respectively. The presence of pitavastatin did not significantly affect the digoxin exposure since the 90% CI of their LS mean ratios are within the 0.8 and 1.25 bioequivalence goalpost. This observation also indicates that pitavastatin is neither a P-gp inhibitor nor P-gp inducer.

The sponsor did not report the digoxin CL_r LS mean and 90% CI. Table shows that the geometric mean digoxin CL_r in the presence and absence of pitavastatin is so close to each other. Thus the presence of pitavastatin is not likely to significantly affect digoxin CL_r.

Figure 58. Mean plasma pitavastatin concentration-time profiles. Figure 59. Mean plasma pitavastatin lactone concentration-time profiles.

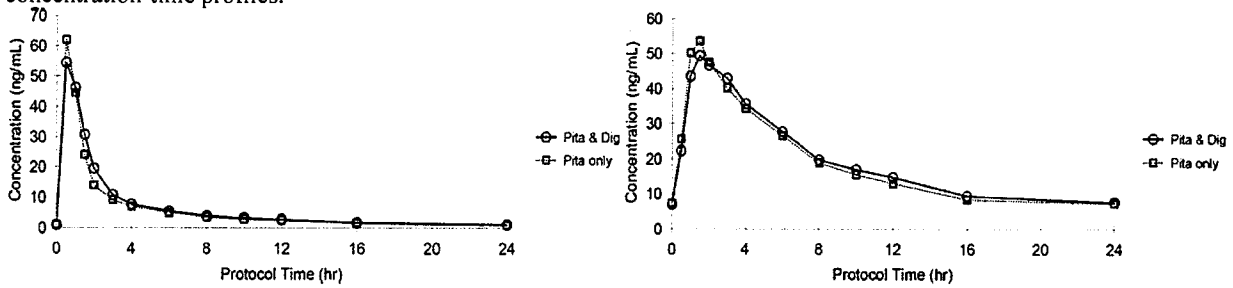


Table 72. Pitavastatin PK parameters

Parameter	Number of subjects in Day 17	Day 17 (pitavastatin and digoxin) Geometric Mean	Day 17 (pitavastatin and digoxin) CV%	Number of subjects in Day 27	Day 27 (pitavastatin) Geometric Mean	Day 27 CV%
T_{max} (h)	18	0.50*	0.50-1.50	18	0.50*	0.50-1.03
C_{max} (ng/mL)	18	58.61	49.71	18	64.58	46.49
$AUC_{0-\tau}$ (ng*h/mL)	18	136.49	44.14	18	131.02	42.70
$t_{1/2}$ (h)	14	9.05	46.23	17	11.20	48.44
V_d/F (L)	14	395.17	33.12	17	500.03	48.41
Cl/F (L/h)	18	29.31	51.24	18	30.53	37.39

* = median

Table 73. Pitavastatin lactone PK parameters

Parameter	Number of subjects in Day 17	Day 17 (pitavastatin and digoxin) Geometric Mean	Day 17 (pitavastatin and digoxin) CV%	Number of subjects in Day 27	Day 27 (pitavastatin) Geometric Mean	Day 27 (pitavastatin) CV%
T_{max} (h)	18	1.50*	1.00-3.00	18	1.50*	1.00-2.00
C_{max} (ng/mL)	18	52.37	30.85	18	53.49	23.69
$AUC_{0-\tau}$ (ng*h/mL)	18	424.28	36.20	18	418.90	32.24
$t_{1/2}$ (h)	16	8.89	43.11	13	8.74	30.61

* = median

Table 74. Pitavastatin PK parameters analyses

Parameter	LS mean Day 27 (pitavastatin)	LS mean Day 17 (pitavastatin and digoxin)	Ratio of geometric means	90% CI
C_{max} (ng/mL)	64.58	58.61	0.91	0.78–1.05
AUC_{0-t} (ng*h/mL)	131.02	136.49	1.04	0.93–1.16

Table 75. Pitavastatin lactone PK parameters analyses

Parameter	LS mean Day 27 (pitavastatin)	LS mean Day 27 (pitavastatin)	Ratio of geometric means	90% CI
C_{max} (ng/mL)	53.49	52.37	0.98	0.91 - 1.06
AUC_{0-t} (ng*h/mL)	418.90	424.28	1.01	0.93 - 1.11

The pitavastatin C_{max} geometric mean ratio in the presence and absence of digoxin as well as that of AUC_{0-t} is 0.91 and 1.04, respectively. The presence of digoxin significantly affected the pitavastatin C_{max} since the 90% CI of its geometric mean ratios are outside the 0.8 and 1.25 bioequivalence goalpost, whereas the presence of digoxin did not significantly affect the pitavastatin AUC_{0-t} since the 90% CI of its geometric mean ratios are within the 0.8 and 1.25 bioequivalence goalpost.

The pitavastatin lactone C_{max} geometric mean ratio in the presence and absence of digoxin as well as that of AUC_{0-t} is 0.98 and 1.01, respectively. The presence of digoxin did not significantly affect both the pitavastatin lactone C_{max} and AUC_{0-t} since the 90% CI of their geometric mean ratios are within the 0.8 and 1.25 bioequivalence goalpost.

	Study -1.26	Reviewer's Comments
Population	Healthy men	OK
Choice of interacting drug	Digoxin	Per the draft Drug Interaction Guidance, digoxin is a known P-gp substrate.
Route of administration	Oral	Relevant to pitavastatin tablet
Number of participants	19	Relative bioavailability, OK.
Dose selection	Both 4 mg pitavastatin daily and 0.25 mg digoxin daily for 7 days	Usual oral pitavastatin dose. 0.25 mg digoxin/d is the dose to treat CHF.

2.4.2.15 Ezetimibe

Study JPC-04-335-18 examined the mutual interaction of multiple-dose ezetimibe and multiple-dose pitavastatin in 18 healthy Mongoloid men. This is a randomized and crossover study with 3 treatments and 6 periods. Each period consisted of the 3 treatments in different sequence. A washout of at least 7 days separated each treatment. Each participant orally received the following test drugs once daily for 7 days (received the test drugs after an over-night fast on Day 7):
Treatment A: a 2 mg pitavastatin tablet
Treatment B: a 10 mg ezetimibe tablet
Treatment C: a 2 mg pitavastatin tablet and a 10 mg ezetimibe tablet
Serial plasma samples were collected on Day 7 predose and 24 hours postdose to determine pitavastatin and its lactone via a validated HPLC/UV bioanalytical assay. Serial plasma samples were collected on Day 7 predose and 24 hours postdose to determine ezetimibe (SCH 58235) and ezetimibe glucuronide (SCH 60663) via a validated LC/MS/MS bioanalytical assay.

Figure 60. Mean plasma ezetimibe concentration-time profiles. Figure 61. Mean plasma ezetimibe glucuronide concentration-time profiles.

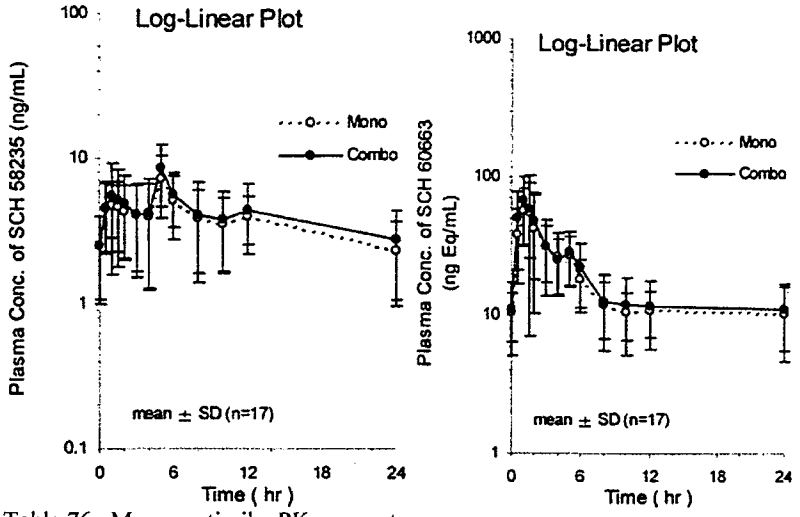


Table 76. Mean ezetimibe PK parameters.

		t_{max} (hr)	$C_{ss\ max}$ (ng/mL)	$C_{24\ hr}$ (ng/mL)	$AUC_{0\text{-}24\ hr}$ (ng•hr/mL)	CLss/F (L/hr)
Ezetimibe alone	Mean	3.29	8.22	2.33	90.7	128
	%CV	64	33	58	37	42
Ezetimibe + pitavastatin	Mean	4.32	8.89	2.77	101	119
	%CV	35	48	61	47	41

Table 77. Mean ezetimibe glucuronide PK parameters.

		t_{max} (hr)	$C_{ss\ max}$ (ng/mL)	$C_{24\ hr}$ (ng/mL)	$AUC_{0\text{-}24\ hr}$ (ng•hr/mL)
Ezetimibe alone	Mean	1.41	68.7	10.4	404
	%CV	81	66	55	35
Ezetimibe + pitavastatin	Mean	0.971	72.0	11.1	440
	%CV	39	47	51	42

Table 78. Ezetimibe PK parameters analysis

		$C_{ss\ max}$ (ng/mL)	$AUC_{0\text{-}24\ hr}$ (ng•hr/mL)
SCH 58235 alone	Mean	8.22	90.7
	%CV	33	37
SCH 58235 + pitavastatin	Mean	8.89	101
	%CV	48	47
p value*		0.8770	0.3914
Point estimate†		**102%**	**109%**
90% CI		84.5%-122%	92.1%-128%

Table 79. Ezetimibe glucuronide PK parameters analysis

		$C_{ss\ max}$ (ng/mL)	$AUC_{0\text{-}24\ hr}$ (ng Eq•hr/mL)
SCH 58235 alone	Mean	68.7	404
	%CV	66	35
SCH 58235 + pitavastatin	Mean	72.0	440
	%CV	47	42
p value*		0.5533	0.4615
Point estimate†		**106%**	**106%**
90% CI		90.1%-124%	93.0%-120%

The ezetimibe $C_{ss\ max}$ point estimate in the presence and absence of pitavastatin as well as that of $AUC_{0\text{-}24\ hr}$ is 102 and 109%, respectively. The ezetimibe glucuronide $C_{ss\ max}$ point estimate in the presence and absence of pitavastatin as well as that of $AUC_{0\text{-}24\ hr}$ are both 106%. The presence of pitavastatin did not significantly affect the ezetimibe and its glucuronide exposure since the 90% CI of their point estimates are within the 0.8 and 1.25 bioequivalence goalpost.

Figure 62 (left). Mean plasma pitavastatin concentration-time profiles. Figure 63 (right). Mean plasma pitavastatin lactone concentration-time profiles.

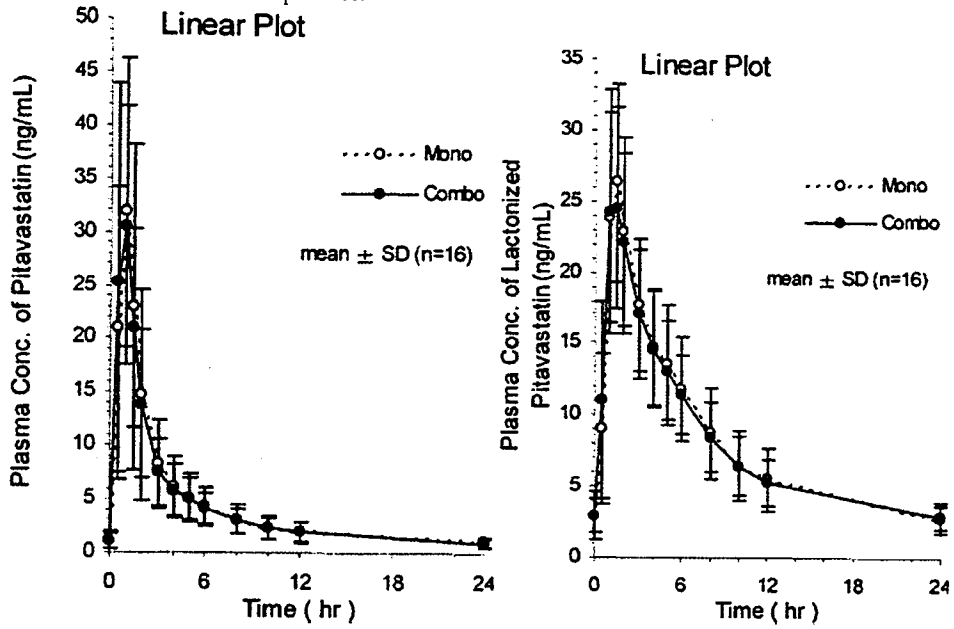


Table 80. Pitavastatin PK parameters.

		t_{max} (hr)	$C_{ss\ max}$ (ng/mL)	$C_{24\ hr}$ (ng/mL)	$^{0\text{-}24\ hr}$ (ng•hr/mL) 0-24hr	0-∞	$t_{1/2\lambda z}$ (hr)	CLss/F (L/hr)	Vz/F
Pitavastatin alone	Mean	0.938	36.4	1.06	106	124	12.0	21.1	369
	%CV	38	43	41	41	40	25	29	40
SCH 58235 + pitavastatin	Mean	0.781	35.3	0.964	103	119	10.8	22.0	325
	%CV	33	32	51	40	40	27	36	27

Table 81. Pitavastatin lactone PK parameters.

		t_{max} (hr)	$C_{ss\ max}$ (ng/mL)	$C_{24\ hr}$ (ng/mL)	$^{0\text{-}24\ hr}$ (ng•hr/mL) 0-24hr	0-∞	$t_{1/2\lambda z}$ (hr)
Pitavastatin alone	Mean	1.28	28.1	2.82	197	241	10.9
	%CV	25	24	37	29	30	18
SCH 58235 + pitavastatin	Mean	1.28	27.8	2.84	193	238	11.2
	%CV	32	29	29	26	26	13

Table 82. Pitavastatin PK parameters analysis.

		$C_{ss\ max}$ (ng/mL)	$AUC_{0\text{-}24\ hr}$ (ng•hr/mL)
Pitavastatin alone	Mean	36.4	106
	%CV	43	41
SCH 58235 + pitavastatin	Mean	35.3	103
	%CV	32	40
p value*		0.9778	0.5678
Point estimate†		**99.8%**	**97.5%**
90% CI		88.3%-113%	90.5%-105%

The pitavastatin $C_{ss\ max}$ point estimate in the presence and absence of ezetimibe as well as that of $AUC_{0\text{-}24\ hr}$ is 99.8 and 97.5%, respectively. The presence of ezetimibe did not significantly affect the pitavastatin exposure since the 90% CI of pitavastatin point estimate is within the 0.8 and 1.25 bioequivalence goalpost.

The sponsor did not report the pitavastatin lactone point estimate and 90% CI. Table 81 shows that both pitavastatin lactone $C_{ss\ max}$ and $AUC_{0\text{-}24\ hr}$'s **respective mean and %CV are so close to each other.** Thus the presence of ezetimibe is not likely to significantly affect the pitavastatin lactone exposure.

	Study JPC-04-335-18	Reviewer's Comments
Population	Healthy men	OK
Choice of interacting drug	Ezetimibe	Common coadministered drug with statins
Route of administration	Oral	Relevant to pitavastatin tablet
Number of participants	18	Relative bioavailability, OK.
Washout	≥ 7 days	Ezetimibe $t_{½}$ is ~ 22 hours. Pitavastatin $t_{½}$ is ~10 hours.
Dose selection	Both 2 mg pitavastatin daily and 10 mg ezetimibe daily for 7 days	Usual oral pitavastatin dose. 10 mg ezetimibe is the approved dose.
Dose group label	SCH 58235	**Should be "SCH 60663" in the top table on report's page 5.**
Dose group label	SCH 58235	**Should be "pitavastatin" in the lower table on report's page 5.**
Dose group label	SCH 58235 alone	**Should be "pitavastatin alone"** in Tables 11, 12, and 15 on **report's pages 58, 60, and 63.**

Pregnancy is a contraindication for statin use. Child-bearing age women may use oral contraceptive (OC) as a contraceptive method. The potential increase or decrease of OC exposure upon coadministration with pitavastatin may have safety and efficacy concerns. However, Clinical Pharmacology does not recommend an OC study with pitavastatin because:

- No strong evidence that there will be an extensive drug-drug interaction (DDI) based on their metabolic pathways (such as CYP3A4 metabolizes ethinyl estradiol) and other DDI (ethinyl estradiol conjugation via glucuronidation; yet pitavastatin does not show significant mutual interaction with ezetimibe; UGTs 1A1, 1A3, and 2B15 primarily metabolize ezetimibe) information.
- Similar extent of DDI is expected for pitavastatin compared to that of rosuvastatin.
- For the 20-30% increase in OC exposure with rosuvastatin, the rosuvastatin label only describes the PK results with no further labeling implication.

2.5 General Biopharmaceutics

2.5.1 What biopharmaceutics classification system (BCS) class does pitavastatin calcium belong?

Pitavastatin calcium's BCS Class status is unknown. The sponsor stated that "pitavastatin would be considered a BCS Class I immediate release solid oral dosage form" (Dissolution Section in page 41/50 of the Drug Product Summary) but without any substantiation that pitavastatin calcium belongs to BCS Class 1. Pitavastatin calcium is very slightly soluble in water (Question 2.1.1 above), which does not support that pitavastatin calcium is a BCS Class I drug per the BCS Guidance [http://www.fda.gov/cder/guidance/3618fnl.pdf].

2.5.2 Does difference exist between the to-be-marketed pitavastatin calcium formulations and the clinically-studied pitavastatin calcium formulations? If so, has the sponsor addressed it satisfactorily?

The to-be-marketed pitavastatin calcium formulation is identical to the pitavastatin calcium formulation that was tested in the Phase 3 clinical studies. The clinically-tested formulation is a round biconvex film coated tablet and is manufactured by Skye Pharma in France, whereas the to-be-marketed formulation is a round white film-coated tablet with debossed markings to aid identification and is manufactured by Patheon Inc. in Cincinnati, OH, U.S.A.

Study -1.37US examined the bioequivalence between the clinically-tested formulation and the to-be-marketed formulation for both 2 and 4 mg pitavastatin tablets in 88 healthy volunteers (44/tablet strength). This is a single-dose, randomized, 2-period, 4-sequence, 4-treatment crossover study. Each fasted (≥ 10 hours) participant orally received either 1 of the treatment sequence as AB, BA, CD, or DC. Treatment A was 2 mg pitavastatin tablet manufactured by Patheon, U.S. and Treatment B was 2 mg pitavastatin tablet manufactured by SkyePharma, France. Treatment C was 4 mg pitavastatin tablet manufactured by Patheon, U.S. and Treatment D was 4 mg pitavastatin tablet manufactured by SkyePharma, France. Serial plasma samples were collected predose and 48 hours postdose to determine pitavastatin and its lactone via a validated LC/MS/MS bioanalytical assay.

Figure 64. Mean plasma pitavastatin concentration-time profiles.

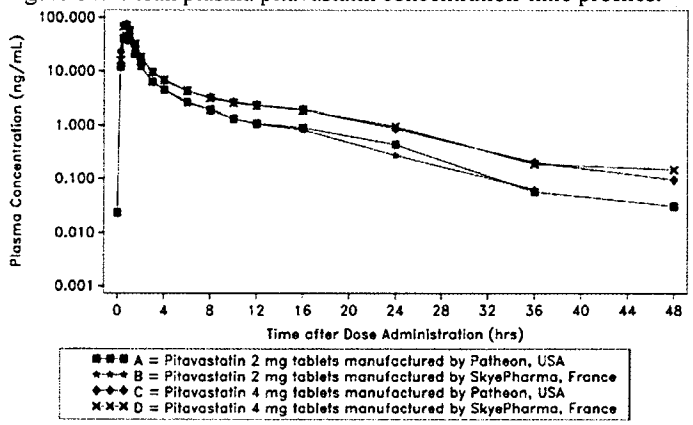


Table 83. Pitavastatin PK parameters.

	2-mg Tablet Patheon	2-mg Tablet SkyePharma	4-mg Tablet Patheon	4-mg Tablet SkyePharma
AUC_{0-t} (ng•h/mL)	92.8 (91) n = 44	88.6 (90) n = 44	156 (100) n = 44	154 (105) n = 44
AUC_{0-inf} (ng•h/mL)	122 (96) n = 26	102 (82) n = 17	209 (98) n = 25	205 (110) n = 25
C_{max} (ng/mL)	48.3 (72) n = 44	46.0 (74) n = 44	82.0 (94) n = 44	77.4 (97) n = 44
T_{max} (h)a	0.75 (0.50, 1.00) n = 44	0.75 (0.37, 1.00) n = 44	0.75 (0.25, 1.00) n = 44	0.658 (0.25, 1.00) n = 44
%AUC	13.2 (49) n = 26	14.5 (54) n = 17	13.1 (33) n = 25	15.3 (47) n = 25
K_{el} (1/h)	0.1723 (72) n = 26	0.1455 (67) n = 17	0.0672 (53) n = 25	0.0662 (66) n = 25
$t_{1/2}$ (h)	7.9 (88) n = 26	8.1 (74) n = 17	12.2 (33) n = 25	14.6 (73) n = 25
Vd/F (L)	203 (47) n = 26	240 (55) n = 17	409 (35) n = 25	491 (45) n = 25
CL/F (L/h)	29.8 (66) n = 26	27.5 (43) n = 17	25.8 (44) n = 25	27.9 (42) n = 25

Table 84. Pitavastatin PK parameters analyses.

Pharmacokinetic Parameter	Treatment A: 2-mg Tablet Patheon	Treatment B: 2-mg Tablet SkyePharma	Treatment C: 4-mg Tablet Patheon	Treatment D: 4-mg Tablet SkyePharma
AUC_{0-t} (ng•h/mL)				
Number of Subjects	N = 44		N = 44	
Geometric Mean	72.157	69.717	130.688	126.799
Ratio	1.035		1.031	
90% Confidence Interval (Lower-Upper)	0.982-1.091		0.998-1.065	
AUC_{0-inf} (ng•h/mL)				
Number of Subjects	N = 11		N = 17	
Geometric Mean	90.142	89.252	189.148	182.536
Ratio	1.010		1.036	
90% Confidence Interval (Lower-Upper)	0.896-1.139		0.983-1.093	
C_{max} (ng/mL)				
Number of Subjects	N = 44		N = 44	
Geometric Mean	40.503	38.612	69.618	65.497
Ratio	1.049		1.063	
90% Confidence Interval (Lower-Upper)	0.982-1.121		0.997-1.133	

For the 2 mg tablet strength, pitavastatin C_{max} geometric mean ratio for the test (Patheon formulation) and reference (SkyePharma formulation) as well as that of AUC_{0-t} and AUC_{0-inf} is 1.049, 1.035, and 1.01, respectively. For the 4 mg tablet strength, pitavastatin C_{max} geometric mean ratio for the test (Patheon) and reference (SkyePharma) as well as that of AUC_{0-t} and AUC_{0-inf} is 1.063, 1.031, and 1.036, respectively. Dr. Manoj Khurana and this reviewer reanalyzed the pitavastatin parameters and **reproduced the sponsor's results above for both the 2** and 4 mg pitavastatin tablet strengths. Hence, the to-be-marketed pitavastatin calcium formulation (2 and 4 mg) is bioequivalent to the pitavastatin calcium formulation that was tested in the Phase 3 clinical studies (2 and 4 mg, respectively) since all the 90% CIs of the geometric mean ratios are within the 0.8 and 1.25 bioequivalence goalpost.

2.6 Bioanalytical

2.6.1 Are the bioanalytical methods properly validated?

The sponsor initially used a method of [redacted] (b) (4) [redacted] (b) (4) liquid chromatography (HPLC) with ultraviolet (UV) detection to determine pitavastatin and its lactone metabolite in plasma and urine samples. Later, they used a

method of liquid chromatography with tandem mass spectrometry (LC/MS/MS) to determine pitavastatin and its lactone metabolite in plasma and urine samples.

Table 85. HPLC/UV bioanalytical assay validation for pitavastatin and its lactone in plasma and urine by (b) (4)

Measure	Result	
	Pitavastatin	Pitavastatin lactone
Plasma		
Linearity test	r = 0.999 over range 0.5-100.0 ng/mL Accuracy 113% at lowest concentration (0.5 ng/mL) and within range 95-101% at other concentrations	r = 0.999 over range 0.5-100.0 ng/mL Accuracy 106% at lowest concentration (0.5 ng/mL) and within range 95-103% at other concentrations
LLOQ	1.0 ng/mL pitavastatin calcium	1.0 ng/mL
Intra-assay reproducibility Precision Accuracy	 55% at 0.5 ng/mL[a], 5.7% at 1.0 ng/mL, 2.0% at 10 ng/mL and 1.6% at 75 ng/mL 110% at 0.5 ng/mL[a], 107% at 1.0 ng/mL, 106% at 10 ng/mL and 104% at 75 ng/mL	 29% at 0.5 ng/mL[a], 9.4% at 1.0 ng/mL, 2.0% at 10 ng/mL and 1.4% at 75 ng/mL 78% at 0.5 ng/mL[a], 93% at 1.0 ng/mL, 96% at 10 ng/mL and 96% at 75 ng/mL
Inter-assay reproducibility Precision Accuracy	 7.7% at 1.0 ng/mL, 2.2% at 10 ng/mL and 2.8% at 75 ng/mL 102% at 1.0 ng/mL, 103% at 10 ng/mL and 101% at 75 ng/mL	 24% at 1.0 ng/mL[a], 3.8% at 10 ng/mL and 3.9% at 75 ng/mL 89% at 1.0 ng/mL, 92% at 10 ng/mL and 91% at 75 ng/mL
Urine		
Linearity test	r = 0.999 over range 2.0-200.0 ng/mL Accuracy 101% at lowest concentration (2.0 ng/mL) and within range 98-103% at other concentrations	r = 0.999 over range 2.0-200.0 ng/mL Accuracy 100% at lowest concentration (2.0 ng/mL) and within range 98-103% at other concentrations
LLOQ	2.0 ng/mL pitavastatin calcium	2.0 ng/mL
Intra-assay reproducibility Precision Accuracy	 11% at 2.0 ng/mL, 3.7% at 4.0 ng/mL 2.6% at 40 ng/mL and 1.4% at 150 ng/mL 103% at 2.0 ng/mL, 101% at 4.0 ng/mL 102% at 40 ng/mL and 99% at 150 ng/mL	 7.8% at 2.0 ng/mL, 7.0% at 4.0 ng/mL 6.9% at 40 ng/mL and 7.9% at 150 ng/mL 107% at 2.0 ng/mL, 101% at 4.0 ng/mL 93% at 40 ng/mL and 93% at 150 ng/mL
Inter-assay reproducibility Precision Accuracy	 8.8% at 4.0 ng/mL, 5.5% at 40 ng/mL and 2.9% at 150 ng/mL 98% at 4.0 ng/mL, 100% at 40 ng/mL and 101% at 150 ng/mL	 5.7% at 4.0 ng/mL, 7.4% at 40 ng/mL and 4.4% at 150 ng/mL 96% at 4.0 ng/mL, 95% at 40 ng/mL and 92% at 150 ng/mL
[a] outside specified range		

Table 86. LC/MS/MS bioanalytical method validation for pitavastatin and its lactone in plasma by (b) (4)

Measure	Result	
	Pitavastatin	Pitavastatin lactone
Plasma		
Calibration curves	r >0.998 1.00 to 200.00 ng/mL 88% ≤ mean accuracy ≤112%	r >0.997 1.00 to 200.00 ng/mL 93% ≤ mean accuracy ≤106%
LLOQ	1.00 ng/mL pitavastatin calcium	1.00 ng/mL
LLOQ Intra-day accuracy Intra-day precision Inter-day accuracy Inter-day precision	 93% 3.1% 97% 8.5%	 99% 2.8% 104% 4.3%
Above LLOQ Intra-day accuracy Intra-day precision Inter-day accuracy Inter-day precision	 87% to 105% 2.8% to 3.9% 88% to 100% 4.4% to 4.7%	 91% to 100% 1.7% to 6.5% 94% to 102% 2.3% to 4.4%

Table 87. LC/MS/MS bioanalytical method validation for pitavastatin and its lactone in urine by (b) (4).

Measure	Result	
	Pitavastatin	Pitavastatin lactone
Urine		
Calibration curves	r >0.998 1.00 to 200.00 ng/mL 92% ≤ mean accuracy ≤108%	r >0.998 1.00 to 200.00 ng/mL 93% ≤ mean accuracy ≤103%
LLOQ	1.00 ng/mL pitavastatin calcium	1.00 ng/mL
LLOQ Intra-run accuracy Intra-run precision Inter-run accuracy Inter-run precision	 106.7% 9.3% 102.7% 13.0%	 91.5% 9.3% 99.8% 11.5%
Above LLOQ Intra-run accuracy Intra-run precision Inter-run accuracy Inter-run precision	 98.6% to 108.3% 1.4% to 3.8% 101.8% to 109.9% 2.9% to 7.0%	 98.9% to 101.1% 2.1% to 3.5% 101.8% to 104.6% 4.8% to 6.1%

Stability testing on samples in the autosampler indicated that pitavastatin and its lactone samples were stable for up to 24 hours after preparation. Both pitavastatin and its lactone were stable in plasma samples for up to 1 month and 2 months, respectively, at temperatures below -10°C and -70°C, respectively. Pitavastatin and its lactone were stable in urine for 2 months at -60°C or below and for 4 hours in a cold place. Exposure of blood or plasma samples to light during processing did not present stability issue; however, temperature during processing had to be maintained at about +4°C.

Both HPLC/UV and LC/MS/MS bioanalytical assays for pitavastatin and its lactone in plasma and urine are acceptable with reasonable precision and accuracy.

The Division of Metabolism and Endocrinology Products had the following comment to the Sponsor at filing NDA 22-363:

Two (b) (4)) sites in Canada have reliability issues. (b) (4) , performed the bioanalytical analyses for pitavastatin and pitavastatin lactone in plasma and urine samples. If you intend to make labeling claims for the interaction results between pitavastatin and fenofibrate plus gemfibrozil (Study NK-104-109), you should do one of the following, in order of preference:

- Repeat the pitavastatin and fenofibrate plus gemfibrozil interaction study.
- Re-assay the samples for pitavastatin and pitavastatin lactone at a different bioanalytical facility. For this option, the integrity of the original samples must be demonstrated for the frozen storage period.
- Commission a scientific audit by a qualified independent expert, who is knowledgeable in the area of human drug interaction studies and bioanalytical data, and is selected by your company rather than by (b) (4), to verify the results obtained by (b) (4)

The sponsor responded to this issue before submitting NDA 22-363 via commissioning Kendle as an independent 3rd **party to audit the Study NK-104-109's results on August 13 – 15 2007. Kendle's audit** conclusion follows:

We examined data for each of the accepted and rejected runs for each of the 4 analytical method validation packages and the 5 analytical studies. We did not find any incidents of the type of issues reported to (b) (4) in the FDA Warning Letter or in the January 2007 letter to sponsors. We found that all raw data examined matched the data that was provided in the (b) (4) reports to Kowa. In addition, we did not find evidence for the items highlighted by FDA in their letter to NDA applicants in the data and studies audited.

In summary, in our opinion, the Kowa method validation and analytical studies which we audited were satisfactorily conducted by (b) (4) *and the analytical data is valid and accurate. We found no reason to question the integrity or accuracy of the data reported.*

Table 88. Characteristics of the LC/MS/MS bioanalytical assay validated by (b) (4)

Measure	Result	
	Pitavastatin	**Pitavastatin lactone**
Plasma		
Standard curve	r = 0.999 0.954 to 191.741 ng/mL pitavastatin (1.00 to 200.40 ng/mL of pitavastatin calcium).	r = 0.999 1.00-199.90 ng/mL
LLOQ	1.0 ng/mL pitavastatin calcium	1.0 ng/mL
LLOQ validation sample Inter-batch precision Inter-batch accuracy Intra-batch precision Intra-batch accuracy	 5.0% 100.0% 6.1% 98.0%	 7.2% 97.0% 4.4% 91.0%
Inter-batch precision	14.9% at 3.0 ng/mL, 3.2% at 50 ng/mL and 6.1% at 160 ng/mL	3.0% at 3.0 ng/mL, 3.2% at 50 ng/mL and 7.4% at 160 ng/mL
Inter-batch accuracy	94.0% at 3.0 ng/mL, 96.7% at 50 ng/mL and 98.6% at 160 ng/mL	98.3% at 3.0 ng/mL, 93.1% at 50 ng/mL and 93.4% at 160 ng/mL
Intra-batch precision	2.9% at 3.0 ng/mL, 2.5% at 50 ng/mL and 2.5% at 160 ng/mL	2.4% at 3.0 ng/mL, 2.2% at 50 ng/mL and 2.4% at 160 ng/mL
Intra-batch accuracy	91.0% at 3.0 ng/mL, 99.0% at 50 ng/mL and 101.1% at 160 ng/mL	97.3% at 3.0 ng/mL, 92.8% at 50 ng/mL and 96.5% at 160 ng/mL
Urine		
Standard curve	r = 0.999 0.954 to 191.741 ng/mL pitavastatin (1.00 to 200.40 ng/mL of pitavastatin calcium).	r = 0.999 1.00-199.90 ng/mL

Measure	Result	
	Pitavastatin	**Pitavastatin lactone**
Urine cont.		
LLOQ	1.0 ng/mL pitavastatin calcium	1.0 ng/mL
LLOQ validation sample Inter-batch precision Inter-batch accuracy Intra-batch precision Intra-batch accuracy	 7.6% 92.0% 6.1% 99.0%	 10.9% 101.0% 4.5% 112.0%
Inter-batch precision	6.5% at 3.0 ng/mL, 3.6% at 50 ng/mL and 4.0% at 160 ng/mL	3.9% at 3.0 ng/mL, 3.3% at 50 ng/mL and 3.5% at 160 ng/mL
Inter-batch accuracy	87.3% at 3.0 ng/mL, 103.6% at 50 ng/mL and 101.5% at 160 ng/mL	101.3% at 3.0 ng/mL, 102.5% at 50 ng/mL and 99.6% at 160 ng/mL
Intra-batch precision	4.6% at 3.0 ng/mL, 1.6% at 50 ng/mL and 1.4% at 160 ng/mL	3.8% at 3.0 ng/mL, 2.7% at 50 ng/mL and 2.3% at 160 ng/mL
Intra-batch accuracy	87.7% at 3.0 ng/mL, 101.5% at 50 ng/mL and 99.7% at 160 ng/mL	105.6% at 3.0 ng/mL, 100.8% at 50 ng/mL and 101.5% at 160 ng/mL

Per the consistency of LC/MS/MS assay validation between (b) (4) and (b) (4) as well as the independent 3rd **party's audit, Study NK-104-109's bioanalytical data for pitavastatin and its lactone are acceptable.**

Table 89. Summary of bioanalytical methods validations for drug interaction studies.

	R-Warfarin	S-Warfarin	Digoxin	Digoxin	Rifampin	Enalapril	Enalaprilat	Atazanavir	Ezetimibe[§]	Total Ezetimibe[§]
Study	-1.25US	-1.25US	-1.26	-1.26	-1.27	-1.28	-1.28	-1.29	JPC 04-335-18	JPC 04-335-18
Method	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS
Matrix*	Plasma	Plasma	Plasma	Urine	Plasma	Plasma	Plasma	Plasma	Plasma	Plasma
Sample size, µL	500	500	500	500	200	500	500	200	200	200
LOQ, ng/mL	25	25	0.1	1	0.1	0.5	0.5	50	0.02	0.025
Linear range, ng/mL	25 – 17500	25 – 17500	0.1 – 5.0	1 – 100	0.1 – 50.0	0.5 – 400	0.5 – 400	50 - 25000	0.02 – 50.0	0.0249 – 249
Accuracy, %										
Intrarun	100.9	99.0	96.2	104.7	96.5	100.8	100.4	100.7	-0.6 LOQ, 5.9	-13.9 LOQ, 14.3
Interrun	94.9	98.0	101.0	98.6	100.6	99.5	95.9	104.9	5.5	3.8
Precision, %										
Intrarun	3.6	3.3	11.5	6.0	5.4	9.9	1.4	4.5	7.8 LOQ, 3.3	2.4 LOQ, 8.2
Interrun	9.4	5.8	13.0	9.9	8.3	10.4	6.7	4.0	4.5	11.3

LC/MS/MS = liquid chromatography and tandem mass spectrometry; *Plasma = heparinized plasma; [§] = intraday and interday experiments

All of the bioanalytical methods validations for the in vivo drug interaction studies are acceptable.

19 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

__X__ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

*Withheld Track Number: Clin Pharm/Bio-*__1__

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA	22-363	Brand Name	LIVALO®
OCP Division	2	Generic Name	Pitavastatin calcium
Medical Division	DMEP, HFD-510	Drug Class	HMG-CoA Reductase Inhibitor
OCP Reviewer	S.W. Johnny Lau	Indication(s)	Treat hypercholesterolemia
OCP Team Leader	Sally Y. Choe	Dosage Form	Immediate release tablet
Date of Submission	1-OCT-2008	Dosing Regimen	1, 2, or 4 mg/day
Estimated Due Date of OCP Review	20-MAY-2009	Route of Administration	Oral
PDUFA Due Date	3-AUG-2009	Sponsor	Kowa Research Institute, Inc.
Division Due Date	3-JUN-2009	Priority Classification	Standard

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Comments (Study number)
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X	[redacted]		annotated
Reference Bioanalytical and Analytical Methods	X	[redacted]		VALID/NK-104, 020019-RPX, 013436-RSC Revision 2, 12-May-2008, DMPK R0201695, DMPK R0200582, KOW/NK-104/06010, KOW/NK-104/07004, KOW/NK-104/06009, KOW/WAR/05001, KOW/DIG/05001, KOW/DIG/05002, KOW/RIF/06001, KOW/ENA/05001, KOW/ATZ/06001
I. Clinical Pharmacology				
In vivo mass balance:	X	1		SNY 419/013926
In vitro isozyme characterization:	X	2		AE-2544, R101029
In vitro metabolite Identity	X	1		Fujino Xenobio Metabol Dispos 14:415-24 1999
In vitro metabolism inhibition:	X			AE-2544
In vitro mechanism of uptake in human liver	X	3		ATR-148-100, Hirano JPET 311:139-46 (2004); Hirano DMD 34:1229-36 (2006)
In vitro plasma protein binding:	X	2		Fujino Xenobio Metabol Dispos 14:415-24 1999, R1107017, R93017
Blood/plasma ratio:				
Pharmacokinetics (e.g., Phase I) -				
Dose proportionality, healthy volunteers – fasting & non-fasting single and multiple doses:	X	2		PKH/NKN98389N/NK104.1.01, HPC/NKN00435N/NK-104.1.19
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	7		477-01, NK-104-109, NK-104-20, NK104-GJ, NK-104-1.25US, NK-104-1.30, NK-104-1.31
In-vivo effects of primary drug:	X	5		JPC-04-335-18, NK-104-1.26, NK-104-1.27, NK-104-1.28, NK-104-1.29,
In-vitro:	X	4		R101113, FBM 06-T350, R99035, ATR-149-035
Subpopulation studies -				
ethnicity:	X	1		NK-104-1.35
pediatrics:				

gender & geriatrics:	X	1		NK-104-1.22US
renal impairment:	X	1		NK-104-1.24
hepatic impairment:	X	2		NK-104-16, NK-104-HK
PD:				
Phase 1:	X			PKH/NKN98389N/NK104.1.01, HPC/NKN00435N/NK-104.1.19
Phase 3:				
PK/PD:				
Phase 2, dose ranging studies:	X	2		HEC/NK98402N/NK-104.2.02, HEC/NKN98403N/NK-104.2.03
Phase 3 clinical STUDIES (placebo controlled):	X	5		HEC/NK98402N/NK-104.2.02, HEC/NKN98403N/NK-104.2.03, NKS104A2204, NK-104-209, NK-104-210
Phase 3 clinical STUDIES (active controlled):	[redacted]	[redacted]		NK-104-301 CSR, NK-104-302 CSR, NK-104-304 CSR, NK-104-305 CSR, NK-104-306 CSR
Population Analyses -				
Meta-analysis:				
NONMEM:				
II. Biopharmaceutics				
Absolute bioavailability:	X	1		NK-104IV.1.02.EU
Bioequivalence studies – traditional design	[redacted]	[redacted]		NK-104-1.36, NK-104-1.37US
Relative bioavailability				
alternate formulation as reference:				
Food-drug interaction studies:	X	1		NK-104-1.21US
Absorption site	X	1		KS104A2115
Dissolution:				
(IVIVC):	X	1		NK-104-1.39US
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Phenotype studies:				
Chronopharmacodynamics	X	1		NK104-1.23US
Pediatric development plan				
Literature References				
QT prolongation assessment	[redacted]	1		NK104-1.34US
Total Number of Studies		67		
Filability and QBR comments				

	"X" if yes	Comments
Application filable?	X	
Comments to be sent to firm?	X	Two (b) (4) sites in Canada have reliability issues. (b) (4) performed the bioanalytical analyses for pitavastatin and pitavastatin lactone in plasma and urine samples. If you intend to make labeling claims for the interaction results between pitavastatin and fenofibrate plus gemfibrozil (Study NK-104-109), you should do one of the following, in order of preference: • Repeat the pitavastatin and fenofibrate plus gemfibrozil interaction study. • Re-assay the samples for pitavastatin and pitavastatin lactone at a different bioanalytical facility. For this option, the integrity of the original samples must be demonstrated for the frozen storage period. • Commission a scientific audit by a qualified independent expert, who is knowledgeable in the area of human drug interaction studies and bioanalytical data, and is selected by your company rather than by (b) (4) to verify the results obtained by (b) (4) Pitavastatin is a 3R- and 5S- specific stereoisomer. You should provide data to demonstrate whether pitavastatin shows any chiral conversion via metabolism. You should submit plasma pitavastatin and pitavastatin lactone concentration data as well as pharmacokinetic parameters for Study NK-104-1.37US.
QBR questions (key issues to be considered)	Exposure-safety and exposure-efficacy analyses, which help determine the risk/benefit ratio for using pitavastatin.	
Other comments or information not included above	Study NK-104-1.37US links the Phase 3 clinically-tested formulation and the to-be-marketed formulation. Hence, a DSI inspection on this pivotal bioequivalence study is in order. Clinical Site (total of 89 planned and 88 completed participants): (b) (4) (b) (4) Study NK-104-1.37US "Single-dose, randomized, open-label, crossover, bioequivalence study of pitavastatin 2-mg and 4-mg tablets manufactured by Skyepharma, France, and pitavastatin 2-mg and 4-mg tablets manufactured by Patheon, USA, in healthy volunteers" Bioanalytical sites: (b) (4) KOW/NK-104/08002 "An analytical investigation to determine the plasma concentrations of NK-104 and its lactone metabolite following a single dose, randomized, open-label, crossover, bioequivalence study of pitavastatin 2-mg and 4-mg tablets manufactured by Skyepharma, France and pitavastatin 2-mg and 4-mg tablets manufactured by Patheon, USA, in healthy volunteers"	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

Filing Memo

CLINICAL PHARMACOLOGY	
NDA:	**22-363**
Compound:	Pitavastatin calcium (LIVALO®; 1, 2, and 4 mg equivalent of pitavastatin)
Sponsor:	Kowa Research Institute, Inc.
Submission Date:	October 1, 2008
Relevant IND:	60,492
From:	S.W. Johnny Lau, R.Ph., Ph.D.

Background

The sponsor submits NDA 22-363 to seek marketing approval for the 1, 2, and 4 mg pitavastatin oral immediate release tablets as an adjunct to diet so as to reduce total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides as well as to increase HDL-cholesterol in adult patients with primary hypercholesterolemia and mixed dyslipidemia. Pitavastatin is a synthetic, competitive HMG-CoA reductase inhibitor, of which 6 (lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, and rosuvastatin) have marketing approval in the US for the same indications.

The proposed starting dose is one 2 mg pitavastatin tablet taken daily rising to one 4 mg tablet taken daily (depending on clinical response) with or without food, at any time of day. The 1 mg pitavastatin tablet is for patients who may benefit from a lower dose such as moderate hepatically impaired patients or patients also receive medications (such as cyclosporine and erythromycin) that may increase the plasma pitavastatin concentrations. Pitavastatin has marketing approval in Japan, South Korea, Thailand and India for the same indication.

Findings

To support NDA 22-363's **Clinical Pharmacology** and Biopharmaceutics sections, the sponsor **submitted studies' results or provided published literature as indicated in the table above. Findings'** highlights follow:

- The formulation used in the pivotal clinical studies is developed and manufactured by SykePharma in France, whereas the to-be-marketed formulation is manufactured by Patheon Inc. in Cincinnati, U.S.A. The sponsor conducted Study NK-104-1.37US and showed that the clinically tested 2 mg and 4 mg pitavastatin tablets are bioequivalent to the to-be-marketed 2 **and 4 mg pitavastatin tablets, respectively. Per this study's results together with the** formulation and dissolution information, the **sponsor proposed to "extend" the bioequivalence** result to the 1 mg pitavastatin tablet.
- (b) (4) conducted the LC/MS/MS bioanalytical assays for pitavastatin and pitavastatin lactone in plasma and urine for 2 studies (477-01 [interaction with bezafibrate] and NK-104-109 [interaction with fenobibrate and gemfibrozil]). These 2 studies were conducted in 2002 and 2003, respectively. Hence, they fall in the period (January 2000 to December 2004) that (b) (4) has data reliability issues. Bezafibrate is not approved to market in the U.S. The sponsor did not propose any labeling claim for bezafibrate.
- The sponsor claims that all other Phase I studies' **bioanalytical assays** for pitavastatin and pitavastatin lactone in plasma and urine were conducted at (b) (4) The pitavastatin and pitavastatin lactone in plasma and urine bioanalytical methods were transferred from (b) (4) to (b) (4).
- The sponsor provided extensive pitavastatin metabolism and drug-drug interaction information. However, the sponsor did not provide the **following information for pitavastatin's:**
  - blood:plasma concentration ratios
  - CYP induction potential
  - UGT induction and inhibition potential
  - transporters induction and inhibition potential

- The sponsor did not conduct PK/PD studies in patients and explained that other statins showed inconsistent relationship between real time plasma drug concentrations and efficacy or safety.
- The sponsor cannot study the 8 mg or higher doses in Phase 3 studies due to adverse events. Other countries **approved the 1 – 4 mg pitavastatin doses for the same indication.**
- **The sponsor submitted a thorough QT study's (NK-104-1.34US) results.**
- The sponsor conducted 2 dose ranging studies in patients with 1, 2, 4, and 8 mg pitavastatin daily doses (HEC/NK98402N/NK-104.2.02, HEC/NKN98403N/NK-104.2.03). The sponsor conducted 5 placebo controlled clinical **studies with dose ranges of 1 – 8 mg pitavastatin** (HEC/NK98402N/NK-104.2.02, HEC/NKN98403N/NK-104.2.03, NKS104A2204, NK-104-209, and NK-104-210) **and 5 active controlled clinical studies with dose ranges of 1 – 4 mg** pitavastatin (NK-104-301 CSR, NK-104-302 CSR, NK-104-304 CSR, NK-104-305 CSR, and NK-104-306 CSR).
- The sponsor did not submit any pharmacogenomic data.
- The sponsor did not submit any population or model-based analysis results.
- **The sponsor stated that "pitavastatin would be considered a BCS Class I immediate release solid oral dosage form"** (Dissolution Section in page 41/50 of the Drug Product Summary) but without the substantiation for pitavastatin calcium being a Biopharmaceutics Classification System Class 1 drug substance.
- Pitavastatin has 2 chiral centers. However, pitavastatin is a 3R- and 5S- specific stereoisomer. The pitavastatin bioanalytical assay is validated. The sponsor did not mention whether pitavastatin showed any chiral conversion via metabolism.
- The sponsor submitted SAS transport files for the Clinical Pharmacology and Biopharmaceutics studies data. However, pitavastatin PK parameter data and concentration-time data are missing for key Clinical Pharmacology and Biopharmaceutics studies.

Attachment starts here.

5.1 Table of Contents

5.2 Tabular Listing of all Clinical Studies

5.3 Clinical Study Reports

5.3.1 Reports of Biopharmaceutic Studies

5.3.1.1 Bioavailability (BA) Study Reports

5.3.1.1.1 A study to investigate the absolute bioavailability of NK-104 in healthy volunteers; [NK-104IV.1.02.EU]

5.3.1.1.2 An open label, randomized, study to assess the relative bioavailability of NKS104 (pitavastatin calcium) when released at targeted regions of the jejunum, ileum and ascending colon compared to oral administration; [NKS104A2115]

5.3.1.1.3 Single-dose, randomized, open-label, crossover study of the effect of food on the pharmacokinetics of pitavastatin 4 mg in healthy adult volunteers; [NK-104-1.21US]

5.3.1.2 Comparative Bioavailability (BA) and Bioequivalence (BE) Study Reports

5.3.1.2.1 A 2-way crossover, open label comparison of the pharmacokinetics of pitavastatin after single doses of 2 tablet formulations in healthy volunteers; [NK-104-1.36]

5.3.1.2.2. Single-dose, randomized, open-label, crossover, bioequivalence study of pitavastatin 2-mg and 4-mg tablets manufactured by SkyePharma, France, and pitavastatin 2-mg and 4-mg tablets manufactured by Patheon, USA, in healthy volunteers; [NK-104-1.37US]

5.3.1.3 *In vitro – In vivo* Correlation Study Reports

5.3.1.3.1 In vitro dissolution profile comparison between Patheon 1 mg tablets and Patheon 2 mg tablets in media (pH 1.2, 4.5 and 6.8); [NK-104-1.39US]

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

5.3.1.4.1 Analytical method of NK-104 and its lactone metabolite in human plasma and urine; [VALID/NK-104]

5.3.2 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials

5.3.2.1 Plasma Protein Binding Study Reports

5.3.2.1.1 Fujino H, Yamada I, Kojima J, Hirano M, Matsumoto H, Yoneda M. Studies on the metabolic fate of NK-104, a new inhibitor of HMG-CoA reductase (5): In vitro metabolism and plasma protein binding in animals and human; Xenobio Metabol Dispos 1999; 14: 415-424. [Fujino *et al.*, 1999b]

5.3.2.1.2 Calculation of the human plasma protein binding ratio of NK-104 lactone by ultracentrifugation method; [RI107017]

5.3.2.1.3 Binding of NK-104 with plasma protein of various animals by equilibrium dialysis method; [R93017]

5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies

5.3.2.2.1 Mechanism of uptake of NK-104 by human liver; [ATR-148-100]

5.3.2.2.2 In vitro study of NK-104 metabolism; [AE-2544]

5.3.2.2.3 *In vitro* studies on NK-104 using human metabolic enzyme system, A novel mechanism of lactonization by UDP-glucuronosyltransferase; [R101029]

5.3.2.2.4 Hirano M, Maeda K, Shitara Y and Sugiyama Y. Contribution of OATP2 (OATP1B1) and OATP8 (OATP1B3) to the hepatic uptake of pitavastatin in humans. J Pharmacol Exp Ther 2004; 311: 139-146. [Hirano *et al* 2004]

5.3.2.2.5 *In vitro* drug interaction between NK-104 and fibrate drugs; [R101113]

5.3.2.2.6 Inhibition studies of concomitant drugs on hOATP1B1 uptake of [^{14}C]NK-104; [FBM 06-T350]

5.3.2.2.7 An *in vitro* study of drug metabolism of NK-104 Report No. 5: A study of drug-drug interaction mediated by CYP2C9; [R99035]

5.3.2.2.8 Hirano M, Maeda K, Shitara Y and Sugiyama Y. Drug-drug interaction between pitavastatin and various drugs via OATP1B1. Drug Metab Dispos 2006; 34: 1229-1236. [Hirano *et al* 2006]

5.3.2.2.9 Interaction with cyclosporine A in the uptake of NK-104 using LST-1 expressing *Xenopus* oocytes; [ATR-149-035]

5.3.5 Reports of Efficacy and Safety Studies

5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

5.3.5.1.1a A multinational, multicentre randomised, double-blind, parallel-group, dose ranging study to evaluate the efficacy and safety of NK-104 1 mg, 2 mg, 4 mg and 8 mg compared to placebo in patients with primary hypercholesterolaemia [HEC/NKN98402N/NK-104.2.02]

5.3.5.1.1b A multinational, multicentre randomised, double-blind, parallel-group, dose ranging study to evaluate the efficacy and safety of NK-104 1 mg, 2 mg, 4 mg and 8 mg compared to placebo in patients with primary hypercholesterolaemia;[HEC/NKN98402N/NK-104.2.02]

5.3.5.1.2a A multinational, multicentre randomised, double-blind, parallel-group, dose ranging study to evaluate the efficacy and safety of NK-104 1 mg, 2 mg, 4 mg and 8 mg compared to placebo in patients with primary mixed or combined hyperlipidaemia; [HEC/NKN98403N/NK-104.2.03]

5.3.5.1.2b A multinational, multicentre randomised, double-blind, parallel-group, dose ranging study to evaluate the efficacy and safety of NK-104 1 mg, 2 mg, 4 mg and 8 mg compared to placebo in patients with primary mixed or combined hyperlipidaemia; [HEC/NKN98403N/NK-104.2.03]

5.3.5.1.3 A dose-ranging study of NK-104 in patients with primary hypercholesterolemia; [NK-104-209]

5.3.5.1.4 A 12-week multicenter, randomized, double-blind placebo- controlled, parallel group study to evaluate the efficacy and safety of pitavastatin (4 and 8 mg) in lowering LDL-C, as compared to placebo and to open label atorvastatin (10, 2(40 mg); [NKS104A2204]

5.3.5.1.5 Multiple dose, comparative study of pitavastatin [NK-104] in patients with primary hypercholesterolemia and an open-label extension study of the safety and tolerability of NK-104 in patients with primary hypercholesterolemia; [NK-104-210/211]

5.3.5.1.6 Study of pitavastatin 2 mg vs. atorvastatin 10 mg and pitavastatin 4 mg vs. atorvastatin 20 mg (following up-titration) in patients with primary hypercholesterolemia or combined dyslipidemia; [NK-104-301]

5.3.5.1.7 Study of pitavastatin 2 mg vs. simvastatin 20 mg and pitavastatin 4 mg vs. simvastatin 40 mg (following up-titration) in patients with primary hypercholesterolemia or combined dyslipidemia; [NK-104-302]

5.3.5.4 Other Clinical Study Reports

5.3.5.4.1 Double-blind follow-on study of pitavastatin (4 mg) versus atorvastatin (20 mg and 40 mg), with a single-blind extension of treatment, in patients with Type II diabetes mellitus and combined dyslipidemia; [NK-104-310]

5.3.5.4.2 Investigation of the bioequivalence of two types of pitavastatin preparations (1 mg tablet and 2 mg tablet); [NK-104-13]

5.3.5.4.3 Bioequivalent study of NK-104 2 mg tablets with score and without score; [NK-104-ST2-01]

5.3.5.4.4 Phase I study of pitavastatin after single oral dosing in healthy male subjects; [NK-104-01]

5.3.5.4.5 Phase I study of pitavastatin after repeat oral dosing in healthy male subjects; [NK-104-02]

5.3.5.4.6 Investigation of the safety and efficacy of pitavastatin over 4 weeks of repeated administration in adult male volunteers with a TC level of ≥200 mg/dL (*5.2 mmol/L*); [NK-104-03]

5.3.5.4.7 Investigation of the pharmacokinetics and safety of pitavastatin 2 mg once daily for 5 days between elderly volunteers and non-elderly volunteers; [NK-104-10]

5.3.5.4.8 Pharmacokinetic study of pitavastatin in healthy adult subjects; [NK-104-15]

5.3.5.4.9 An open label, ascending single and multiple oral dose study to assess the safety, tolerability and pharmacokinetics of NK-104 in healthy male Chinese subjects; [NK-104 1.01 CH]

5.3.5.4.10 Phase I study of pitavastatin – randomised, placebo-controlled, double-blind, group-comparison, dose-escalation study to investigate safety, tolerability and pharmacokinetics of pitavastatin after single oral dosing in healthy subjects; [CWP-PTV-002]

5.3.5.4.11 Investigation of the efficacy and safety of pitavastatin at 4 mg regarding the serum lipids by administration for 8 weeks in hyperlipidaemia patients by open study; [NK-104-04]

5.3.5.4.12 Investigation of the efficacy, dose-response and safety of pitavastatin in relation to serum lipids in hyperlipidaemia patients by double-blind three dose parallel design; [NK-104-05]

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

S.W. Johnny Lau
7/17/2009 09:10:21 AM
BIOPHARMACEUTICS

Manoj Khurana
7/17/2009 11:27:25 AM
BIOPHARMACEUTICS

Justin C Earp
7/17/2009 02:48:22 PM
BIOPHARMACEUTICS

Christoffer Tornoe
7/17/2009 03:52:28 PM
BIOPHARMACEUTICS

Wei Qiu
7/17/2009 03:58:28 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 22-363

12/22/08

NDA Number: 22-363 **Applicant: Kowa Research Institute, Inc.** **Stamp Date: October 1, 2008**

Drug Name: Pitavastatin calcium **NDA Type: Standard**

On **initial** overview of the NDA application for RTF:

	Content Parameter	Yes	No	Comment
Criteria for Refusal to File (RTF)				
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	Yes		
2	Has the applicant provided metabolism and drug-drug interaction information?	Yes		
Criteria for Assessing Quality of an NDA				
	Data			
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g. CDISC)?	Yes		
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?		No	The sponsor did not submit pharmacogenomic data nor propose pharmacogenomic claim in the labeling.
	Studies and Analyses			
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	Yes		
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?			Not applicable
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?			Not applicable
8	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	Yes		Dose reduction to 1 mg qd for moderate hepatically impaired, concomitantly taking cyclosporine and erythromycin
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?		No	There are no adequate and well-controlled studies investigating the safety and efficacy of pitavastatin in the pediatric population.
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?		No	
11	Is the appropriate pharmacokinetic information	Yes		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 22-363

	submitted?			
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	Yes		
	General			
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?	Yes		
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	Yes		
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	Yes		
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	Yes		
17	Was the translation from another language important or needed for publication?		No	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ___Yes_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

S. W. Johnny Lau, R.Ph., Ph.D.

Reviewing Pharmacologist Date

Sally Y. Choe, Ph.D.

Team Leader/Supervisor Date

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 22-363

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA	22-363	Brand Name	LIVALO®
OCP Division	2	Generic Name	Pitavastatin calcium
Medical Division	DMEP, HFD-510	Drug Class	HMG-CoA Reductase Inhibitor
OCP Reviewer	S.W. Johnny Lau	Indication(s)	Treat hypercholesterolemia
OCP Team Leader	Sally Y. Choe	Dosage Form	Immediate release tablet
Date of Submission	1-OCT-2008	Dosing Regimen	1, 2, or 4 mg/day
Estimated Due Date of OCP Review	20-MAY-2009	Route of Administration	Oral
PDUFA Due Date	3-AUG-2009	Sponsor	Kowa Research Institute, Inc.
Division Due Date	3-JUN-2009	Priority Classification	Standard

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Comments (Study number)
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X	[redacted]		annotated
Reference Bioanalytical and Analytical Methods	X	[redacted]		VALID/NK-104, 020019-RPX, 013436-RSC Revision 2, 12-May-2008, DMPK R0201695, DMPK R0200582, KOW/NK-104/06010, KOW/NK-104/07004, KOW/NK-104/06009, KOW/WAR/05001, KOW/DIG/05001, KOW/DIG/05002, KOW/RIF/06001, KOW/ENA/05001, KOW/ATZ/06001
I. Clinical Pharmacology				
In vivo mass balance:	X	1		SNY 419/013926
In vitro isozyme characterization:	X	2		AE-2544, R101029
In vitro metabolite Identity	X	1		Fujino Xenobio Metabol Dispos 14:415-24 1999
In vitro metabolism inhibition:	X			AE-2544
In vitro mechanism of uptake in human liver	X	3		ATR-148-100, Hirano JPET 311:139-46 (2004); Hirano DMD 34:1229-36 (2006)
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Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	7		477-01, NK-104-109, NK-104-20, NK104-GJ, NK-104-1.25US, NK-104-1.30, NK-104-1.31
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In-vitro:	X	4		R101113, FBM 06-T350, R99035, ATR-149-035
Subpopulation studies -				
ethnicity:	X	1		NK-104-1.35
pediatrics:				
gender & geriatrics:	X	1		NK-104-1.22US

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 22-363

renal impairment:	X	1		NK-104-1.24
hepatic impairment:	X	2		NK-104-16, NK-104-HK
PD:				
Phase 1:	X			PKH/NKN98389N/NK104.1.01, HPC/NKN00435N/NK-104.1.19
Phase 3:				
PK/PD:				
Phase 2, dose ranging studies:	X	2		HEC/NK98402N/NK-104.2.02, HEC/NKN98403N/NK-104.2.03
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Meta-analysis:				
NONMEM:				
II. Biopharmaceutics				
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Bioequivalence studies – traditional design	X	2		NK-104-1.36, NK-104-1.37US
Relative bioavailability				
alternate formulation as reference:				
Food-drug interaction studies:	X	1		NK-104-1.21US
Absorption site	X	1		KS104A2115
Dissolution:				
(IVIVC):	X	1		NK-104-1.39US
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Phenotype studies:				
Chronopharmacodynamics	X	1		NK104-1.23US
Pediatric development plan				
Literature References				
QT prolongation assessment	X	1		NK104-1.34US
Total Number of Studies		67		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 22-363

Filability and QBR comments				
	"X" if yes	Comments		
Application filable?	X			
Comments to be sent to firm?	X	Two (b) (4) sites in Canada have reliability issues. (b) (4) performed the bioanalytical analyses for pitavastatin and pitavastatin lactone in plasma and urine samples. If you intend to make labeling claims for the interaction results between pitavastatin and fenofibrate plus gemfibrozil (Study NK-104-109), you should do one of the following, in order of preference: • Repeat the pitavastatin and fenofibrate plus gemfibrozil interaction study. • Re-assay the samples for pitavastatin and pitavastatin lactone at a different bioanalytical facility. For this option, the integrity of the original samples must be demonstrated for the frozen storage period. • Commission a scientific audit by a qualified independent expert, who is knowledgeable in the area of human drug interaction studies and bioanalytical data, and is selected by your company rather than by (b) (4), to verify the results obtained by (b) (4) Pitavastatin is a 3R- and 5S- specific stereoisomer. You should provide data to demonstrate whether pitavastatin shows any chiral conversion via metabolism. You should submit plasma pitavastatin and pitavastatin lactone concentration data as well as pharmacokinetic parameters for Study NK-104-1.37US.		
QBR questions (key issues to be considered)	Exposure-safety and exposure-efficacy analyses, which help determine the risk/benefit ratio for using pitavastatin.			
Other comments or information not included above	Study **NK-104-1.37US links the Phase 3 clinically-tested formulation and the to-be-marketed formulation.** Hence, a DSI inspection on this pivotal bioequivalence study is in order. Clinical Site (total of 89 planned and 88 completed participants): (b) (4) Study **NK-104-1.37US** "Single-dose, randomized, open-label, crossover, bioequivalence study of pitavastatin 2-mg and 4-mg tablets manufactured by Skyepharma, France, and pitavastatin 2-mg and 4-mg tablets manufactured by Patheon, USA, in healthy volunteers" Bioanalytical sites: (b) (4) KOW/NK-104/08002 "An analytical investigation to determine the plasma concentrations of NK-104 and its lactone metabolite following a single dose, randomized, open-label, crossover, bioequivalence study of pitavastatin 2-mg and 4-mg tablets manufactured by Skyepharma, France and pitavastatin 2-mg and 4-mg tablets manufactured by Patheon, USA, in healthy volunteers"			
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				